OPTIMIZING THE USE OF CAPSULE ENDOSCOPY IN THE DETECTION OF SMALL-BOWEL PATHOLOGY

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Declaration

I, Anastasios Koulaouzidis, hereby declare that the work described herein has been composed by myself, except where stated in the text, and has not been submitted for any other degree or professional qualification. I also declare that for the papers attached in the appendix appropriate permission has been sought and obtained.

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To the treasured memory of my father Klearchos

To my beloved brother George Koulaouzidis

Abstract

Background Wireless capsule endoscopy (CE) was introduced in clinical practice just over a decade ago; it has since established a new era in the investigation and diagnosis of small-bowel diseases. Nevertheless, the detection of small-bowel pathology can be limited by issues related to the current level of CE technology. Furthermore, the clinical validity of the use of surrogate markers of diagnostic yield such as the ampulla of Vater (AoV), or that of various prokinetics, to increase the completion rate – and theoretically, the diagnostic yield – have not been clearly established. Other factors that could optimize the rate of detection of small-bowel pathology in CE are: 'speedy' video sequence review, chromoendoscopy and/or the application of three-dimensional (3-D) image-reproduction software. Three-dimensional imaging in CE is not currently feasible due to hardware limitations. However, software algorithms (shape-from-shading, SfS) that enable 3-D reconstruction in CE are available.

Methods The database of capsule endoscopy examinations of our centre includes procedures performed with two different models of capsule endoscopes. The detection rate of the duodenal papilla was examined in the largest – to date – cohort of small-bowel capsule endoscopy videos obtained with two different capsule endoscopy systems. Using meta-analysis software, the impact of various prokinetics was analysed. Furthermore, the validity and safety of QuickView pre-read was examined. In regard to proprietary chromoendoscopy software, Blue Mode filter offers better image enhancement when compared with Fujinon Intelligent Chromoendoscopy (FICE).

Out of four publicly available SfS algorithms, Tsai's method is the one that gives the better results. Tested on still-capsule endoscopy images, the application of a 3-D reconstruction software leads to image enhancement for a significant proportion of

vascular, but less so for inflammatory and protruding, lesions. Furthermore, the adjunct of 3-D reconstruction to the standard two-dimensional video reading software significantly improves the performance of novice small-bowel CE readers in distinguishing masses from mucosal bulges, thus potentially shortening their learning curve.

Results This thesis demonstrates that the selective and judicious use of prokinetics – and specifically that of metoclopramide with purgative and/or real-time viewer – in capsule endoscopy improves the completion rate. My results also show that the persistently low rate of AoV detection using two different small-bowel CE systems underlines the weakness of non-steerable CE. Although the benefits of QuickView are outweighed to some extent by a decrease in the overall detection rate, this mode can be used confidently in overt obscure gastrointestinal bleeding in an urgent inpatient setting and in outpatients with occult obscure gastrointestinal bleeding or suspected Crohn's disease. FICE (especially I) and Blue Mode is useful for the characterization of small-bowel findings.

Conclusion There are limitations in the current commercially available software for CE review. The inclusion of a 3-D representation algorithm may be of training and diagnostic benefit. Until optics technology allows hardware-enabled three-dimensional reconstruction, it seems a plausible alternative. Further clinical and development work is required in order to optimize the currently available reading software.

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Abbreviations

2-D two-dimensional

3-D three-dimensional

alt. h. alternate hours

ANOVA analysis of variance

AoV ampulla of Vater

ASGE American Society of Gastrointestinal Endoscopy

AUC area under the curve

AVM arteriovenous malformation

BF Blue Filter

BM Blue Mode

CCD charge-coupled device

CD Crohn's disease

CE capsule endoscopy

CI confidence interval

CMOS complementary metal-oxide-semiconductor

CR completion rate

CT computed tomography

CTE computed tomography enterography

DDW Digestive Diseases Week

DKT Daikenchuto

DY diagnostic yield

EFP electric field propagation

EPROM Erasable Programmable Read Only Memory

F females

FAP familial adenomatous polyposis

FDA U.S. Food and Drug Administration

FICE Fujinon Intelligent Chromo Endoscopy

FN false negative

FoV field of view

Fps frames per second

GI gastrointestinal

GTT gastric transit time

GUI graphical user interface

HBC human body communication

IA inter-observer agreement

IBD inflammatory bowel disease

IDA iron-deficiency anaemia

IMC Intelligent Microsystem Center

IV intravenous

LED light emitting diodes

LICS lesions of indeterminate significance

LR likelihood ratio

LS Lewis Score

M males

MeSH Medical Subject Headings

min minutes

Mirco Intelligent Robotic Object Camera

MRE magnetic resonance enterography

MRI magnetic resonance imaging

N/a non-applicable or non-available

N/s not stated

NaPhospho sodium phosphate

NaPico sodium picosulphate

NBI NarrowBand Imaging

NLH nodular lymphoid hyperplasia

NPV negative predictive value

OGD oesophagogastroduodenoscopy

OGIB obscure gastrointestinal bleeding

OR odds ratio

Pc piece

PEG polyethylene glycol

PHE portal hypertensive enteropathy

Pk packet

PO per os

PPV positive predictive value

QV QuickView

QVBM QuickView Blue Mode

QVWL QuickView white light

RF radio frequency

RGB red green blue colour model

RLP right lateral position

ROC receiver operating characteristics

ROI region of interest

RR risk ratio

RTV Real Time Viewer

s2D standard two-dimensional

SBI suspected blood indicator

SBTT small-bowel transit time

SD standard deviation

SE standard error

Sens sensitivity

SfS shape-from-shading

Spec specificity

TN true negative

TP true positive

VC virtual chromoendoscopy

vs versus

VQ visualisation quality

WL white light

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CHAPTER 1

The problem of optimizing the use of capsule endoscopy in the detection of small-bowel disease

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1.1 Brief history

The idea for a wireless endoscopic capsule device belongs to Gavriel Iddan, an Israeli electro-optical engineer (Iddan et al. 2000; Eliakim 2013). Working concurrently on the same fundamental idea in London, Professor Paul Swain published the first conceptual studies on a wireless capsule in 1994 (Iddan and Swain 2004). Swain's team possessed the necessary anatomical expertise and medical knowledge for the demands and objectives that would be placed on such a device, while Iddan was more familiar with the engineering and electro-optical aspects of capsule endoscopy (CE) (Filip 2013). Eventually, the two teams joined forces and the outcome of their combined efforts was the first wireless capsule endoscope, which was presented and published at the Digestive Diseases Week (DDW) of the Millennium in San Diego, USA, and in *Nature*, respectively (Iddan and Swain 2004; Koulaouzidis, Rondonotti and Karargyris 2013).

Since its official introduction in clinical practice (2001), CE has drastically changed clinical decision making and the diagnostic algorithms of investigating the small bowel. A wealth of evidence has confirmed the validity of the use of CE in obscure gastrointestinal bleeding (OGIB) – the latter accounts for 60–70% of all small-bowel CE examinations worldwide – and Crohn's disease (CD; known and/or suspected). Other clinical indications, although less common, are coeliac disease, small-bowel polyposis syndromes and clinical suspicion of small-bowel neoplasia (Wang et al. 2013; Ladas et al. 2010; Sidhu et al. 2008). To date, more than 2 million capsules have been ingested worldwide and more than 3,000 PubMed-listed publications have appeared in the medical literature.

1.2 Principles of capsule endoscopy technology

Overall, CE approaches an almost 'physiological' endoscopy; the capsule moves passively - propelled by bowel peristalsis - and images the mucosa in a collapsed state, as there is no air insufflation (Woods and Constandinou 2011). All commercially available CE devices are constructed following the same baseline principles. At first, the shape and volume of any CE device should be sufficiently small to allow it to pass through the main anatomical sphincters (cricopharyngeous, lower oesophageal sphincter, pylorus and ileocaecal valve) without becoming an obstruction risk (Woods and Constandinou 2013). However, this size in conjunction with the peristaltic movements of the small bowel, are also the 'Achilles heel' of the capsule, as they predispose the capsule to rotate (or tumble) within the small-bowel lumen resulting - frequently - in deficient luminal and mucosal coverage. The movements of the capsule (oblique-forward, oblique-reverse, perpendicular movements) often result in temporary visual interference that may render the images unsuitable for diagnostic purposes (Filip 2013). Furthermore, it is already know that even expert reviewers have a limited ability to recognize the vector of capsule movement in the small-bowel lumen or through anatomical sphincters (Koulaouzidis, Douglas and Plevris 2012; Kopylov et al. 2012).

The sheath is made of disposable and biocompatible plastic material, resistant to digestive fluids (in order to seal and protect its internal components in the 'milieu' of the GI tract) and weighs between 3.3–6 g (depending on the CE model: see Table 1) (Koulaouzidis, Rondonotti and Karargyris 2013). The internal compartment of any CE device includes a complementary metal-oxide-semiconductor (CMOS) imager or a high-resolution charge-coupled device-based chip camera (CCD), a short focal-length (hemispheric) compact lens, a white light illumination system (provided by 4–6 light emitting diodes (LEDs)), two silver oxide batteries and a transmitter. The CMOS imager suits the packaging/space constraints of the capsule device due to its low light requirements (Swain 2010).

The CE's device imager, which has no shutter, operates by taking still frames in a dark environment intermittently illuminated by LEDs throughout the capsule passage. Capsule endoscopes offer an 8× magnification, and a minimum size of

lesion detection in the range of 0.1–0.2 mm. Depending on the manufacturer, the operating time of capsules can vary between 8–12 hours (**Table 1**) (Koulaouzidis, Rondonotti and Karargyris 2013). The CE device is activated by its removal from a magnetic holder. Commercially available small-bowel CE models can acquire and transmit between 0.5–16 frames per second (fps) (Koulaouzidis, Rondonotti and Karargyris 2013). This results in a total of 50,000–120,000 transmitted images that are 'stitched' together and converted into a continuous video that gives the illusion of continuous digital video-stream recording without gaps.

Ü	Company, Country	FoV(°)	Image	Transmission	Fps	Dimensions (mm)	Weight (g)	Battery life (h)	Reviewing software	Optical enhancements
PillCam*SB2	Given*Imaging, Israel	156	CMOS	Radiofrequency	2-4	11 × 26	3.45	9->11.5	RAPID~v8	Blue-mode; FICE 1,2,3
MiroCam*v2	IntroMedic ^a Co., Korea	170	СМОЅ	EFP	6	ø11 × 24	3.2	12	MiroView*v2	ALICE; colour- mode
EndoCapsule*	Olympus" Co., Japan	145	CCD	Radiofrequency	23	ø11 × 26	3.45	10	OLYMPUS•WS-1	Contrast imaging
OMOM*	Chongding Jinshan Science and Technology Co., China	140	CCD	Radiofrequency	2 (variable)	13 × 27.9	9	80	OMOM* workstation	N/A
CapsoCam*SV1	CapsoVision* Inc., USA	360	N/A	On-board-EPROM flash	16 (4 per camera)	11×31	N/A	15	CapsoView*	N/A
Table 1: Abbreviation coupled device	Table 1: Available types of small-bowel capsule endoscopes, specifications and operating characteristics. Abbreviations: CE, capsule endoscopy; FoV, field of view; Fps, frames per second; CMOS, complementary metal-oxide-semiconductor; CCD, charge-coupled device; EFP, electric field propagation; EPROM, Erasable Programmable Read Only Memory; FICE, Fujinon Intelligent Chromo Endoscopy; N/A, n/A, n/A, n/A, n/A, n/A, n/A, n/A, n	of y; FoV, agation;	small-bowel field of view; EPROM, Era	wel capsule iew; Fps, frames Erasable Progra	endoscopes, per second; CMI mmable Read Or	opes, speci ; CMOS, compl ad Only Memor	specifications complementary Aemory; FICE, 1	and metal-oxi Fujinon Int	operating de-semiconduc elligent Chromo	wel capsule endoscopes, specifications and operating characteristics. ew; Fps, frames per second; CMOS, complementary metal-oxide-semiconductor; CCD, charge- Erasable Programmable Read Only Memory; FICE, Fujinon Intelligent Chromo Endoscopy; N/A,

1.2.1 PillCam® small-bowel capsule endoscopy system

The first commercially available CE device (M2A®) was developed by Given®Imaging Ltd (Yoqneam, Israel) and it was approved for clinical use in humans in Europe and the United States in August 2000. The first generation of PillCam®SB – essentially a renamed M2A® – was released in 2001, while the second generation of PillCam®SB was released in 2007 (PillCam®SB2). The latest commercial small-bowel CE model of this company (PillCam®SB3) was released in 2013.

PillCam®SB2 measures 11 × 26 mm and weighs less than 4g (Koulaouzidis, Rondonotti and Karargyris 2013; Wang et al. 2013). It contains a miniature colour video CMOS-chip camera with four illuminating LEDs, two batteries, a radiofrequency transmitter and an antenna. Images are captured at a rate of 2 frames per second (fps) for PillCam®SB2 or 4 fps (PillCam®SB2-4), while the battery life is between 8 hours (PillCam®SB) and 12 hours (PillCam®SB2ex, see Table 1.) (Wang et al. 2013). PillCam®SB2 has a broader mucosal coverage due to its increased field of view of 156°degrees, as compared with the 140°degrees of its predecessor, and an effective visibility distance of 30 mm (Metzger et al. 2009). The image resolution of PillCam®SB is 256 × 256 pixels. Advanced optics and automatic light control provide optimal image quality and illumination. Therefore, at a reference working distance of 4.5 mm, the coverage mucosal area of PillCam®SB2 is 1,100 mm²- as compared with the 500 mm² of its predecessor (Metzger et al. 2009).

The proprietary reading software of Given®Imaging Ltd is the *RAPID™* Reader and through repeated developments it has now reached its eighth version. This software interface provides single, dual or quadruple window video review, as well as additional diagnostic features and study reviewing aids. It contains an improved user interface similar to the ribbon toolbar concept used in Microsoft® products, the Lewis Score (LS) calculator, the Fujinon Intelligent Colour Enhancement (FICE), the suspected blood indicator (SBI) (Koulaouzidis, Rondonotti

and Karargyris 2013), QuickView (QV), a thumbnail comparison feature, backwards compatibility with studies from previous *RAPID*TM software versions, and an improved progress indicator/localization guide.

The tracking of the capsule within the body is important for the localization of abnormal findings and planning of further therapeutic interventions. Currently, localization is based on transit time. Once the pylorus and caecum are identified, the location of a lesion in the small intestine is an estimate based on the time from one of these two points. Most commercially available software packages provide a two-dimensional (2-D) tracking application of the capsule route. The output of these localization modules is a graphic trajectory of the capsule while it moves along the intestinal lumen (Fisher and Hasler 2012). This method uses signal strength analysis from aerial antennae attached to the patient's abdomen which has been validated on healthy volunteers against fluoroscopy (Fischer et al. 2004). However, this technique has been criticized for its inability to definitively localize small-bowel lesions, mainly because it is prone to inaccuracy due to differences in small-bowel transit time or variant anatomy (Than et al. 2012). The average position error reported for this technique is 37.7 mm, with a maximum error reaching 114 mm (Iakovidis et al. 2013).

1.2.2 MiroCam small-bowel capsule endoscopy system

MiroCam® (which stands for Mirco Intelligent Robotic Object Camera) has been developed by the Intelligent Microsystem Center (IMC) established by the Korean Ministry of Science and Technology in Seoul, South Korea, which was renamed to IntroMedic Co Ltd in 2006 (Filip 2013). The company's small-bowel CE device passed European medical standards and received certification (CE mark) in 2007; it also received U.S. Foods and Drugs Administration (FDA) approval in May 2011 (Fisher and Hasler 2012). MiroCam®, currently version 2 with version 3 to be released in 2014, utilizes a novel transmission technology, electric-field propagation (EFP). This technology uses the capsule itself to generate an electrical field and the human body as a conductive medium for data transmission in so-called 'human body communication' (HBC). Perhaps this, in conjunction with the set array of sensors, is the main reason for the persistent failure of this CE model to capture

upper-oesophageal and gastro-oesophageal junction (Z-line) images (Koulaouzidis 2013).

Specifications of the MiroCam® CE device include a size of 10.8 × 24.5 mm, a weight of 3.4 g, a field of view of 170° degrees (150° degrees in the first model), a resolution of 102,400 (320 × 320) pixels and an image capture rate of 3 fps (Koulaouzidis, Rondonotti and Karargyris 2013). Illumination is provided by six LEDs. As a power-saving method it incorporates two external electrodes and a single-skin electrode for electric data conduction across the human body. Hence, it avoids the need for radio frequency (RF) and allows for a long battery life without any need for image compression and a safer use in the ever-increasing group of patients with implantable pacemakers or in-situ defibrillator devices. Furthermore, MiroCam® remains the smallest commercially available small-bowel CE device. The extra available space (10% free internal space) could be used for additional internal components, such as different sensors or stabilizing components for advanced CE. The two systems have been repeatedly checked in head-to-head trials and have been shown to have at least equivalent capability in detecting small-bowel disease (Koulaouzidis, Rondonotti and Karargyris 2013).

MiroView™ v2.0, the proprietary reading software of IntroMedic Co Ltd, offers a variety of tools and functions to aid reporting processes. For instance, the function 'Range View' displays a range of images to readily identify landmarks in the GI tract. In this mode, the side bar images will move 1 image per/second while the centre images will display images per user selection, i.e. 15 fps. Another function, the 'Map View', which is similar to the Given®Imaging Ltd colour bar but uses a different technology and patent, displays a range of thumbnail images to readily identify landmarks in the GI tract. Furthermore, the 'Express View' eliminates similar images and the Range View can be used to identify landmarks and disease pathologies by viewing a total of nine images before and after the main image. In the image-enhancement field MiroView™ offers the ALICE and colour-mode functions. Admittedly, they have not attracted clinicians' attention or any clinical studies.

1.3 Reading capsule endoscopy video sequences

CE procedure is not operator dependent and does not require the same technical skills as conventional GI endoscopy (Davison 2006; Drew et al. 2013). In fact, capsule administration and swallowing requires only a couple of minutes. Therefore, expertise with CE lies in the ability of an individual to read and interpret the CE findings (Rajan et al. 2013). The average CE footage reading time varies between 30 and 120 minutes depending on the small-bowel transit, the quality of images, and the experience of the reader (Lo 2006). Moreover, a small-bowel lesion may only be visible in just a few or even just a single frame (Rondonotti et al. 2012). Therefore, this large amount of visual information requires focused and undivided attention for careful evaluation by the CE reviewer (Lo 2006; Iakovidis et al. 2013). Nevertheless, going (at low reviewing speed) through a rather monotonous video recording, in a room with dimmed lights, is the perfect way for someone to become hypnotized (Lo 2006). To date, there is limited data which can address errors in CE interpretation (Lewis 2004; Lo 2006; Rondonotti et al. 2012; Koulaouzidis, Rondonotti and Karargyris 2013). As such, there is much heterogeneity in techniques used to interpret capsule endoscopy (Rondonotti et al. 2012). Furthermore, there are limited published data concerning optimizing operator performance for the interpretation of capsule endoscopy (Rondonotti et al. 2012). In fact, the majority of current evidence on the best reading mode (single, dual or quadruple view and reading speed) of CE video sequences comes from expert opinion papers and/or performance comparison studies between physicians and non-physician reviewers. Therefore, although the reporting time is a major clinical issue, other factors such as the distance of the reviewer from the reviewing monitor, the amount of ambient room light and/or the use of image-enhancement tools are equally important to the final outcome.

One proposed strategy to reduce CE reading times would be to use trained non-physician readers (e.g. endoscopy assistants/scientists) to pre-read the CE footage (Dokoustidou et al. 2011; Shiotani et al. 2011; Drew et al. 2012). Another approach is to use to special software programs to select significant images for subsequent viewing (Shiotani et al. 2012; Koulaouzidis, Rondonotti and Karargyris 2013).

Although several studies have showed that non-physician readers are at least as competent as physician capsule endoscopists (Drew et al. 2013), the lack of an homogeneous approach (viewing speed and/or mode) in CE reviews seems to account for some of the reported discrepancies in diagnostic yield (DY) and the inter-observer agreement on CE video interpretation (Jensen et al. 2010; Jang et al. 2010; Rondonotti et al. 2012).

In light of all of the above, several attempts have been made to develop technical software features, in order to make CE video analysis easier and shorter without jeopardizing its accuracy or, in other words, its DY. The first software feature designed for this purpose was the SBI, an automatic system able to pick up, in a completely automatic fashion, frames containing several red pixels and, therefore in theory to detect blood and/or other red-coloured lesions such as large angioectasias. Nevertheless, the accuracy profile of this tool is suboptimal and, at the present time, it can be used only as a supportive/addition tool in CE reporting (Koulaouzidis, Rondonotti and Karargyris 2013).

1.4 Diagnostic yield and key performance indicators

CE has advantages and disadvantages compared to other diagnostic modalities that evaluate the small intestine (Dionisio et al. 2010; Triester et al. 2005; Marmo et al. 2005). The main advantage of CE is that it is a non-invasive technique with little or no side effects or complications (Eliakim 2011). Perhaps one the main disadvantage of CE is that its diagnostic accuracy is difficult to determine due to a lack of an adequate 'gold standard'. Therefore, in the early days of CE, the term diagnostic accuracy has been substituted with the term DY. Due to the unique and intriguing nature of CE, DY is defined as the likelihood that a test or procedure will provide the information needed to establish a diagnosis (Koulaouzidis et al. 2012).

In CE, the DY is influenced by several factors integral to the capabilities the capsule device, for example, CE device technological specifications, quality and percentage of intestinal mucosal coverage, and the challenging 'environment' of the small bowel and the reviewer's performance. To date, human studies have compared different methods of small-bowel examination, reporting their comparative DY (Koulaouzidis, Rondonotti and Karargyris 2013). The true negative diagnostic rate was defined as the number of cases in which both methods of examination were negative. This is certainly an approximation of a true yield. Historically, the DY of CE varies between 38–83% (Liao et al. 2010; Rondonotti et al. 2013).

One method to determine – and at a second stage, attempt to improve – the DY of any diagnostic procedure is to use markers (at least some of which are in a difficult position to be seen) that are present in every intestine and confirmed to be there with another test. This was first done in 2000, when Appleyard et al. (2000) sewed glass beads into the intestines of dogs and then performed capsule endoscopy and push enteroscopy. The sensitivities were 64% and 37%, respectively. Another solution (more applicable to humans) is to look for an anatomical finding, i.e. a surrogate marker present in everyone (Cass 2006).

In conventional colonoscopy, caecal completion rate and withdrawal time are two of the main performance indicators (Ward et al. 2014). It is known that a longer withdrawal phase leads to a higher polyp detection rate (Butterly et al. 2014). However, other factors such as sleep deprivation of the endoscopist due to being on call the night prior and/or performing an emergent procedure lead – despite longer withdrawal times – to a significant 24% decrease in the adenoma detection rates. Furthemore, it has been shown that colonoscopy quality-measure reporting is important to patients, influencing colonoscopist selection (Solad et al. 2014).

In CE, currently an uncontrollable in regard to movement in the small-bowel, speed and vector direction device, the above operator-dependent factors and performance indicators cannot be applied. Therefore, over the last few years, clinical researchers have highlighted the use of markers (some are in a position where they are difficult to spot) which are present in the intestine as quality assurance indicators in smallbowel CE. (Cass 2006). The major duodenal papilla, or ampulla of Vater (AoV), which is present in all individuals who have not undergone duodenal resection and is located on the posteromedial aspect of the duodenal sweep, 8-10 cm distal to the pylorus, is a reasonable such candidate marker. It is difficult to see, as the translucent dome of the propelled CE tends to point towards the outer aspect of sharply angulated bowel loops. On the other hand, choosing the AoV as the marker and extrapolating the results of the detection to polyp lesions may not be completely reliable. The factors that make the AoV difficult to observe, such as the proximal location, size/luminal protrusion and capsule transit speed, are at least part of the reason why small-bowel lesions such as polyps may be missed in smallbowel CE examinations (Clarke et al. 2008).

1.5 The issue of prokinetics in small-bowel capsule endoscopy

Maximum DY in small-bowel CE requires not only optimal visualization of the intestinal mucosal surface but also complete capsule transit through the entire small-bowel (Rokkas et al. 2009). Currently, one of the major limitations of small-bowel CE is the high rate of incomplete examinations, i.e. the percentage of cases in which the capsule does not reach the caecum by the end of the recording period and/or exhaustion of the capsule's battery life. Recent systematic reviews showed that the completion rate (CR) of small-bowel CE varies between 81.3–83.5% for retrospective and prospective studies, respectively (Liao et al. 2010). If complete enteroscopy is not achieved, concerns remain over missed small-bowel pathology (Mergener et al. 2007). This could lead to repeated or new investigations increasing health-care costs.

Risk factors for incomplete CE include intestinal dysmotility (e.g. prior small-bowel surgery, diabetes mellitus), immobility/hospitalization, patient's age, moderate or poor bowel cleansing, and a delayed gastric transit time (GTT)> 45 min (Yazici et al. 2012; Triantafyllou et al. 2009; Westerhof et al. 2009; Shibuya et al. 2012). Furthermore, the presence of small-intestinal debris, chyme, biliary secretions, and/or air bubbles can interfere with the visualization quality (VQ) and potentially affect the DY. However, reducing small-bowel transit time (SBTT) may influence the DY of CE. With colonoscopy, the detection rate of neoplastic lesions is higher when the time to withdraw the colonoscope is longer (Fatima et al. 2008). It is conceivable that a similar principle also applies for small-bowel CE.

Therefore, it is expected that decreasing GTT and SBTT will allow a capsule to successfully reach the caecum by the end of its battery life. Therefore, different prokinetic agents have been used. Metoclopramide remains the most commonly administered prokinetic (Ladas et al. 2010). Domperidone, an antidopaminergic agent, on the other hand, has not been widely used in small-bowel CE and the evidence base is limited (Ladas et al. 2010). Unlike metoclopramide, it does not readily cross the blood-brain barrier; hence it lacks extrapyramidal adverse effects

(Champion et al. 1986). Recently, few studies evaluated the use of metoclopramide, erythromycin, mosapride, chewing gum, lubiprostone, daikenchuto or even postural 'tricks'.

The issue of improving CR in small-bowel CE is contentious. Although some evidence exists, current guidelines indicate that there is no strict recommendation on the use, type and/or mode of administration of prokinetics in small-bowel CE. (Rondonotti et al. 2010). However, no systematic review or meta-analysis has examined the role of prokinetics in combination with other modalities such as real-time viewer and/or purge, before or during a small-bowel CE procedure.

1.6 Fujinon intelligent colour-enhancement (FICE)

In recent years, virtual chromoendoscopy techniques have been proposed to enhance micro-vascular contrast and facilitate minute resolution of superficial patterns and colour differences. In 2005, Fujinon Corporation (Saitama, Japan) developed the FICE as a new type of image-enhanced endoscopy with the potential to improve detection of lesions in the upper gastrointestinal tract and enhance differentiation between neoplastic and non-neoplastic tissue (Pohl et al. 2008).

FICE is a digital-imaging technology based on arithmetical processing of ordinary images; this is executed by external software and allows processing of ordinary images that were captured by the standard video CE devices. The spectrum of wavelength used for creation of optical images is influenced by several factors such as the light spectrum of the light source, the optical device, and the spectral sensitivity of the sensing elements. The wavelengths are associated with laminar structures and blood flow in the GI mucosa that have been altered by inflammation or neoplasm, which act as a scattering element and interfere with the reflectance spectrum (Imagawa et al. 2011).

The FICE software was successfully implemented within the *RAPID®* Reader reporting software (Given®Imaging Ltd, Yokneam, Israel). The CE reviewer can select flexibly between standard imaging and three different FICE-enhanced settings with different wavelength patterns by a simple push on the relevant toggle button (Imagawa et al. 2011). Essentially, FICE can provide high-contrast images by selecting the wavelength suitable for a specific structure of mucosal structures or vessels. In CE, three FICE settings with different spectral specifications (wavelengths) have been introduced.

An additional filter the *RAPID*® interface offers is the Blue Mode (BM) filter. BM filter is a colour coefficient shift of light in the short wavelength range (490–430 nm) superimposed on to a white (red, blue, green; RGB) light image. There is a growing pool of experts' opinion that BM improves lesion visualization in the majority of cases.

Both the validity of FICE and BM in small-bowel CE, as well as the optimal settings for improved image recognition in various small-bowel lesions, have been studied only in a limited fashion to the present date (Pohl et al. 2010; Imagawa et al. 2011).

1.7 QuickView (QV) and capsule endoscopy

Nevertheless, one of the limitations of small-bowel CE is the reading time required for the interpretation of lengthy video streams. It is generally accepted that the average time for video sequence analysis is between 40 and 120 minutes, depending on the overall recording time and the reviewer's experience (Shiotani et al. 2012). QV is a computational tool which scans all images and scores them according to the possible level of significance. Eventually its output is CE images of potential interest to the CE reader, providing a fast pre-viewing option (Westerhof et al. 2009). The number of images to be considered 'frames of interest' can be set as a percentage (5%, 10%, 20% ... 80%) of the full video. Then, according to the percentage level set by the user, QV displays a shortened video compared with normal-mode view. Recently published data give evidence that this target seems to be accomplished in small-bowel CE video readings with a high sensitivity in the per-patient per-lesion analysis (Shiotani et al. 2012).

However, the QV mode is still under clinical validation and there are only a handful of studies that have examined the utility of this informatics algorithm (Shiotani et al. 2011; Saurin et al. 2012; Hosoe et al. 2012; Westerhof et al. 2009; Shiotani et al. 2012). Furthermore, there is no evaluation of QV in combination with non-white light images such as with the BM filter; the latter yields promising results and researchers have recommended further study of this as the main viewing mode, especially in cases of OGIB.

1.8 Three-dimensional reconstruction in capsule endoscopy

To date, limited research has been carried out in developing methods and materials that offer three-dimensional (3-D) representation of the digestive tract. Since the capsule needs 6-8 hours to traverse through the small-bowel (Koulaouzidis and Douglas 2009; Westerhof et al. 2012), cameras within the currently marketed capsule endoscopes work at a capture rate of 2-3 fps in order to comply with power requirements (Fisher and Hasler 2012). Nonetheless, this has an adverse effect on the smoothness of motion between consecutive frames and creates a visually unpleasant effect on the human eye (Karargyris and Bourbakis 2010; Woods and Constandinou 2011). Furthermore, shape is an important element in human perception; yet, unlike other diagnostic modalities, i.e. computed tomography and magnetic resonance imaging, CE suffers from a lack of 3-D information (Koulaouzidis and Karargyris 2011).

Three-dimensional (3-D) technology is currently in use, e.g. a magnetometer can provide not only acceleration values on the three axes, but also the 3-D orientation of the device. Commercial time-of-flight range cameras, i.e. Microsoft's Kinect Project, already exist in the market and in the near future this may be further improved and miniaturised for use inside a capsule endoscope (Karargyris and Bourbakis 2011). These cameras offer information on depth and colour. Furthermore, we should not forget that 3-D-guidance systems are already used for endoscopic surgeries offering 3-D-position information of the sensor. Therefore, using the acquired information (orientation, acceleration, depth values, position etc.) from these miniature sensors in conjunction with sophisticated registration software algorithms, an accurate 3-D representation of the digestive tract could be created successfully (Koulaouzidis and Karargyris 2011).

In radiology, it is known that increasing the visual field of view angle to 120 degrees allows for a decrease in the total number of supine and prone 3-D endoluminal flythrough passes from four to two without negatively impacting on overall polyp detection (Pickhardt, Schumacher and Kim 2009). Furthermore, 3-D CT colonography interpretation using a unidirectional panoramic view is equally accurate, but significantly faster than an interpretation based on a bidirectional

standard view (Mang et al. 2011). Lastly, it has been shown that the addition of video to static 2-D and 3-D images may lead to improved perception and classification of CT colonography (McKenna et al. 2012).

For conventional endoscopy systems, stereo technology has been introduced to capture stereo images and to create depth information and therefore 3-D reconstruction of digestive structures. However, due to issues with size, such systems have not been widely accepted (Kolar et al. 2010; Fisher and Hasler 2012). Likewise, in CE there has been a hardware approach that provides in real time both 3-D information and texture using an infrared projector and a CMOS camera. The major drawbacks of this system are its size, power consumption and packaging issues (Fisher and Hasler 2012).

Therefore, in order to tackle the problem of the current hardware limitations, a software approach based on monocular images - shape-from-shading (SfS) - has been proposed to approximate a 3-D representation of digestive tract surface utilizing current CE technology. The SfS technique, firstly proposed by Horn (Horn and Brooks 1986), is a member of a family of shape-recovery algorithms called shape-from-X techniques (Karargyris and Bourbakis 2011), and has the capability to recover the shape of objects presenting a single image using the gradual variation of shading. The SfS problem is to compute a 3-D shape from a greyscale image, however, this is a problem that has no single solution (Koulaouzidis and Karagryris 2012). Hence, SfS techniques can be divided into four groups: minimization approaches, propagation approaches, local approaches, and linear approaches. Minimization approaches obtain the solution by minimizing an energy function. Propagation approaches propagate the shape information from a set of surface points. Local approaches derive the shape based on the assumption of surface type. Linear approaches compute the solution based on the linearization of the reflectance map.

1.9 Aims

The aims of this thesis are to optimize the use of CE in the diagnosis and detection of small-bowel pathology. Therefore, this thesis aims:

- To evaluate the detection rate of the AoV by two different small-bowel CE systems in our cohort and to compare the results from our centre with published reports.
- 2. To assess the current evidence base on the use of prokinetics for CR and explore their effect on GTT and SBTT by meta-analysing all relevant studies.
- 3. To assess the validity of FICE and BM filter in capsule endoscopy.
- 4. To assess the use of QV in certain clinical scenarios and in combination with the BM filter.
- 5. To test innovative new software (3-D) in the visualization of small-bowel pathology.

CHAPTER 2

Detection of the ampulla of Vater in small-bowel capsule endoscopy: experience of two different systems

- 2.1 Introduction
- 2.2 Patients and methods
- 2.2.1 General information on CE procedures
- 2.2.2 CE-reviewing software
- 2.2.3 Statistical analysis
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- 2.3 Results
- 2.3.1 General information on CE procedures
- 2.3.2 CE reviewing software
- 2.3.3 Detection of the AoV
- 2.4 Discussion
- 2.5 Conclusion

2.1 Introduction

Over the last decade, CE has been established as a very useful tool in the investigation of small-bowel diseases (de Franchis et al. 2007). A recent pooled analysis has demonstrated that a small-bowel CE has a minimal miss rate of < 1% for small-bowel ulcers (Lewis et al. 2005). Although the small-bowel CE provides a high information yield on mucosal lesions (Leighton et al. 2006), it does not permit the assessment of small-bowel wall thickness or extraluminal findings (Hara et al. 2006). As evidence of pathology detected by device-assisted enteroscopy, computed tomography enteroclysis or magnetic resonance imaging, but missed by CE have increased (Hakim et al. 2011; Gupta et al. 2010; Mavrogenis et al. 2011; Crook et al. 2009), concerns have arisen that the small-bowel CE may underestimate the number of small-bowel polyps in patients with a known high polyp burden, such as patients with hereditary or familial polyposis syndromes or other sinister pathologies (Wong et al. 2006; Chong et al. 2006; Ross et al. 2008; Hakim et al. 2011). In CE, the amount of information we get (or in fact, do not get) is a combination of its technical limitations, i.e. its rigid structure, inability to insufflate, lack of directionality or steer control and a set field of view (Clarke et al. 2008), SBTT, the amount and transparency of intraluminal liquids and, finally, the degree of small-bowel contraction.

Over the last five years clinical researchers have highlighted the use of markers (some are in a position where they are difficult to spot) which are present in the intestine as quality assurance indicators in an small-bowel CE (Cass 2006). The major duodenal papilla, or AoV, which is present in all individuals who have not undergone duodenal resection and is located on the posteromedial aspect of the duodenal sweep, (Cass 2006) 8–10 cm distal to the pylorus, is a reasonable such candidate marker. The factors that make the AoV difficult to observe during a CE examination, such as the location, size/lumen protrusion, the capsule transit speed and the fact that translucent dome of the propelled CE tends to point towards the outer aspect of sharply angulated bowel loops (Cass 2006), are – at least in part – the reasons why small-bowel lesions such as polyps may be missed in the small-bowel CE examination.

Therefore, the present study aims to evaluate the detection rate of the AoV by two different small-bowel CE systems in a cohort of patients who underwent CE for the purpose of clinical need and to compare the results from our centre with previously published report.

2.2 Patients and Methods

2.2.1 General information on CE procedures

Data of all the SBCE procedures that were carried out in our centre from March 2005 to June 2011 were reviewed retrospectively. Duplicate examinations, performed for clinical needs, were included. The small-bowel CE was performed with a PillCam®SB1/SB2 (Given®Imaging Ltd, Yokneam, Israel) and a MiroCam® (IntroMedic Co, Seoul, Korea) CE, using the departmental procedural protocol (Appendix 1). The AoV was detected by its distinct anatomical shape, i.e. a papilla-shaped polypoid protrusion with a pin-point or slit opening at its tip. Every frame in which the AoV appeared either in whole or in part was counted positive for detection. In cases of concern, the opinion of a second experienced (JP) reviewer was sought.

Also recorded were age, gender, AoV detection, the number of frames at which the papilla was visible, the presence of bile spout, indication and date of the small-bowel CE, the type of CE used, the type and dose of prokinetics used as well as transit parameters including the time of duodenal entry, i.e. GTT, SBTT and the transit time from pylorus-to-first duodenal papilla frame, the completion to caecum or not and the quality of small-bowel cleansing (and, where available, the quantity of laxatives used).

To date, there is no standardized bowel cleansing score for a small-bowel CE, hence we adopted a modified four-point grading scale from the study by Park et al. (2010) depending on the proportion of visualized mucosa and the extent of obscuration by intraluminal food debris, turbid fluids, bubbles or bile, as follows: (1) **Score 3** (very good visibility), > 75% mucosa visible; (2) **Score 2** (good visibility), 50–75%; (3) **Score 1** (average visibility), 25–50%; and (3) **Score 0** (poor visibility), < 25% mucosa seen. Cleansing scores refer to the first 30 minutes of the small-bowel recording.

2.2.2 CE reviewing software

All the small-bowel CE sequences were reviewed using a detailed protocol for the identification of the AoV, outlined below with the RAPID® v7 (Given®Imaging Ltd)

and the MiroViewTM2.0 (IntroMedic® Co). Small-bowel CE video sequences were not de-identified, but any previously captured thumbnails were deleted. For maximal pick-up yield, the automatic viewing mode at the lowest possible speed that allowed smooth video play (6fps) in a single frame mode with the reviewer seated at arm's length from the screen in a room with dimmed light, was chosen. Only a desktop spotlight was employed when illumination was required for data input in the data-collecting Excel 2007 spreadsheet (Microsoft®, Redmond, WA, USA). A 'roll-through' mode was utilized, where needed, to aid the delineation of mucosal/surface details (Selby and Prakoso 2011). Fujinon intelligent colour enhancement or Blue Mode in *RAPID*® software, ALICE or colour mode in MiroViewTM, were not used in the study.

The predefined settings for the white-light CE video-sequence review with *RAPID*® software in our centre are sharpness 1, brightness 1 and colour 2. Equivalent settings for the MiroView™ software are 2, 0 and 0, respectively. Video reviews, from point of duodenal entry, were prolonged from that of 15 minutes in a previous study (Katsinelos et al. 2009) to 30 minutes to minimize the possibility of missing the AoV. If the small-bowel CE was realized to be going into a to-and-forth movement after its first duodenal entry (Nakamura 2009), the reviewing time was adjusted accordingly to the start from the point of permanent duodenal entry.

2.2.3 Statistical analysis

Statistical analyses were carried out with StatsDirectTM 2.7.8 (StatsDirect, Altrincham, UK). Continuous data were presented as mean \pm standard deviation (SD) and range. Student's t-test was used to compare parametric variables. A one-way ANOVA (analysis of variance) for independent samples was used to compare the papilla detection rate based on indication and diagnosis. A two-tailed P value < 0.05 was considered statistically significant. Bonferroni and Sidak adjustment of critical P-values was applied when performing multiple comparisons.

2.2.4 Ethics consideration

This study was conducted in accordance with the Research Ethics Guidelines of the UK. After being reviewed by the local ethics committee, further specific ethical reviews and approval were not required, as the study was considered to be an audit using data obtained as part of regular patient car

2.3 Results

2.3.1 Baseline characteristics of the patients

A total of 839 small-bowel CE procedures performed in 758 patients were recorded in our institution between March 2005 and June 2011. Due to the technical issues (i.e. only initial written reports available, corrupt small-bowel CE video sequences stored in compact disks and/or failure to re-download), 189 small-bowel CE videos were not available for review. Another 22 examinations with gastric or proximal duodenal capsule retention and nine of endoscopic capsule delivery in the duodenum were also excluded. Therefore, a total of 619 small-bowel CE procedures on 533 patients were included in this study for further analysis.

Of these, 208 (39.0%) were men and 325 (61.0%) were women, with a mean age of 52.8 years (range 14–90 years). Of the small-bowel CE procedures, 262 examinations were performed with a PillCam®SB1, 148 with a PillCam®SB2 and the remaining 209 with a MiroCam®. The indications for the SBCE are presented in **Table 1**. More than half the examinations were performed for overt and/or occult gastrointestinal bleeding.

In 591 procedures (95.5%), pre-procedure bowel preparation was used. A total of 273 procedures (44.1%) were performed without the use of prokinetics. Of the remainder, 267 (43.1%) were done with the administration of domperidone (mean dose 5.6 mg) and 79 (12.8%) with metoclopramide (mean dose 5.3 mg).

The mean small-bowel cleansing score for the first 30 minutes was 2.14. Out of the 619 small-bowel CE, 540 CE (87.2%) were realized at the caecum by the end of the recording. The positive diagnostic yield for all indications was 34.6%.

Indications for small-bowel CE		CE procedures,	n (%)
Obscure GI bleeding		138 (22.3)	
Iron deficiency anaemia		206 (33.3)	
Clinical suspicion of CD		101 (16.3)	
Reassessment of known CD		30 (4.8)	
Polyposis syndrome		11 (1.8)	
Coeliac disease		12 (1.9)	
Others		121 (19.6)	
Type of CE model	PillCam ®SB1	PillCam® SB2	MiroCam®
Small-bowel CE (n)	262	148	209
Detection of AoV, n (%)	28 (10.7)	13 (8.8)	18 (8.6)
Frames AoV visible (mean ±SD)	36.35 ±73.24	42.46 ±69.30	87.20 ±248.40

Table 2.1: Indications for small-bowel capsule endoscopy in our cohort and number of small-bowel examinations per capsule endoscopy.

Abbreviations: CE, capsule endoscopy; GI, gastrointestinal; CD, Crohn's disease; AoV,

Ampulla of Vater; SD, standard deviation.

2.3.2 Detection of the AoV

The AoV was detected in 59 small-bowel CE procedures (9.5%; Table 2.1). No difference was observed in the detection rate between either of the two generations of PillCam $^{\$}$ SB (P = 0.07) or the two technically different small-bowel CE systems (PillCam® vs MiroCam®, P = 0.095). Furthermore, the mean number of frames of the duodenal papilla visualized was 53.2 (range 1-1056), with no significant difference between either of the two generations of PillCam[®] (P = 0.103) or the two different small-bowel CE systems (P = 0.07). Bile spout was detected in 62.2% of small-bowel CE (385/619) and in 81.4% of the procedures (48/59) in which the AoV was seen (P = 0.003). The mean time of AoV detection after the first duodenal image capture was 3.56 minutes (range 0.05-29.60 min for the whole cohort), and there was no statistical difference between the two small-bowel CE systems (3.53 ± 5.65 min for the PillCam® vs 3.63 ± 5.40 min for the MiroCam®; P = 0.95). The detection rate of papilla was independent of the indication for small-bowel CE, the type of CE system used, DY, patients' characteristics, and use of prokinetics or gut transit parameters. Furthermore, there was no significant difference in the detection rates of the AoV among the small-bowel CE in regard to either caecal completion or small-bowel cleansing (P < 0.05; **Table 2.2**).

Interestingly, the detection rate of duodenal papilla in small-bowel CE performed after bowel preparation was lower than that in patients who received no bowel preparation for the test (small-bowel CE [43/509, 8.4%] vs small-bowel CE [6/28, 21.4%]; P = 0.033), demonstrating that patients who received bowel preparation had a more rapid movement of CE.

Finally, in the group of patients who for the purpose of clinical work-up/care (n = 17) had a repeat small-bowel CE with a different CE system from that initially employed, the AoV detection rate was identical (PillCam®: MiroCam® = 1:17). Eight patients had repeat examinations with the same type of CE, including four with a PillCam®SB1, one with a PillCam®SB2 and three with a MiroCam®. The AoV was not identified in any of the first examinations and in only one of the repeat studies with a PillCam®SB1. Interestingly, four patients underwent CE examinations with all the three small-bowel CE types, and in one patient, the AoV was visible with both types of PillCam but not with the MiroCam®.

			CD	8		Coeliac	
Indication	OGIB	IDA	Suspected	reassessment	Polyposis	disease	Others
Small-bowel CE, n (%)	138 (23.2)	206 (33.2)	101 (16.3)	30 (4.6)	11 (1.6)	12 (1.7)	121 (19.4)
AoV visible, n (%)	16 (27.2)	13 (22)	11 (18.6)	5 (8.4)	0 (0)	(0) 0	14 (23.8)
Bile spout, n (%)	76 (20.1)	136 (36.2)	66 (17.6)	15 (3.9)	4 (1.1)	8 (2.1)	71 (18.8)
GTT (min, (mean ± SD)	42.8 ± 53.4	43.3 ± 42.5	37.1 ± 32.8	41.6 ± 36.2	33.9 ± 116.5	47.9 ± 50.8	45.3 ± 41.5
SBTT (min, mean ± SD)	267.9 ± 108.7	226.8 ± 94.2	229.3 ± 92.2	319.3 ± 116.7	329.4 ± 140.13	212.5 ± 104.2	312.5 ± 105
MiroCam®, n (%)	47 (22.5)	80 (38.2)	29 (13.9)	10 (4.8)	3 (1.4)	5 (2.4)	35 (16.8)
PillCam®SB1, n (%)	64 (24.4)	84 (32.1)	45 (17.3)	9 (3.4)	5 (1.9)	2 (0.7)	53 (20.2)
PillCam®SB2, n (%)	27 (18.2)	42 (28.4)	27 (18.2)	11 (7.4)	3 (2.1)	5 (3.4)	33 (22.3)
(+) DY, n (%)	54 (25.3)	62 (28.9)	41 (19.2)	21 (9.8)	7 (3.3)	3 (1.4)	26 (12.1)
(-) DY, n (%)	84 (20.7)	144 (35.5)	60 (14.9)	9 (2.3)	4 (0.9)	9 (2.2)	95 (23.5)
No prokinetic, n (%)	72 (26.2)	85 (30.9)	46 (16.7)	10 (3.6)	4 (1.4)	2 (0.8)	56 (20.4)
Domperidone, n (%)	49 (19.4)	98 (38.6)	38 (14.9)	17 (6.7)	4 (1.6)	8 (3.1)	40 (15.7)
Metoclopramide, n (%)	17 (19.2)	23 (25.8)	16 (17.9)	3 (3.4)	3 (3.4)	2 (2.2)	25 (28.1)
Complete to cecum, n (%)	119 (22.5)	186 (35.1)	93 (17.6)	18 (3.5)	10 (1.9)	11 (2)	92 (17.4)
Mean cleansing score	2.14	2.13	3	1.73	2	2.6	2

Table 2.2: Details on number and characteristics or small-bowel capsule endoscopy per indication group in our cohort.

Abbreviations: CE, capsule endoscopy; AoV, ampulla of Vater; GTT, gastric transit time; SBTT small-bowel transit time; SD, standard deviation; OGIB, obscure gastrointestinal bleeding; IDA, iron-deficiency anaemia; CD, Crohn's disease; DY, diagnostic dield.

2.4 Discussion

In the current study, the biggest single-centre study on the detection rate of the AoV to date, we included small-bowel CE examinations with different CE systems and confirmed results from the existing literature. Firstly, the AoV detection in unselected patients is a difficult task in CE; and secondly, visualization of the AoV is not related to the CE system, the indications, DY, caecal completion, administration of prokinetics or patient characteristics such as age and gender. Interestingly, the DY in our study, which included more than 300 small-bowel CE procedures performed for overt/occult gastrointestinal bleeding, was lower than that of a previous report (Clarke et al. 2008). This probably represents not only accumulated experience in CE reporting, hence avoidance of over-interpretation of clinically insignificant findings, but also a more widespread use of CE with easier access to the service and implementation of CE sooner in the diagnostic work-up.

Bile spout, as described earlier (Kong et al. 2006; Crook et al. 2009), is a reliable marker and the main factor that helps in the identification of the AoV, although bile spurting is an accidental phenomenon in endoscopy. Essentially, the spurting of bile physiologically occurs when the duodenal wall, together with the smooth muscle of the sphincter of Oddi, is relaxing. Therefore, bile spout should be seen as a surrogate marker of reduced mucosal folding, slower capsule propulsion and, hence, greater detection ability. However, it is likely that patients with slower capsule propulsion who have not taken a purgative preparation may explain the higher AoV detection in this group, compared with those who had been given laxatives for small-bowel cleansing.

Although two different small-bowel CE systems were used, their performances, as reflected by the detection rate of the AoV, were similar. Despite the similar size and weight, the two systems have a different transmission technology, image capture rate and pixel resolution. At a working distance of 2.2 mm from the tip of the translucent CE dome, PillCam®SB1 and SB2 and MiroCam® offer a field of view of 140°, 165° and 150° (recently replaced with version 2 of 175°), respectively. Their mucosal coverage area at 4.5 mm working distance is 500 mm², 1100 mm² and 202 mm², respectively (Metzger et al. 2009).

Several authors recommend the AoV detection rate as a quality assurance measurement for CE. Kong et al. (2006) performed a retrospective study on the detection rate of the AoV in 110 consecutive small-bowel CE patients. An inclusion criterion was a normal – in shape and position – duodenal papilla, as confirmed by conventional oesophagogastroduodenoscopy (OGD); those with an abnormally positioned papilla, or whose papilla was not readily identified by an OGD, were excluded. Therefore, it is not surprising that although they used a high video sequence reviewing speed (15 fps) and only the first generation M2A® Given®Imaging Ltd model, they detected the AoV in 43.6% of the patients (48/110). As visualization of the AoV by conventional front-viewing endoscopes is not always an easy task, it is likely that this study suffered from significant selection bias, as only the more prominent and, hence, easy to detect AoV were included for CE.

Clarke et al. (2008) repeated the study with a similar number (n = 125) of consecutive small-bowel CE patients (again with M2A®; Given®Imaging Ltd) and a more realistic setting. Two reviewers, blinded to each other, used the lowest possible automated viewing speed (5 fps) and found that the AoV was detected in 10.4% of the patients (13/125). Wijeratne and Condon have demonstrated that the AoV is identified only in 6% of small-bowel CE examinations (9/138) (Wijeratne and Condon 2006). Lee et al. reviewed 30 small-bowel CEs performed with a PillCam® SB and the same number of examinations with a PillCam®SB2 and concluded that the AoV detection rate was 46.6% (28/60), equivalent for both PillCam® types (Table 3) (Lee et al. 2010). However, other investigators presented with less favourable results (Iaquinto et al. 2008; Selby and Prakoso 2011). One would think that results should improve with advanced CE technical characteristics, but the experience from studies using double-headed CE with improved optics and frame acquisition rate are only partially concordant (Koulaouzidis, Douglas and Plevris 2011; Selby and Prakoso 2011; Karagiannis et al. 2010). Furthermore, although different generations of small-bowel PillCam® models and types have been scrutinized with regard to the AoV detection rate, other CE systems have not been put under the test (Metzger et al. 2009; Lee et al. 2010; Selby and Prakoso 2011; Park et al. 2012).

The limitations of this study are its retrospective nature and the use of a single CE reviewer, although the small-bowel CE evaluation was performed using a strict protocol and blinded review to any archived thumbnail images with a second opinion available on demand. Furthermore, a large number of studies were not available for review due to either corrupt compact discs or loss of sequences during the transfer from one large-capacity storage device to another. Of note, the inclusion of repeat CE examinations can be seen as another potential source of bias. However, this group was included because of its unique nature (same anatomy), which could potentially highlight CE examination-related factors. Moreover, the fact that the comparison was not done on the same patients (other than a subgroup of 17 patients) and the same day, together with the unavailability of systematic endoscopic confirmation of visibility of the papilla by a conventional side-viewing duodenoscope, might be seen by some as a further limiting factor.

Study	CE (n)	Type of CE	AoV seen n (%)	Reviewers (n)	Reviewers Reviewing (n) speed (fps)	Frames AoV visible (n) , mean \pm SD	Comments
Clarke et al. 2008	125	M2A®	13 (10.4)	2	5	n/s	
Kong et al. 2006	110	M2A®	48 (43.6)	2	15	3.5 ± 2.5	
Katsinelos et al. 2009	14	s/u	0 (0)	1	s/u	s/u	FAP patients
Nakamura et al. 2009	96	PillCam®SB1	18 (18)	2	10	s/u	
Koulaouzidis et	11	PillCam®ESO1	4 (36.4)		7	<i>3</i> -	
al. 2011	7	PillCam®ESO2	1 (14.3)	1	6	n/s	
Metzger et al.	20	PillCam®SB1	1 (5)	- /-	- /-	-	Repeat
2009		PillCam®SB2	5 (25)	n/s	n/s	11/5	exams
Wijeratne and Condon 2006†	138	s/u	(9) 6	1	s/u	n/s	
10000	30	PillCam®SB	13 (43.3)	-1-	-1-	e) ==	
Lee et al. 2010Ţ	30	PillCam®SB2	15 (50.0)	n/s	n/s	n/s	
	20	PillCam®SB1	0 (0)			n/a	
Selby and	20	PillCam®SB2	9 (18)	c	- 1-	n/s	
Prakoso 2011	8	PillCam®ESO1	0 (0)	7	n/s	n/a	
	12	PillCam®ESO2	1 (8)			n/s	
laquinto et al. 2008	23	PillCam®SB	0 (0)	2	s/u	n/a	FAP patients
Karagiannis et al. 2010	10	PillCam®Colon	(09) 9	s/u	s/u	s/u	
Park et al. 2012	30	PillCam®SB	13 (43.3)	s/u	s/u	n/s	

Table 2.3: Studies on the ampulla of Vater detection rate.

Abbreviations: CE, capsule endoscopy, AoV, ampulla of Vater, fps, frames per second; FAP, familial adenomatous polyposis

2.5 Conclusion

In conclusion, this study raises awareness regarding the limitations of CE. More specifically, it raises important issues on the usefulness of CE in the detection of periampullary lesions. In such cases, standard practice remains to use a sideviewing duodenoscope for inspection of these areas if a standard forward-viewing endoscope cannot provide satisfactory views. This study also highlights the technical limitations of CE in the identification of sub-centimetre small lesions with a non-steerable device.

CHAPTER 3

Do prokinetics influence the completion rate in smallbowel capsule endoscopy? A systematic review and meta-analysis

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3.1 Introduction

Optimal DY in small-bowel CE requires not only optimal visualization of the small-bowel mucosal surface and lumen but also complete capsule transit through the entire small-bowel, i.e. total enteroscopy (Kaffes 2009; Wu et al. 2011; Höög et al. 2012). If results are negative and/or inconclusive and complete enteroscopy is not achieved, concerns remain over missed small-bowel pathology. Recent systematic reviews showed that small-bowel CR varies between 81.3–83.5%, for retrospective and prospective studies, respectively (Liao et al. 2010; Rondonotti et al. 2010). Besides small-bowel structural integrity, hospitalization, advancing age and diabetes are considered high-risk factors for incomplete enteroscopy with small-bowel CE (Enns 2007; Triantafyllou et al. 2009; Westerhof et al. 2009). Therefore, it is expected that decreasing the GTT and SBTT will allow a capsule to successfully reach the caecum by the end of its battery life (Kaffes 2009). Hence, prokinetics, e.g. metoclopramide and erythromycin, as well as postural 'tricks', i.e. change of patient position following capsule ingestion, have been applied to improve small-bowel CE CR (Villa et al. 2006).

Erythromycin, a macrolide antibiotic with an appealing safety profile, acts on motilin receptors of the endocrine cells of the duodenum (Caddy et al. 2006) and has well-known prokinetic properties. It induces high amplitude gastric propulsive contractions. As a result, it accelerates gastric emptying for both liquids and solids including that of non-digestible particles (Niv et al. 2008). Its commonest side effect is nausea, which in the case of SBCE may limit its use (Selby 2005).

Metoclopramide, a dopamine D2 receptor agonist, has a combination action of relaxing the pyloric sphincter and improving the antro-duodenal co-ordination (Schwarzberg 2005). It has a good rapid oral absorption (Almeida et al. 2010), with a peak plasma concentration at 56 min and half-life of 5 h. Tardive dyskinesia and other extrapyramidal/dystonic reactions have been − not infrequently − reported as idiosyncratic adverse effects of its use.

Mosapride citrate is a prokinetic agent that acts as a serotonin 5-hydroxytryptamine-4 (5-HT4) agonist that is mostly available in Asia and increases gastrointestinal motility.

Tegaserod, another 5-HT4 agonist is available in Western countries (Ida et al. 2012). The latter was initially approved by the FDA in 2002, but it was subsequently removed from the market in 2007 due to FDA concerns about possible adverse cardiovascular effects

(http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm1 08879.htm). A few years earlier, cisapride – an effective gastrokinetic agent – was associated with fatal arrhythmias in susceptible individuals and was withdrawn by the FDA in 1999 (Wysowski et al. 2001).

Lubiprostone (Amitiza, Takeda Pharmaceuticals North America, Deerfield, IL, USA) activates selectively the type 2 chloride channels in the apical membrane of the GI epithelium, resulting in net fluid secretion (Hooks 3rd et al. 2009). It has been approved by the FDA for the treatment of chronic idiopathic constipation and constipation-predominant IBS. Recent studies revealed that it accelerates small-bowel transit as well as colonic transit time (Camilleri 2011).

Daikenchuto (DKT) is well known in Japan as an effective treatment for reduced GI motility, but the mechanism of action remains largely unknown. However, one of the ingredients in DKT, Sancho (Xanthoxylum piperitum) promotes acetylcholine release at the neuromuscular junction of the digestive tract. It also increases motilin release, hence gastrointestinal peristalsis (Nakaji et al. 2011).

Chewing gum, as a proxy for sham feeding, acts by a cephalic-vagal axis. It increases salivary flow leading to increased gastric emptying. It also increases the motility of the small-bowel and the colon (Schwarzberg 2005). Apostolopoulos et al. (2008) used commercially available sugarless chewing gum, containing xylitol as the sweetener.

Recent meta-analyses on the use of bowel preparation in small-bowel CE showed – in subgroup analysis – that there is no difference in the use of erythromycin (Niv 2008; Rokkas 2009; Belsey 2012). Although some evidence exists, current guidelines indicate that there is no strict recommendation on the use, type and/or mode of administration of prokinetics in small-bowel CE (Enns 2007). Moreover, no previous systematic review and/or meta-analysis have been carried out to address whether adding prokinetics prior to capsule ingestion can increase the CR of the small-bowel CE and/or the DY. This study was performed to assess the current evidence base on the use of prokinetics for CR and explore their effect on GTT and SBTT by meta-analysing all relevant studies.

3.2 Materials and methods

3.2.1 Literature search strategy

A recursive search of PubMed/Medline, Embase and Scopus databases for studies published up to the end of November 2012 was performed. The last computerized search was carried out on 30th November 2012. No language, start date or age search limits were applied. In order to capture as many articles as possible, a broad search strategy was employed, using the MeSH term 'capsule endoscopy' (with 'automatic explosion' and 'all fields' search) linked in simple search strings by 'AND' with the following text terms:

'antiemetic', 'completion', 'domperidone', 'erythromycin', 'gastric emptying', 'ingestion', 'intramuscular', 'metoclopramide', 'ondansetron', 'oral/liquid', 'preparation', 'prokinetic', 'promotility', 'retention', 'tegaserod', and 'transit'.

Furthermore, a combined recursive/manual search of all pertinent review articles and recently published editorials was performed.

3.2.2 Publications selection

After retrieving the full text of selected papers, data were extracted by the first author (AK) using a predefined form and were (at parts) verified by another author (KJD). A full manual search for potentially suitable references was also performed in the reference list of all retrieved original studies. As no language restriction was applied, publications were translated into English as required by one of the authors (DEY). In the event of uncertainty, any discrepancies were resolved by discussion with the senior co-author and consensus.

3.2.3 Selection criteria

Inclusion and exclusion criteria were drafted before commencing the literature search. Therefore, studies eligible for inclusion in this meta-analysis were those meeting all of the following criteria:

- published as full articles, reporting (prospective or retrospective) comparative data;
- o used prokinetics in (at least) one of the reported patient subgroups;
- o contained information on the type of the small-bowel CE system/model used;
- o specified the type, mode of administration and dose of prokinetics used, and;
- contained data on one or more of the following SBCE parameters: CR, DY, GTT, and SBTT.

DY was defined as the total number of positive (diagnostic and suspicious) findings. GTT was defined as the time interval between the first gastric image and the first duodenal image. SBTT was defined as the time interval between the first duodenal images and the first caecal image.

Studies not meeting the aforementioned inclusion criteria – those examining the effect of postural 'tricks'; and/or duplicate publications – were excluded. We also excluded cohort studies with no control arm, review articles, and/or case reports or case series. It was decided that when two papers reported the same study, the most recent and/or the more informative publication would be selected. A flow chart describing the process of data/study identification and selection is shown in **Figure 3.1**.

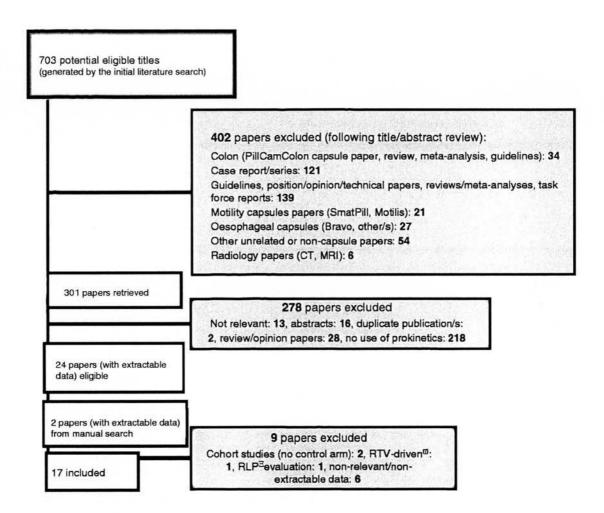


Figure 3.1: Flow diagram of the identification of studies and of the selection process of this meta-analysis.

Abbreviations: ^ωRTV-driven, real-time viewer driven; ^ΞRLP, right lateral position; CT, computed tomography; MRI, magnetic resonance imaging.

3.2.4 Statistical analysis

Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated and the outcomes of individual studies were compared by using the fixed-effects model - Mantel-Haenszel method - unless significant statistical heterogeneity was detected where the random-effects model was applied - theDerSimonian-Laird method (Mantel and Haenszel 1959; DerSimonian and Laird 1986). Heterogeneity was assessed using the inconsistency index (l^2) and the chi-square (χ^2) test for heterogeneity; evidence of heterogeneity was considered to be present if P = < 0.10(Higgins et al. 2003). In case of significant heterogeneity in the study design, results were pooled using the DerSimonian-Laird random-effects model. This is preferable to a fixed-effects model (Mantel-Haenszel method), as it takes into account the differences between studies and treatments when estimating 95% CI and P values. Apart from adjusting for heterogeneity by applying the random-effects model, reasons for heterogeneity were explored. This leads to the stratification of the studies into more homogeneous groups, and therefore more reliable estimates (Moayyedi 2004). The candidate factors for stratification were: the randomization quality (Jadad score); the study design (prospective vs retrospective); the use of bowel purging (bowel purging and prokinetic vs prokinetic alone); and the most readily available, and therefore more frequently used, prokinetics, metoclopramide and erythromycin versus the rest (Jadad et al. 1996).

A sensitivity analysis was performed in order to evaluate the consistency of our results. Firstly, to evaluate any possible excessive influence of a single study, we examined whether the exclusion of this study substantially altered the magnitude or heterogeneity of the summary estimate. This was achieved by repeating the meta-analysis with exclusion of each individual study one at a time, and to assess the overall effect of the exclusion on the pooled ORs (Sutton et al. 2000). Forest plots were constructed for the visual display of ORs across selected studies. Statistical analysis was performed by using the Metan package of Stata version 12.1 (StataCorp, College Station, TX, USA) (Harris et al. 2010).

3.2.5 Publication bias assessment

The likelihood of publication bias was assessed by constructing funnel plots, which were obtained by plotting the log ORs versus SE (log [OR]) of individual studies (Sterne and Egger 2001).

3.2.6 Methodological quality assessment

The methodological quality of randomization of the studies was assessed and graded according to criteria described in the Jadad scale which has already been extensively described elsewhere (Jadad et al. 1996). Therefore, the following items were independently scored for each study:

- Was the study described as randomized (this includes words such as randomly, random, and randomization)? (0/1);
- Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)? (0/1);
- Was the study described as double-blind? (0/1);
- Was the method of double-blinding described and appropriate (identical placebo, active placebo, dummy, etc.)? (0/1), and;
- Was there a description of withdrawals and dropouts? (0/1).

Furthermore, one (1) point was deducted for each of the following two:

- if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.); and
- if the study was described as double-blind but the method of blinding was inappropriate (e.g. comparison of tablet vs injection with no double dummy). See Figure 3.2.

Study, year	Country	Study type	Centre	Jadad	Exclusion criteria	RTV used (n)	Purgative used Type/dose	Simethicone
Selby, 2005	Australia	Prospective	Single centre	0	Unclear	No	No (26)/Yes (113+11) NaPico (10mg)/PEG (11)	Yes
Leung et al, 2005*	China	Retrospective	Single centre	0	Yes	No	No	Yes
Caddy et al. 2006	Australia	Prospective	Single centre	2	Yes	No	Yes NaPico (250ml)/PEG (500ml)	No
Apostolopoulos et al. 2008	Greece	Prospective	Single centre	3	Yes	No	Yes NaPhospho (45ml)	No
Wei et al. 2008◆	China	Prospective	Single centre	8	Yes	No	No	No
Niv et al. 2008*	Israel	Prospective	Two-centre	0	Unclear	No	No	No
Postgate et al. 2009*	UK	Prospective	Single centre	3	Yes	No	Yes/No Citramag [®] (2l)+Senna(2 pk)	No
Hooks 3rd et al. 2009*	USA	Prospective	Single centre	22	Yes	No	No	No
Almeida et al. 2010*	Portugal	Prospective	Single centre	3	Yes	No	No	Yes
Song et al. 2010*	China	Retrospective	Single centre	-1	Yes	No	No	No
Iwamoto et al. 2010*	Japan	Prospective	Single centre	0	Yes	No	No	No
Nakaji et al. 2011	Japan	Prospective	Single centre	0	Yes	Yes (16)	Yes Citramag [®] (900ml) proingestion	Yes
Zhang et al. 2011	China	Prospective	Single centre	3	Yes	Yes (177)	PEG(41)	No
Hosono et al, 2011	Japan	Prospective	Single centre	2	Yes	Yes (40)	PEG (500ml post-RTV)	Yes
Shiotani et al. 2010	Japan	Prospective	Single centre	-1	Yes	Yes (100)	No	No
Xiong et al. 2012	China	Retrospective	Single centre	-1	Yes	Yes (109)	NaPhospho (45ml)	No
Ida et al. 2012	Japan	Prospective	Single centre	-1	Yes	No	PEG (1 or 21)	No

Table 3.1: Main characteristics of the included studies in the prokinetics meta-analysis.

Abbreviations: RTV, real-time viewer; NaPico, sodium picosulphate; PEG, polyethylene glycol; pk, packages; RTV, real-time viewer; NaPhospho, sobium phosphate.

Authore year	Prokinetic used	Dose/mode/time	CE used	# Controls (M/F)	Outcome data
Selby, 2005	Metoclopramide	10mg/PO/15'pro-ingestion	PillCam®SB/ M2A®	83 (45/38)	CR, DY, GTT, SBTT
Leung et al. 2005*	Erythromycin	250mg/PO/pro-ingestion	M2A®	14 (8/6)	CR, n/a, GTT, SBTT
Caddy et al. 2006	Erythromycin	250mg/PO/60'pro-ingestion	PillCam®SB	23 (8/15)	CR, n/a, GTT, SBTT
Apostolopoulos et	Chewing gum	1pc/PO/chewed for 30' alt. h.	PillCam*SB	46 (24/22)	CR, n/a, GTT, SBTT
Wei et al. 2008*	Mosapride	10mg/PO/60'pro-ingestion	M2A®	30 (19/11)	CR, DY, GTT, SBTT
Niv et al. 2008*	Erythromycin	200mg/PO/60' pro-ingestion	PillCam®SB	50 (32/18) 50 (36/14)	CR, n/a, GTT, SBTT
Postgate et al.	Metoclopramide	10mg/PO/10' pro-ingestion	PillCam®SB	37 (14/23) + 39 (17/22) 37 (10/27) + 37 (19/18)	CR, DY, GTT, SBTT
Hooks 3rd et al.	Lubirpostone	24μg/PO/pro-ingestion	PillCam®SB1	20 (5/15)(placebo) – healthy 20 (8/12) – healthy subjects	CR, n/a, GTT, SBTT
Almeida et al.	Metoclopramide	10mg/PO/15'pro-ingestion	PillCam@SB	48 (25/23)	CR, DY, GTT, SBTT
Song et al. 2010*	Metoclopramide	10mg/IM/15'pro-ingestion	M2A®	74 (v/a) 26 (u/a)	CR, n/a (total), GTT, SRTT
Iwamoto et al.	Metoclopramide	10mg/IV/pro-ingestion	PillCam [®] SB	57 (36/21)	CR, DY, GTT, SBTT
MIN	Daikenchuto	7.5gr x 2/PO/pro-ingestion	PillCam*SB/SB2	99 (59/40)	CR, n/a, n/a, n/a
Nakajı et al. 2011	Metoclopramide (12 post-RTV)	10mg/IV/60 post-ingestion			
Zhang et al. 2011	Metoclopramide	10mg/IM/15'pro-ingestion	OMOM®	88 (47/41)	CR, n/a, GTT, SBTT
Hosono et al. 2011	Metoclopramide (7 post-RTV)	10mg/IM/60'post-ingestion	PillCam®SB1/SB2	40 (23/17)	CR, DY, GTT, SBTT
0000	Metoclopramide (26 post-RTV)	10mg/IV/90'post-ingestion (12)	PillCam*SB	100 (54/46)	CR, DY, GTT, SBTT
Shiotani et al. 2010		10mg/IV/7-8hpost-ingestion (14)			
Xiong et al. 2012	Metoclopramide (post-RTV)	10mg/IM/60'post-ingestion	OMOM®	69 (38/31)	CR, n/a, n/a, n/a
Ida et al. 2012	Mosapride	10mg/PO/30-60' pro-ingestion	PillCam®SB1/SB2 FndoCansulo®	106 (n/a) 126 (n/a)	CR, w/a, w/a, w/a

Table 3.2: Studies characteristics as per prokinetic used (dose, mode of administration), capsule device used and patients included.

Abbreviations: PO, per os; alt. h., alternate hour; IV, intravascular; IM, intramuscular; pc, piece; M, male; F, female; CR, completion rate; DY, diagnostic yield; SBTT, small-bowel transit time; GTT, gastric transit time; n/a, non-applicable or non-available.

Furthermore, it is known that evidence based on retrospective studies begins as low quality, with a potential to decrease further because of study limitations, inconsistency of results (heterogeneity), impression and other considerations, including publications bias (Leontiadis et al. 2013). Therefore, the overall quality, for each study, was a combination classified as high, moderate or low, according to a combination of Jadad scores and types of study design.

3.2.7 Data extraction

For each included study, the following variables were extracted and entered into an Excel data sheet: author, year of publication, number of participants, type of SBCE system, use of prokinetic/promotility agent, dose, mode and time of administration (in regard to capsule ingestion), GTT, SBTT, CR or rate of total enteroscopy and DY. Furthermore, the retention/obstruction rate (RR), where reported, was extracted. Relevant studies were analysed according to the type of prokinetic used with the following primary and secondary end-points: (a) CR, (b) GGT, (c) SBTT, and (d) DY.

3.3 Results

3.3.1 Descriptive assessment and study characteristics

A total of 703 titles were initially identified with the aforementioned search strategy. Of those, 402 were excluded after preliminary review of the titles and/or abstracts, leaving 301 articles for further/detailed evaluation. Of those, 278 were excluded following thorough review of the abstracts. Moreover, a further two articles were identified from reference review. Therefore, the full text of 26 articles (with potentially extractable data) was evaluated further. Consequently, 17 articles met the inclusion criteria and entered this meta-analysis (Selby 2005; Leung et al. 2005; Caddy et al. 2006; Wei et al. 2007; Apostolopoulos et al. 2008; Niv et al. 2008; Postgate et al. 2009; Hooks 3rd et al. 2009; Almeida et al. 2010; Song et al. 2010; Iwamoto et al. 2010; Nakaji et al. 2011; Zhang et al. 2011; Hosono et al. 2011; Shiotani et al. 2011; Xiong et al. 2012; Ida et al. 2012). The main characteristics of the studies eligible for review, including their Jadad scores, are shown in **Table 3.1** and **Table 3.2**.



Figure 3.2: Jadad scores of the studies included in this meta-analysis

A total of 1899 individuals (1859 patients and 40 healthy participants; 1028 subjects ingested the capsule with no prokinetic [n = 1008] or placebo [n = 20] and 876 with a prokinetic; 982 males/917 females; mean age: 54.73 ±21.1 years) were included in these studies. There were fifteen studies which were retrospective (n = 1690 subjects) (Selby 2005; Leung et al. 2005; Caddy et al. 2006; Wei et al. 2207; Apostolopoulos et al. 2008; Niv et al. 2008; Postgate et al. 2009; Hooks 3rd et al. 2009; Almeida et al. 2010; Iwamoto et al. 2010; Nakaji et al. 2011; Zhang et al. 2011; Hosono et al. 2011; Shiotani et al. 2011; Ida et al. 2012) and published in English and two (n=209)patients) (Song et al. 2010; Xiong et al. 2012) in the Chinese language. All, apart from one study (Niv et al. 2008), were single-centre papers; ten studies (58.8%) were conducted in the Far East, i.e. five studies in China (Wei et al. 2007; Leung et al. 2005; Song et al. 2010; Zhang et al. 2011; Xiong et al. 2012) and five studies in Japan (Iwamoto et al. 2010; Nakaji et al. 2011; Hosono et al. 2011; Shiotani et al. 2011; Ida et al. 2012), two in Australia (Selby 2005; Caddy et al. 2006) and one in each of the following countries: Greece, Israel, Portugal, UK and USA (Apostolopoulos et al. 2008; Niv et al. 2008; Almeida et al. 2010; Postgate et al. 2009; Hooks 3rd et al. 2009) Fourteen of them (Selby 2005; Caddy et al. 2006; Wei et al. 2007; Apostolopoulos et al. 2008; Niv et al. 2008; Postgate et al. 2009; Hooks 3rd et al. 2009; Almeida et al. 2010; Iwamoto et al. 2010; Nakaji et al. 2011; Zhang et al. 2011; Hosono et al. 2011; Shiotani et al. 2011; Ida et al. 2012) were prospective and three (Leung et al. 2005; Song et al. 2010; Xiong et al. 2012) were retrospective studies. Capsule endoscopy was performed with M2A® and/or PillCam®SB capsule-endoscope models (Given®Imaging Ltd, Yokneam, Israel) in all but two Chinese studies (Zhang et al. 2011; Xiong et al. 2012), including a total of 286 patients, where the OMOM® capsule endoscope (Jinshan Science and Technology Company, Chongqing, China) was used. Furthermore, in one study both EndoCapsule® (Olympus Medical Systems, Tokyo, Japan) and PillCam®SB were utilized (Ida et al. 2012). Nine studies (Selby 2005; Postgate et al. 2009; Almeida et al. 2010; Song et al. 2010; Iwamoto et al. 2010; Zhang et al. 2011; Hosono et al. 2011; Shiotani et al. 2011; Xiong et al. 2012) evaluated the use of metoclopramide; three studies (Leung et al. 2005; Caddy et al. 2006; Apostolopoulos et al. 2008) evaluated the use of erythromycin; two studies (Wei et al. 2007; Ida et al. 2012) that of mosapride; and from one the effect of chewing gum (Apostolopoulos et al. 2008), lubiprostone(Hooks 3rd et al. 2009), and the combined effect of deikenchuto+metoclopramide (Nakaji et al. 2011), the latter post real-time viewer check.

All subjects were prepared with overnight fasting and in nine studies purgatives were used either prior to and/or during capsule endoscopy (Selby 2005; Caddy et al. 2006; Wei et al. 2007; Postgate et al. 2009; Nakaji et al. 2011; Zhang et al. 2011; Hosono et al. 2011; Xiong et al. 2012; Ida et al. 2012). Furthermore, in five studies simeticone was administered for capsule ingestion (Selby 2005; Leung et al. 2005; Almeida et al. 2010; Nakaji et al. 2011; Hosono et al. 2011). Lastly, a real-time viewer (RTV) was utilized in the protocol of five studies (Nakaji et al. 2011; Zhang et al. 2011; Hosono et al. 2011; Shiotani et al. 2011; Xiong et al. 2012), although external RTV should be considered instrumental only in the protocol of two metoclopramide studies (Shiotani et al. 2011; Xiong et al. 2012).

Lastly, eight studies (four on metoclopramide, two on erythromycin, one on lubiprostone and one on mosapride) (Leung et al. 2005; Wei et al. 2007; Niv et al. 2008; Postgate et al. 2009; Hooks 3rd et al. 2009; Almeida et al. 2010; Song et al. 2010) examined the usefulness of the aforementioned prokinetics, without potential external interference/bias effect by laxatives, RTV and/or complex study protocols, and are considered separately in the sensitivity analysis (**subgroup 1**). Overall, in the meta-analysed studies, there were 17 sets of primary endpoint data (CR) and 24 sets of secondary endpoint data (GGT: 8, SBTT: 9, and DY: 7).

3.3.2 Primary endpoint

3.3.2.1 Small-bowel CE CR

Small-bowel CE CR was defined as the capsule reaching the caecum. All included studies presenting such data (17 sets), examining the small-bowel CE CR in 1028

subjects who ingested the capsule without a prokinetic as opposed to 876 individuals who received a prokinetic. There was evidence of heterogeneity between study results ($I^2=37.9\%$, P=0.058; Figure 3.3). Because of heterogeneity, the DerSimonian-Laird random-effects model was used for the pooling of results; this model is recommended - as the method of choice - by the International Cochrane Collaboration (Leontiadis et al. 2013; Hayden et al. 2006) in order to avoid unrealistically low 95% CIs that may arise from a fixed-effects model analysis (Leontiadis et al. 2013). The results indicated that the odds of having a complete small-bowel CE were superior for patients who ingested the capsule with a prokinetic than for those who did not receive a prokinetic agent; OR (95% CI)=1.96 (1.38-2.78), Figure 3.3. Furthermore, studies of the same prokinetic were grouped together; for the erythromycin studies (Leung et al. 2005; Wei et al. 2007; Niv et al. 2008), no heterogeneity - in study design or results - was detected (I2=37.6%, P=0.201; Figure 3.3) and the pooled OR (95% CI) was 1.36 (0.61-3.03). In the metoclopramide group (Selby 2005; Postgate et al. 2009; Almeida et al. 2010; Song et al. 2010; Iwamoto et al. 2010; Nikaji et al. 2011; Zhang et al. 2011; Hosono et al. 2011; Shiotani et al. 2011; Xiong et al. 2012), evidence of heterogeneity between the studies was weak but present (I2=38.3%, P=0.103; Figure 3.3); the pooled random-effect estimate of the OR (95% CI) for small-bowel CE CR was 2.08 (1.35-3.21). Lastly, for the remaining four studies, some evidence of heterogeneity was detected (I²=58.7%, P=0.064; Figure 3.3); the random-effect estimate of the OR (95% CI) was 1.89 (0.75– 4.82).

Studies that used prokinetics with no bowel purge and a straightforward study protocol (subgroup 1) (Leung et al. 2005; Wei et al. 2007; Niv et al. 2008; Postgate et al. 2009; Hooks 3rd et al. 2009; Almeida et al. 2010; Song et al. 2010) were chosen to investigate further the reasons for heterogeneity. In order to exclude any possible influence of a single study, we repeated the meta-analysis with exclusion of each individual study one at a time. This did not alter the pooled results. Moreover, we performed sensitivity analyses by stratifying studies by factors which could potentially influence the pooled results, i.e. study design (prospective vs retrospective), use of bowel purge (bowel purge+prokinetic vs prokinetic alone), the most frequently and readily available prokinetics used (metoclopramide vs

erythromycin vs rest), and Jadad scores. The results of these subgroup analyses are shown in **Figure 3.4**. The number of included studies was not sufficient to draw a conclusion regarding other stratification factors.

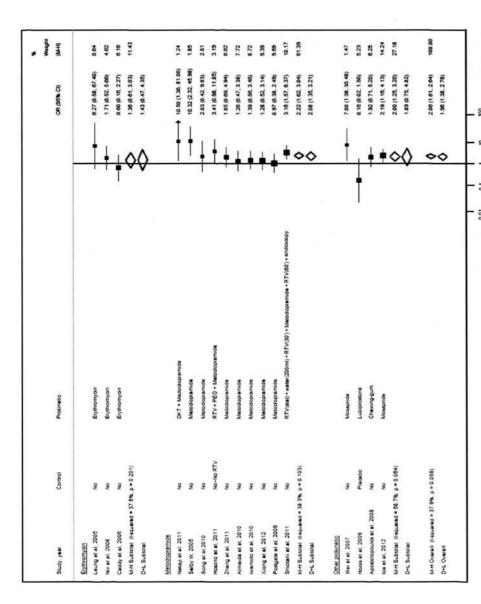
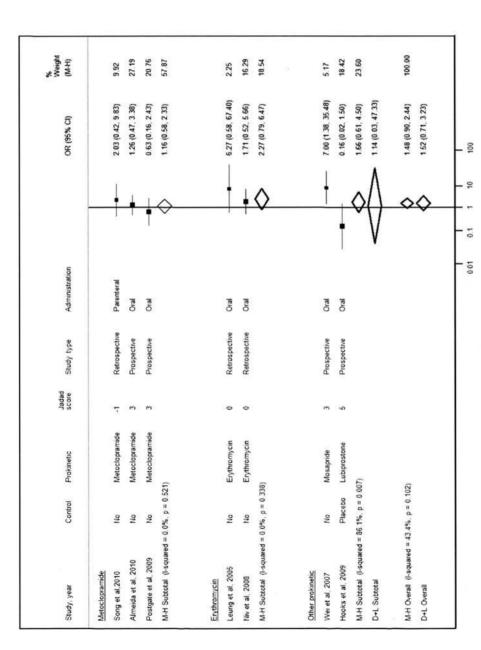


Figure 3.3: Forest plot of CR, showing individual and pooled OR with 95% CI of studies comparing capsule ingestion with prokinetics vs no prokinetics. Overall, prokinetics improve the CR. This is more obvious with those studies that used metoclopramide for capsule ingestion.

Abbreviations: CR, completion rate; OR, odds ratio; CI, confidence interval; DKT, daikenchuto; RTV, real-time viewer; PEG, polyethylene glycol; stat, immediately post-ingestion.



In this subgroup of studies, there is no evidence of improved CR when the capsule was ingested with metoclopramide, erythromycin, mosapride or Figure 3.4: Forest plot of CR, showing individual and pooled OR with 95% CI of subgroup 1 studies, i.e. studies with more homogenous protocols in which purging and/or real-time monitoring were not used, comparing capsule ingestion with prokinetics vs no prokinetics. lubiprostone. Abbreviations: CR, completion rate; OR, odds ratio; CI, confidence intervals.

3.3.3 Secondary endpoints

3.3.3.1 Diagnostic yield (DY)

Seven studies (Selby 2005; Wei et al. 2007; Postgate et al. 2009; Almeida et al. 2010; Iwamoto et al. 2010; Hosono et al. 2011; Shiotani et al. 2011) examined small-bowel CE DY in 401 patients who ingested the capsule with prokinetics (371 metoclopramide/30 mosapride) as opposed to 434 patients who did not use prokinetics for capsule ingestion. Six of the seven meta-analysed studies used metoclopramide as the prokinetic. There was no evidence of heterogeneity between these studies (I2=0, P=0.914), therefore, the fixed-effects model was used for synthesis and presentation of pooled results. There was a weak trend that the smallbowel CE DY ratio (pooled DY in the group who receive prokinetic/total number of cases in the prokinetic group)/(pooled DY in the control group/total number of control cases) was superior for the patients who received prokinetics for capsule ingestion as opposed to controls, pooled RR (95% CI)=1.10 (0.96-1.27) (Figure 3.5). This may be due to the small number of studies and the heterogeneity due to the different prokinetic agents used and diverse study designs.

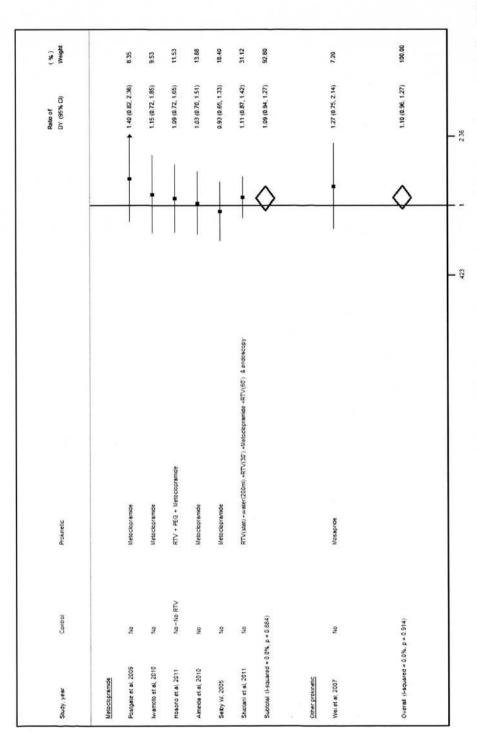


Figure 3.5: Forest plot of DY, showing individual and pooled RR with 95% CI of studies comparingcapsule ingestion with prokinetics vs no prokinetics (data from studies reporting relevant data).

Abbreviations: DY, diagnostic yield; RR, relative ratio; CI, confidence interval; RTV, real-time viewer; PEG, polyethylene glycol; stat, immediately post-

ingestion.

3.3.3.2 Gastric transit time (GTT)

Eight studies (Selby 2005; Lueng et al. 2005; Apostolopoulos et al. 2008; Niv et al. 2008; Hooks 3rd et al. 2009; Iwamoto et al. 2010; Hosono et al. 2011; Shiotani et al. 2011) measured the average small-bowel CE GTT (min) in 391 subjects who ingested capsule with prokinetics (250 metoclopramide/74 erythromycin/20 lubiprostone/47 chewing gum) as opposed to 410 subjects (20 placebo) who used no prokinetic for capsule ingestion. There was evidence of heterogeneity between studies (I²=64.5%, P=0.006). More specifically, heterogeneity was detected in the erythromycin group (Leung et al. 2005; Niv et al. 2008) (I^2 =73.8%, P=0.051) and lubiprostone/chewing gum studies (Apostolopoulos et al. 2008; Hooks 3rd et al. 2009) (I^2 =87.2%, P=0.005). However, no difference between prokinetic and control in GTT was noted. In the metoclopramide studies group, there was no evidence of heterogeneity and the use of metoclopramide seemed to affect GTT over controls; pooled difference in the means in this group (GTT of control - GTT of prokinetic group) was 16.83 (14.30–19.37) (Figure 3.6). It is noteworthy that although the latter group included the two studies that had RTV in their protocol (Hosono et al. 2011; Shiotani et al. 2011), a clear effect of metoclopramide on GTT was also evident in the studies (Selby 2005; Iwamoto et al. 2010), which did not utilize real-time monitoring.

3.3.3.3 Small-bowel transit time (SBTT)

Nine studies (Selby 2005; Leung et al. 2005; Apostolopoulos et al. 2008; Niv et al. 2008; Hooks 3rd et al. 2009; Almeida et al. 2010; Iwamoto et al. 2010; Hosono et al. 2011; Shiotani et al. 2011) measured the average small-bowel CE SBTT (min) in 438 subjects who ingested the capsule with prokinetics (297 metoclopramide/74 erythromycin/20 lubiprostone/47 chewing gum) and 458 controls (20 placebos) who did not receive prokinetics for capsule ingestion. There was no evidence of heterogeneity within the prokinetic groups. More specifically, the erythromycin studies (Leung et al. 2005; Caddy et al. 2006; Niv et al. 2008) showed I^2 =0%, P=0.342 (and lubiprostone/chewing gum I^2 =0%, P=0.8616) in the heterogeneity test. In the erythromycin group, no difference between prokinetic and control in SBTT was noted (pooled difference in the means [95% CI]: -20.41 [-54.28, 13.45]). In the metoclopramide group, there was no evidence of heterogeneity (I^2 =37.3, I^2 =0.173)

and its use had an effect on SBTT over controls; pooled difference in the means (GTT of control - GTT of prokinetic group) [95% CI])=24.30 [20.90-27.70] (**Figure 3.7**).

3.3.4 Publication bias

Evidence of publication bias was also present (Figure 3.8) as, when looking at the metoclopramide group, small studies with small effect were not found in the literature review.

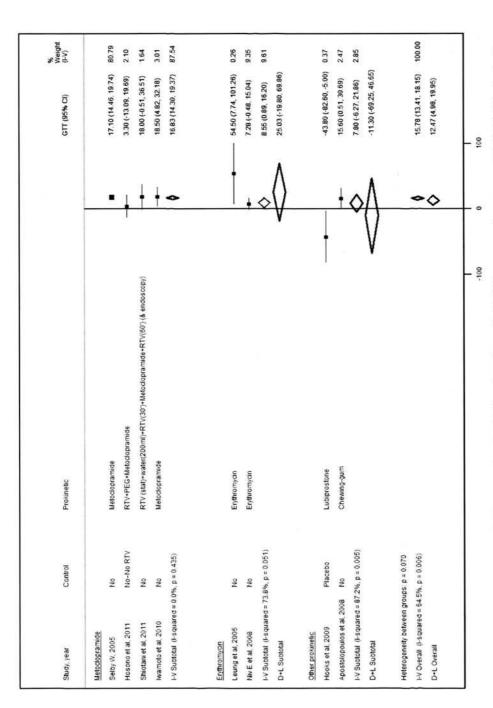
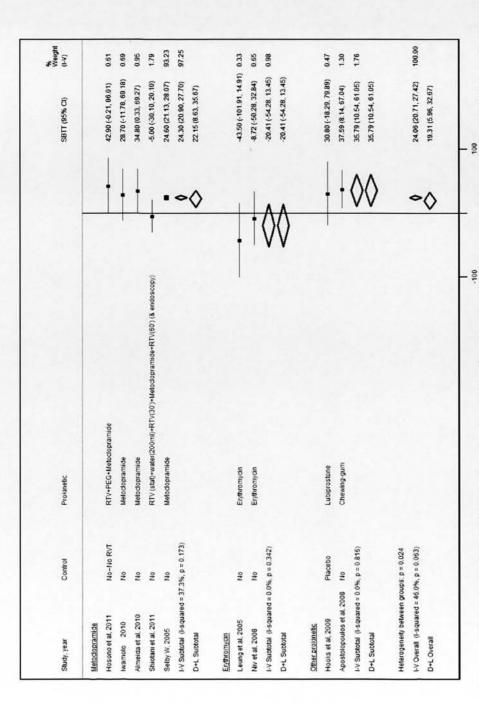


Figure 3.6: Forest plot of GTT, showing individual and pooled difference of means with 95% CI of studies comparing capsule ingestion with prokinetics vs no prokinetics (data from studies reporting relevant data).

Abbreviations: GTT, gastric transit time; CI, confidence intervals; RTV, real-time viewer; PEG, polyethylene glycol; stat, immediately postingestion.



Abbreviations: SBTT, small-bowel transit time; CI, confidence intervals; RTV, real-time viewer; PEG, polyethylene glycol; stat, immediately post-Figure 3.7: Forest plot of SBTT, showing individual and pooled difference of means with 95% CI of studies comparing capsule ingestion with prokinetics vs no prokinetics (data from studies reporting relevant data). ingestion.

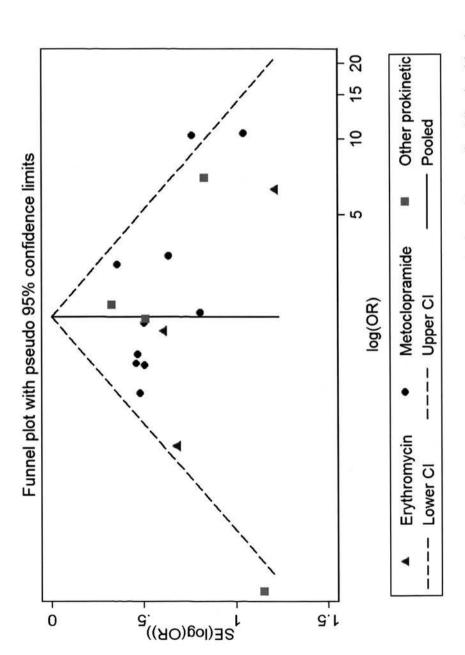


Figure 3.8: Funnel plot of studies included in this meta-analysis; evidence of publication bias is present. Abbreviations: SE, standard error; OR, odds ratio

3.3.5 Safety

No fatal complications were reported in any of the studies included in this metaanalysis. More specifically, cases of capsule retention were reported (Höög et al. 2012), but no capsule aspiration was recorded and no bowel obstruction (**Table 3.3**). More importantly, no sinister adverse effects from the use of prokinetics were reported.

Author, year	Exclusion Criteria	Capsule retention	Bowel obstruction/	Prokinetic-related side effects;
			Capsule Aspiration	(prokinetic used)
Selby, 2005	n/a	None	None	None; (Metoclopramide)
_eung et al. 2005❖	Swallowing difficulties; Previous gastric/bowel surgery; Prior use of prokinetic agents	None	None	None; (Erythromycin)
Caddy et al. 2006	Age<18 years; Diabetes Mellitus; Unwillingness to participate	None	None	None; (Erythromycin)
Apostolopoulos et al. 2008	Diabetes Mellitus; Dysthyroidism; Prior gastric/abdominal surgery; Unwillingness to participate	None	None	None; (Chewing-gum)
⁄Vei et al. 2008❖	Diabetes Mellitus; Known bowel obstruction; Prior gastric or bowel surgery Stricture/Fistula; Pregnancy; Prior narcotic drug use; Dysthyroidism;	None	None	None; (Mosapride)
Viv et al. 2008❖	n/a	None	None	None; (Erythromycin)
Postgate et al. 2009❖	n/a	None	None	None; (Metoclopramide)
Hooks 3rd et al. 2009❖	Age<19 years; Known/suspected bowel obstruction; Previous bowel perforation and/or resection; Current ileus; severe IBD; faecal impaction/diarrhoea; Current pregnancy or lactation	None	None	Diarrhoea (n= 4F), Headache/nausea (n= 1F), Abdominal cramping (n= 1M); (Lubiprostone)
Almeida et al. 2010�	Cardiac pacemaker/defibrillator; Age<18 years; Pregnancy; Swallowing difficulties; Stricture or previous gastric/bowel surgery	None	None	None; (Metoclopramide)
òong et al. 2010❖	Known/suspected bowel obstruction; Cardiac pacemaker/defibrillator; Severe/reported swallowing difficulties	None	None	None; (Metoclopramide)
wamoto et al. 2010*	Known/suspected bowel obstruction	None	None	None; (Metoclopramide)

Table 3.3: Exclusion criteria, reported capsule retention episodes, bowel obstruction/capsule aspiration cases and adverse effects of the prokinetics used in the studies of this meta-analysis.

Cont'd Overleaf

Author, year	Exclusion Criteria	Capsule retention*	Bowel obstruction/ Capsule Aspiration	Prokinetic-related side effects (prokinetic used)
Nakaji et al. 2011	Known or suspected bowel stenosis; Cardiac pacemaker/defibrillator; Pregnancy	None	Cricopharyngeous (n= 1): Small- bowel retention (n= 1)	None; (DKT + Metoclopramide)
Zhang et al. 2011	Known/suspected bowel obstruction; Stricture/fistula or known Crohn's disease; Age<18 years; Pregnancy; Diabetes Mellitus	None	None	None; (Metoclopramide)
Hosono et al. 2011	Gastric/bowel surgery; Gastric dysmotility; Age<18 years; Pregnancy; Prior use of medications that affect GI motility	None	None	None; (Metoclopramide)
Shiotani et al. 2010	Known/suspected bowel obstruction; Stricture/fistula; Prior use of medications that affect GI motility	None	None	None; (Metoclopramide)
Gong et al. 2012	Criteria of exclusion for small-bowel CE by the Chinese Society of Digestive Endoscopy Guidelines	None	None	None; (Metoclopramide)
da et al. 2012,	Participation in other clinical trial; Total gastrectomy; Inability to swallow capsule; Recorder malfunction; Missing medical records	None	None	None; (Metoclopramide)

Table 3.3 (cont'd): Exclusion criteria, reported capsule retention episodes, bowel obstruction/capsule aspiration cases and adverse effects of the prokinetics used in the studies of this meta-analysis.

*Capsule retention: refers only to study participants and not excluded cases (especially for retrospective studies). Defined as the presence of the capsule

in the gut (confirmed by imaging) >14 days following ingestion.

*Studies of subgroup 1 (studies with homogeneous protocol, i.e. no real-time monitoring for intervention and no prior use of prokinetics).

Abbreviations: IBD, inflammatory bowel disease; Gl, gastrointestinal; CE, capsule endoscopy; M, male; F, female; DKT, Daikenchuto.

3.3.6 Discussion

There have been data to suggest that it is in fact the prolonged small-bowel passage that may be associated with increased DY (Buscaglia et al. 2008; Westerhof et al. 2012). Therefore, various techniques and interventions have been developed aiming to improve the clinical chances for total enteroscopy (Kaffes 2009). To date, there are three published meta-analyses (Niv 2008; Rokkas et al. 2009; Belsey et al. 2012) showing that purgative cleansing of the small-bowel before SBCE significantly improves the quality of mucosal visualization, in comparison to a clear fluid diet, although it does not seem to affect the small-bowel CE completion rate (Rokkas et al. 2009). In fact, data suggest that up to 20–25% of patients undergoing small-bowel CE have an incomplete examination (Liao et al. 2010; Eliakim 2013). As a direct comparison, if we were to measure colonoscopy caecal intubation rates ≤80%, this would undoubtedly be considered very low, and every effort would be made to improve it (Kaffes 2009). It is possible that hypertonic purge regimens may delay gastric emptying (Postgate et al. 2009). With all that in mind, several prokinetics (Villa et al. 2006; Enns 2007) have been assessed, yet there is still no consensus on their use in SBCE. At the ICCE Consensus Meeting in Miami (2006), it was recognized that although there were several studies involving promotility preparations and manoeuvres, this remains to date a contentious issue (Villa et al. 2006; Enns 2007). Although different in regard to weight/size (3.6g vs 6.2g/11×26mm vs 13×27.9mm, for PillCam®/EndoCapsule® and OMOM®, respectively), all these systems have comparable battery life (8h) (Fisher and Hasler 2012).

Our study demonstrates a lack of consensus in using prokinetics in SBCE as well as a variety in study designs, which included different mode (oral or parenteral) and timing of administration of prokinetics (Villa et al. 2006). We found that erythromycin studies (Leung et al. 2005; Caddy et al. 2006; Niv et al. 2008) were more homogeneous in terms of study design (no RTV used, no concurrently administered prokinetic or postural tricks), but there were only a few studies regarding numbers of participants. On the other hand, metoclopramide-based studies (Selby 2005; Postgate et al. 2009; Almeida et al. 2010; Song et al. 2010;

Iwamoto et al. 2010; Nakaji et al. 2011; Zhang et al. 2011; Hosono et al. 2011; Shiotani et al. 2011; Xiong et al. 2012) were higher in number and larger in terms of participants, yet they were more heterogeneous in design and mode/time of administration of the medication. Lastly, prokinetics used in a number of studies (Wei et al. 2007; Hooks 3rd et al. 2009; Nakaji et al. 2011; Ida et al. 2012) are not widely available (Wei et al. 2007; Nakaji et al. 2011; Ida et al. 2012) and/or associated with mild or significant side effects (Hooks 3rd 2009). Another one, Tegaserod, considered as the 'Western-world counterpart' of mosapride, has been since withdrawn due to its potential cardiovascular side effects.

Pooled results on CR show that ingesting the capsule with prokinetics leads to a higher rate of complete small-bowel examination than in controls (OR [95% CI]: 1.96 [1.38–2.78]). More specifically, metoclopramide is associated with higher CR (OR [95% CI]: 2.8 [1.35–3.20]); no such effect is seen with erythromycin (OR [95% CI]: 1.36 [0.61–3.03]). Furthermore, when a smaller group of 'clear', i.e. more homogeneous in design, studies were examined (**subgroup 1**), where bowel purging and real-time monitoring were not used (Leung et al. 2005; Wei et al. 2007; Niv et al. 2008; Postgate et al. 2009; Hooks 3rd et al. 2009; Almeida et al. 2010; Song et al. 2010), the effect of either prokinetic (metoclopramide and erythromycin) on completion rate was not significant (**Figure 3.2**); metoclopramide CR pooled OR (95% CI): 1.16 (0.58–2.33), erythromycin CR pooled OR (95% CI): 2.27 (0.79–6.47) and for the whole group pooled OR (95% CI) for CR of prokinetic versus control was 1.52 (0.71–3.23).

With regard to capsule transit parameters (GTT and SBTT), the effect of prokinetics over control was clear for both parameters. Metoclopramide administration for capsule ingestion resulted in a shorter GTT and SBTT (pooled difference in the means [95% CI]: 12.47 [4.98–19.95] and 19.31 [5.96–32.67], respectively). When the RR of DY was calculated, there was no evidence that the use of prokinetics confers any benefit in increasing the DY.

In order to avoid further bias, we have excluded abstracts and cohort studies that may have reported further useful results on the field (Westerhof et al. 2012). Furthermore, we excluded studies published as full papers, that looked mainly at the effect of positional tricks, i.e. right lateral position at capsule ingestion (Aparicio

et al. 2009; Liao et al. 2008). There were only four studies using a more rational and flexible approach by means of external or integrated real-time monitoring (nowadays an indispensable accessory in small-bowel CE practice) and only two used the combination approach of certain predefined non-invasive interventions prompted by RTV results. The latter method should be considered most applicable in selected inpatients with poor mobility, advanced age and/or diabetes. Moreover, some retrospective studies excluded the participants who developed gastric capsule retention and/or prolonged gastric stasis of the capsule. Although it is unlikely that future research will refute the results of existing evidence, it is worth noting that as technology advances and batteries are getting smaller and more potent, incomplete small-bowel CE (due to slow transit time) will probably be phased out. Furthermore, future studies should evaluate specifically the benefit of a complete small-bowel CE in patient management.

The present study had certain limitations. As with every meta-analysis, conclusions are as reliable as the underlying evidence available. The majority of the included studies were heterogeneous and of low quality with regard to randomization and design for the purpose of meta-analysis. It is noteworthy that patient populations are heterogeneous as some studies have excluded participation of individuals with diabetes mellitus (Caddy et al. 2006; Wei et al. 2007; Zhang et al. 2011), one of the main patient groups to get benefit from the use of prokinetics. Furthermore, although we studied the pooled DY in our meta-analysis, we did not examine the effect of prokinetics on image quality and mucosal visualization for two reasons: (a) prokinetics are unlikely to have any significant effect on the intraluminal content (quantity and/or consistency), and (b) there is no standardized or validated scoring system for visualization/preparation quality of small-bowel CE.

3.3.7 Conclusion

In conclusion, the results of this meta-analysis show that the use of prokinetics in small-bowel CE, and specifically that of metoclopramide with purgative and/or RTV, improves completion rate. Although CR may appear as less of a problem, due to new capsule technology with extended battery life as described in this manuscript, it is important, at this stage, to conclude on the efficacy of prokinetics. Therefore, our results complement similar, and extensive, recent work in the field, and relevant guidelines (Song et al. 2013; Mathus-Vliegen et al. 2013; Ladas et al. 2010).

CHAPTER 4

Chromoendoscopy in small-bowel capsule endoscopy: Blue mode or Fuji Intelligent Colour Enhancement?

- 4.1 Introduction
- 4.2 Materials and methods
- 4.2.1 Review and FICE settings
- 4.2.2 Blue mode filter
- 4.2.3 Statistics
- 4.3 Results
- 4.4 Discussion
- 4.5 Conclusion

4.1 Introduction

Virtual chromoendoscopy (VC) techniques are applied to enhance the micro-vascular contour and improve resolution of surface patterns and colour differences (Pohl et al. 2007). The two VC modalities in current clinical use are narrow-band imaging (NBI) (Gono et al. 2004) and computed VC with the Fuji Intelligent Colour Enhancement (FICE) system (Pohl et al. 2007). Computed VC technology, developed at Chiba University by Miyake et al. (Haneishi et al. 2000), is based on the selection of spectral transmittance with a dedicated wavelength by narrowing the bandwidth of white light to narrowed blue and green light. In contrast to NBI though, where the bandwidth of the spectral transmittance is narrowed by optical filters (Gono et al. 2004), in computed VC, imaging is based on a new spectral estimation technique that replaces the need for optical filters. In essence, the computed VC software takes a conventional endoscopic image from the video processor and arithmetically processes the reflected photons to reconstitute virtual images for a choice of different wavelengths (Haneishi et al. 2000; Pohl et al. 2007).

Over the past few years, several studies have examined the efficacy of VC in the detailed analysis of mucosal pit pattern, vascular intensity and enhancing detection and differentiation of neoplastic and non-neoplastic lesions of the upper and the lower GI tract (Haneishi et al. 2000; Pohl et al. 2008; Pohl et al. 2009; Osawa et al. 2009; Togashi et al. 2009; Parra-Blanco et al. 2009; East et al. 2008; Yoshida et al. 2010). FICE has been used both in upper and lower GI endoscopy and proved to be effective in improving diagnostic yield by enhancing contrast between background and surface abnormalities.

In the upper GI tract, the wavelength that generated the optimal difference of the spectral reflectance between the normal gastric mucosa and the early gastric cancers was 530 nm. The score of the FICE observation improved in 46% of cases (Mouri et al. 2009). In trans-nasal endoscopy, the FICE system wavelengths settings [RBG; 470 nm, 500 nm, 550 nm] enables greater colour difference between palisade vessels and provides better contrasting images of the demarcation between the Barrett's oesophagus mucosa and the gastric mucosa, and thus contributes to easier diagnosis of endoscopic Barrett's, comparing with white-light endoscopy (Osawa et al. 2009).

The classification of colorectal tumours by FICE (RGB wavelengths of 540, 460, and 460 nm) with magnification correlated well with the histopathological diagnoses, whereas the findings were similar to NBI magnification (Yoshida et al. 2010).

Currently in the published literature, there is no agreement evaluating the accuracy of FICE, especially in regard to the optimal wavelength filters (Oka et al. 2011). In one recent study, FICE-filter 4 [red, green, and blue (RGB) wavelengths of 520, 500, and 405 nm, respectively] with magnification, has been shown to improve the image quality of the colonic vascular patterns obtained with white-light endoscopy (Parra-Blanco et al. 2009). In another one, the combination of the following three FICE wavelengths (RBG): 420 nm, 490 nm, and 540 nm proved to be superior to conventional endoscopy for capillary-pattern diagnosis but not adding much to pit-pattern diagnosis, in regard to prediction of histology for small colourectal polyps (Togashi et al. 2009).

Although VC is widely applied in conventional bidirectional endoscopy and recently studied in double-balloon enteroscopy as well (Neumann et al. 2009), its role in the detection of small-bowel lesions has not yet been clearly established (Pohl et al. 2010). Furthermore, the application of NBI (a real-time imaging modality) in CE – with its current level of technology – is limited. In contrast, FICE does not require re-engineering of the capsule device as such, but only integration of the FICE software in the reading platform (Pohl et al. 2007). The integration of the FICE digital processing system in the *RAPID*® versions 6.0 and 7.0 (Given®Imaging Ltd, Yoqneam, Israel) enables an instant switchover between an unmodified image and a FICE image, at a click of a tab at the workstation.

The spectrum of wavelength used for the creation of optical images differs between flexible endoscopy and CE, thus up to three mode settings have been selected as most suitable wavelengths required for the evaluation of the CE (Pohl et al. 2010). Both the validity of FICE in small-bowel CE as well as the optimal settings for improved image recognition in various small-bowel lesions have been studied only limited to present (Pohl et al. 2010; Oka et al. 2011). Blue Filter (BF), an additional setting incorporated into the *RAPID*® software, is a colour coefficient shift of light in

the short wavelength range (490-430 nm) superimposed onto a white (red, blue, green; RGB) light image.

The aim of this retrospective study was to qualitatively evaluate the use of modified imaging with enhanced vascular and mucosal contrast (FICE and BF enhancement) by examining lesion characterization/visibility on FICE-derived images obtained during small-bowel CE and comparing them with similar images under white light (predefined settings–Quick Adjust) without any filters.

4.2 Materials and methods

We evaluated FICE and BM filter, using images captured as thumbnails during small-bowel CE examinations performed in our department between December 2008 and January 2010. These images were selected from CE video sequences of consecutive patients who underwent small-bowel CE as part of their regular diagnostic work-up. Patient demographics and clinical characteristics, as well as SBCE indications and types of lesions examined, are summarised in **Table 4.1**.

Small-bowel CE was performed with Pillcam®SB1/SB2 (Given®Imaging Ltd, Yoqneam, Israel) capsule endoscopes, using the predefined for our unit small-bowel preparation regimen and procedural protocol (Appendix 1). One of the authors (SD), with extensive experience in CE reading, selected thumbnail frames depicting pathology from a total of 200 consecutive small-bowel CE examinations, and classified them in six different lesion-groups. These groups were: <code>ulcer/aphthae</code>, <code>villous oedema</code>, <code>intraluminal blood</code>, <code>lesions of indeterminate clinical significance, <code>angioectasias/arterio-venous malformations</code>, <code>and mucosal cobblestoning. Normal- or low-quality images were excluded from further review. This author did not participate in further evaluation of the images.</code></code>

4.2.1 Review and FICE settings

Two certified gastroenterologists, both familiar with small-bowel CE (CK) with SBCE reviewing experience >50 videos and (AK) with extensive SBCE reviewing experience >700 CE video sequences, evaluated the images using the *RAPID®* version 7 software and were blinded to each other. Both authors are familiar with FICE and use it regularly in conventional endoscopy.

The images were initially examined with white light and thereafter with the FICE mode. The FICE settings used were as follows:

FICE 1 [RGB wavelength, nm (595, 540, 535)];

FICE 2 [RBG wavelength, nm (420, 520, 530)]; and

FICE 3 [RBG wavelength, nm (595, 570, 415)].

4.2.2. Blue mode filter

In addition, BF (wavelength 490-430 nm) was also applied. Patient demographic, clinical characteristics and indications for small-bowel CE were also recorded. We had previously found that a specific combination of sharpness level (grade 3) and brightness level (grade 0) enhanced all images, even before the application of any filters, and therefore we agreed to adopt those settings as our standard baseline for this study (Quick Adjust settings) (unpublished author's data).

White light (with Quick Adjust toggle button on) small-bowel CE images were compared with FICE and BF images applying the following criteria:

- (a) the visibility of blood vessels;
- (b) the contrast of the mucosal surface; and
- (c) the demarcation of lesion borders.

The side-by-side comparison between white light and FICE or BF images was qualitatively evaluated using three quality scores: Improved, Similar and Worse.

- o Improved was defined as: 'improved visualization, aiding lesion characterization, and enhanced delineation of lesion surface or borders'.
- Similar was defined as: 'no change in any of the aforementioned parameters'.
- Worse was defined as: 'poor visualization or inability to characterise a specific lesion'.

4.2.3 Statistics

The *t*-test for continuous variables and the chi-square (χ^2) test for categorical variables were used. A *P* value of <0.05 was considered statistically significant. Inter-observer agreement between two rates was calculated using Cohen's kappa (*K*) coefficient. *Kappa* < 0.4 was considered as poor agreement, whereas between 0.41–0.6 as moderate, 0.61–0.80 as substantial and 0.81–1.00 as excellent agreement.

4.3 Results

A total of 167 small-bowel images/lesions, from 52 patients (21 male/31 female, mean age 56.13 ± 19.13 years; median age: 58 years) who underwent SBCE for a variety of indications, were included in our study (Figure 4.1).

Overall, with BF, as compared with white light, image improvement was observed in 83%, no change in 12% and worse in 3%.

With FICE 1, an improvement was observed in 34%, no change in 8.9% and worse in 55.9%. With FICE 2, an improvement was observed in 8.6%, no change in 13% and worse in 77.5%. With FICE 3, an improvement was observed in 7.7%, no change in 12% and worse in 79.9%.

Inter-observer agreement was 0.786 for BM, 0.646, 0.617, 0.669 for FICE 1, FICE 2, FICE 3, respectively.

In the ulcer/aphthae images group: BF offered an image improvement in 93%, no change in 5.8% and made it worse in 3.3%.

With FICE 1, an improvement was observed in 36.6%, no change in 9% and worse in 54%. With FICE 2, an improvement was observed in 3%, no change in 13% and worse in 83%. With FICE 3, an improvement was observed in 3%, no change in 6.6% and worse in 90%.

Inter-observer agreement was 0.476, 0.487, 0.710 and 0.642 for BF, FICE 1, FICE 2 and FICE 3, respectively.

<u>In the villous oedema images group</u>: with BF, an improvement was observed in 73.5%, no change in 26.4% and worse in 0%.

With FICE 1, an improvement was observed in 14.7%, no change in 14.7% and worse in 70.6%. With FICE 2, an improvement was observed in 5.8%, no change in 14.7% and worse in 79.5%. With FICE 3, an improvement was observed in 14.7%, no change in 0% and worst in 85.3%.

Inter-observer agreement was 0.549, 0.625, 0.553 and 0.767 with BF, FICE 1, FICE 2 and FICE 3, respectively.

In intraluminal blood images group: with BF, an improvement was observed in 73.3%, no change in 20% and worse in 6.7%.

With FICE 1, an improvement was observed in 56.6%, no change in 6.6% and worse in 30%. With FICE 2, an improvement was observed in 20%, no change in 6.6% and worse in 73.4%. With FICE 3, an improvement was observed in 13.3%, no change in 6.6% and worse in 80%.

Inter-observer agreement was 0.4, 0.528, 0.675 and 0.643 with BM, FICE 1, FICE 2 and FICE 3, respectively.

<u>In lesions of indeterminate clinical significance (LICS) images group</u>: with BF, an improvement was observed in 92.3%, no change in 7.7% and worse in 0%.

With FICE 1, an improvement was seen in 50%, no change in 7.6% and worse in 42.4%.

With FICE 2 an improvement was observed in 19.2%, no change in 19.2% and worse in 61.6%.

With FICE 3, an improvement was observed in 11.5%, no change in 3.8% and worse in 84.7%.

Inter-observer agreement was 1, 0.610, 0.604 and 0.536 for BF, FICE 1, FICE 2 and FICE 3, respectively.

In the angioectasias/arterio-venous malformations (AVM) images group: with BF, an improvement was observed in all patients (100%). For FICE 1, an improvement was observed in 77.7%, no change in 8.3% and worse in 11.1%. For FICE 2, an improvement was observed in 27.7%, no change in 13.8% and worst in 50%. For FICE 3, an improvement was observed in 5.5%, no change in 38.8% and worse in 55.57%.

Inter-observer agreement was 1 in BF, 0.557 in FICE 1, 0.688 in FICE 2 and 0.583 in FICE 3.

In the mucosal cobblestoning images group: with BF, an improvement was observed in 86.36%, no change in 13.6% and worse in 0%. For FICE 1, no improvement was

observed, no change was observed in 13.6% and worse in 86.36%. For FICE 2, an improvement was observed in 9%, no change in 0% and worse in 91%. For FICE 3, worse images were observed in all patients.

Inter-observer agreement was 0.621 in BF, 0.621 in FICE 1, 0.633 in FICE 2 and 1 in FICE 3.

A summary of the results is presented in Table 4.2.

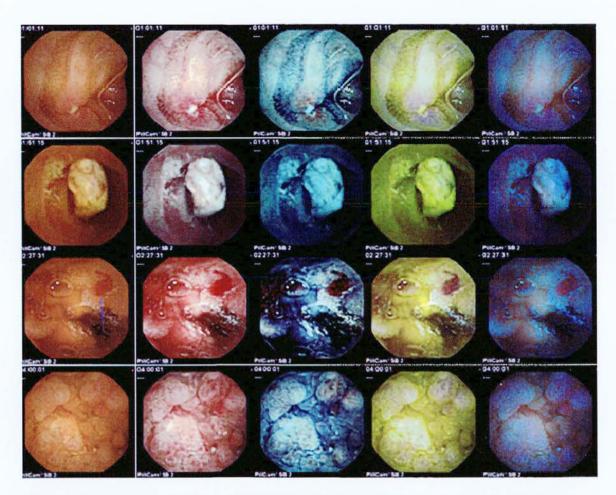


Figure 4.1: Comprehensive table of images with white light, FICE 1, FICE 2, FICE 3 and Blue filter of: ulcer (row 1), polyp (row 2), angioectasia (row 3), cobblestone mucosa (row 4).

No. of patients (M/F)	52(21/31)
Age (years) mean ±SD, median	56.1 ±19.1, 58
Indications for SBCE Nine patients presented with >1 indication	
Iron deficiency anaemia	30
Obscure GI bleeding	9
Chronic abdominal pain	6
Diarrhoea	4
Weight loss	3
Raised faecal calprotectin	5
Definitive lesions	
Ulcers/aphthae	60
Villous oedema	17
Blood in lumen	15
Angioectasia/arterio-venous malformations	18
Mucosal cobblestoning	11
PHE	6
Lesions of indeterminate clinical significance	
Lymphangiectasias	13
Polypoid lesion/structure	3
Denuded mucosal patches	2
Radiation enteritis	4
Fissure	1
Thickened fold	1
Pyloric erythema	1
Black stool	1
Stricture	1

Table 4.1: Demographics and indications for small-bowel capsule endoscopy, small-bowel CE, type of lesions examined with white light, FICE and Blue filter. Abbreviations: SBCE, small-bowel capsule endoscopy; M/F, male / female; SD, standard deviation; GI, gastro-intestinal; PHE, portal hypertensive enteropathy.

	Improved (%)	Similar (%)	Worse (%)	I/A (kappa)
FICE 1				
Ulcer/aphthae	36.6	9	54	0.487
Villous oedema	14.7	14.7	70.6	0.625
Blood in lumen	56.6	6.6	30	0.528
LICS	50	7.6	42.4	0.610
AVM	77.7	8.3	11.1	0.557
Cobblestoning	0	13.6	86.3	0.621
Overall	34	8.9	55.9	0.646
FICE 2				
Ulcer/aphthae	3	13	83	0.710
Villous oedema	5.8	14.7	79.5	0.553
Blood in lumen	20	6.6	73.4	0.675
LICS	19.2	19.2	61.6	0.610
AVM	27.7	13.8	50	0.688
Cobblestoning	9	0	91	.633
Overall	8.6	13	77.5	.617
FICE 3				
Ulcer/aphthae	3	6.6	90	0.642
Villous oedema	14.7	0	85.3	0.767
Blood in lumen	13.3	6.6	80	0.643
LICS	11.5	3.8	84.7	0.536
AVM	5.5	38.8	55.6	0.557
Cobblestoning	0	0	100	1.0
Overall	7.7	12	79.9	0.669
Blue filter				
Ulcer/aphthae	93	5.8	3.3	0.476
Villous oedema	73.5	26.5	0	0.549
Blood in lumen	73.3	20	6.7	0.4
LICS	92.3	7.7	0	1.0
AVM	100	0	0	1.0
Cobblestoning	86.3	13.6	0	0.621
Overall	83	12	3	0.786

Table 4.2: Results of the study of FICE 1, 2, 3 and Blue filter in image enhancement in small-bowel CE. (All observations had statistical significance, P <0.001.)

Abbreviations: CE, capsule endoscopy; FICE, Fujinon intelligent colour enhancement, IA, inter-observer agreement; LICS, lesions of indeterminate clinical significance; AVM, anterio-venous malformations.

4.4 Discussion

There are only limited data in the literature evaluating the use of FICE system in small-bowel capsule images (Pohl et al. 2010; Oka et al. 2011). Furthermore, there are no studies examining the validity of BM in image enhancement. Therefore, we conducted a study of the newly developed computed VC system (incorporated in RAPID® versions 6 and 7), in order to confirm whether the application of FICE led to enhanced micro-vascular contour, and improved resolution of surface patterns and colour differences, thereby leading to better characterization of a variety of small-bowel lesions/findings.

Furthermore, we sought to confirm the validity of BM in CE.

FICE was only partially effective in the ulcer/aphthae group with an image improvement in 36.6% of cases. In that respect, our results differ from those reported in the study by Oka et al. 2011, where a much higher image-enhancement rate (55.3%) was perceived. There was no significant image improvement in other lesion subgroups. FICE 2 and FICE 3 were ineffective in improving images (overall 8.6 and 7.7% improvement in FICE 2 and 3, respectively) with a significant agreement between the two readers. These results differ completely from the study by Oka et al. 2011, reporting image-quality improvement of FICE 2 settings in 87% and 25.5% of AVM and ulcerations, respectively. Thus, our opinion is that the use of FICE in the small-bowel capsule is limited.

Moreover, FICE 1 improved the definition in 34% of the images. FICE was effective in improving images in 56.6, 50 and 77.7% in blood in lumen, LICS and AVM, respectively. The inter-observer agreement was similar in these three subgroups. The results regarding AVM are comparable to the recent study by Oka et al. 2011, reporting an improvement in 87% of cases.

BM improved most of the images (overall image enhancement 83%), with a range between 73.3% and 100%, in different lesions groups. Although we report an overall substantial inter-observer agreement of 0.786, the κ coefficient varied between different groups. Ulcers, villous oedema, and blood in lumen presented a moderate

inter-observer agreement, Crohn's mucosal cobblestoning, substantial agreement, whereas angioectasias/AVMs and LICS, excellent agreement.

There are certain limitations in this study: the model of using two reviewers is open to bias. Furthermore, the side-by-side review of the images in WL, FICE and BM may have led to memory or bias and interfered with assessment. Lastly, one might consider the fact that only still images (for lesion/finding characrerization with FICE/BF) were reviewed, and not video clips for assessment of lesion detection rate and outcome, as possible limitations of this study.

4.5 Conclusion

FICE 1 was only partially effective in the ulcer/aphthae image group. There was no significant image improvement in other lesion subgroups. FICE 2 and FICE 3 was ineffective in improving images. On the contrary, BF showed promising results and its use as the main viewing mode, especially in cases of obscure GI bleeding, should be further examined in regard to feasibility and in connection with the DY.

CHAPTER 5

QuickView in small-bowel capsule endoscopy is useful in certain clinical settings, but QuickView with Blue Mode is of no additional benefit

- 5.1 Introduction
- 5.2 Materials and methods
- 5.2.1 Patients and small-bowel capsule endoscopy procedure
- 5.2.2 Classifications of lesions
- 5.2.3 Ethics consideration
- 5.2.4 Statistical analysis
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- 5.4 Discussion
- 5.5 Conclusion

5.1 Introduction

In most centres, CE remains the first-line option over more invasive tools that is, deep (or device-assisted) enteroscopy (Sidhu et al. 2012). One of the limitations of small-bowel CE is the reading time required for the interpretation of lengthy video streams. It is generally accepted that the average time for video sequence analysis is between 40 and 120 minutes, depending on the overall recording time and the reviewer's experience (Shiotani et al. 2011).

Because of high workloads, attempts have been made to reduce physician involvement through the use of assistants/extenders for the preliminary review of the video sequence or through the use of software that aids interpretation (Shiotani et al. 2011; Davison 2006). The main question with the latter approach is whether a rapid review, where a percentage of images are discarded, would miss clinically relevant pathology? The current version of *RAPID®* capsule review software incorporates the QV mode, allowing a speedy video review.

However, the QV mode is still under clinical validation and there are only four studies that have examined the utility of this informatics algorithm (Shiotani et al. 2011; Saurin et al. 2012; Hosoe et al. 2012; Westerhof et al. 2009; Shiotani et al. 2012). In chapter 4 it was shown that small-bowel CE evaluation with BM filter yields promising results and further study of this is recommended as the main viewing mode, especially in cases of OGIB (Krystallis et al. 2011). BM or a blue filter is a colour coefficient shift of light in the short wavelength range (490–430 nm) superimposed onto a white light (WL) [red, blue, green (RGB)] image. It can be applied easily through the quick adjust toggle button menu.

Therefore, there is immense interest in techniques and methods that reduce the evaluation time in capsule endoscopy without jeopardizing diagnostic accuracy. Software approaches have been developed to fulfil this requirement. One example is the QV reading mode. QV creates a preview of the entire video sequence, thus allowing a fast-forward-type review of interesting sites. It highlights sample images, using different sampling rates, within each region of the video by analysing colours and patterns. *RAPID®* current version allows the reviewer to set the QV sampling

rate from 5% to 80% of video images at 5% increments. To date, studies have shown conflicting results in the clinical use of QV (**Table 5.3**) (Shiotani et al. 2011; Saurin et al. 2012; Hosoe et al. 2012; Westerhof et al. 2009; Shiotani et al. 2012; Schmelkin 2006; Diaz et al. 2006; Appalaneni et al. 2007).

The aim of this study was to assess the validity of QV under white light (QVWL) and QV under BM (QVBM) reading mode, in a group of patients who had undergone small-bowel CE in our centre, by comparing it with the standard (reference) video-sequence reviewing by experienced small-bowel CE readers.

5.2 Materials and methods

5.2.1. Patients and small-bowel capsule endoscopy procedure

Between August 2008 and November 2011, 248 patients underwent small-bowel CE with PillCam®SB in our centre (132 performed with PillCam®SB1 and 116 with PillCam®SB2; Given®Imaging Ltd, Yokneam, Israel). The demographics and clinical characteristics of this group are presented in **Table 5.1**. Our standard procedure protocol is presented in Appendix 1.

For the purpose of this study, only small-bowel CE videos with complete small-bowel transit were included for further QV analysis. The videos had already been reviewed – for the purpose of regular clinical care – by at least one of two experienced in small-bowel CE readers (AK and SD >800 reviews each). Our standard viewing mode is Single View or Dual View on automatic speed at 12–20 fps, respectively.

A research fellow (with experience in both conventional and capsule endoscopy; >200 SBCE reviews), who had not been involved in either patient care or the initial small-bowel CE review, analysed the video sequences with QV (under both WL and BM). The reviewer was blinded to any previously captured landmark or thumbnailed findings and to patients' clinical history and indications for the test.

QV mode reading SBCE analysis was performed using the *RAPID®7* workstation (Given®Imaging Ltd). One reviewer (AS) used only QV, selecting landmarks and thumbnailing abnormal images. All pathological images and times were entered in a spreadsheet. The reviewer used QVWL first (for the entire cohort) and QVBM second, reviewing sequences in a random order to minimize observer bias. He used QV with an image-sampling rate (sensitivity) of 35% in the Dual View display mode at 18 fps, sitting at arm's length from a 19-inch monitor in a quiet room with dimmed lights.

The small-bowel evaluation time (time from entry to exit from the small-bowel) was recorded for each patient. This included both the reading time and the thumbnail capture time for each of the two QV modes. To minimize reviewer tiredness,

reviewing sessions were restricted to 10 video sequences per day. The results of QVWL and QVBM reviews were compared with the results of the conventional (reference) reviews, by checking each thumbnail against all previously captured thumbnails, by two reviewers (AK and AS).

	N (%)	N (%)
Participants	Complete small-bowel CE 200 (included)	Incomplete small-bowel CE 48 (excluded)
Male	85 (42.5)	22
Age (±SD)	57.5 (±14.2)	63.1 (±13)
SBCE with PillCam®SB1	125 (62.5)	30 (62.5)
Indications for CE		
OGIB	106 (53)	21 (43.7)
CD (suspected or known)	81 (40.5)	26 (54.2)
Polyposis syndromes	4 (2)	0
Coeliac disease	3 (1.5)	0
Possible lesion or mass	6 (3)	1 (3.4)

Table 5.1: Demographics and indications for small-bowel capsule endoscopy in the study cohort. Abbreviations: CE, capsule endoscopy; SD, standard deviation; CD: Crohn's disease; OGIB: obscure gastrointestinal bleeding; SBCE: small-bowel capsule endoscopy.

5.2.2 Classifications of lesions

Findings in the OGIB group were classified as P0 (non-pathological), P1 (low/intermediate) or P2 (high bleeding potential) lesions (Saurin et al. 2003) To avoid reporting bias, in the suspected or the known CD group, only the most objective CE parameters and descriptors of mucosal inflammation were used, that is ulcer (defined as any pale or yellow-based mucosal break surrounded by a red or a pink collar) less than 1/4 of the intestinal lumen circumference, ulcer 1/4–1/2 of the lumen circumference, ulcer more than 1/2 of the lumen circumference ± luminal stenosis, as defined by the Lewis score (Granlek et al. 2008).

The performance of QV was defined as concordance between frames thumbnailed by the QV reader and frames selected during the standard/conventional review. The sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) for QVWL and QVBM – compared with the reference review – for clinically relevant (i.e. P1/P2) vascular lesions and for mucosal ulcers of any size were calculated in the OGIB and suspected/known CD referral groups, respectively.

5.2.3 Ethics consideration

This study was carried out in accordance with UK research ethics guidelines. After review by the local ethics committee, further specific ethical review and approval were not required, as the study was considered a retrospective clinical audit work using data already obtained as part of regular patient care.

5.2.4 Statistical analysis

Values are expressed as mean ±SD. A two-sided *P* value less than 0.05 was considered statistically significant. Statistical analysis was performed using the Graph Pad InStat software (GraphPad Software, La Jolla, California, USA) for Windows.

5.3 Results

A total of 200 SBCE examinations were completed to the caecum and included in this study. The mean evaluation time (including reading and time to mark thumbnails) in this cohort was 475 (\pm 270) s and 450 (\pm 156) s for QVWL and QVBM, respectively (P =0.363). If all findings (i.e. any P category lesion, any size ulcer and any size polyp) were counted; QVWL detected 129 lesions (49.6%), QVBM detected 135 lesions (51.9%) and the conventional (reference) review detected 260 lesions (P <0.0001) (**Table 5.2**).

5.3.1 Results - Obscure gastrointestinal bleeding

One hundred and six (53%) SBCEs were performed for OGIB, 21 (10.5% included videos) for overt OGIB and 85 (42.5% of included videos) for occult OGIB. With QVWL, 54 (55.1%) lesions [P0 (28), P1 (18), P2 (8)] were detected, whereas with QVBM, 63 (64.3%) lesions were detected [P0 (48), P1 (13), P2 (2)]. Standard (reference) SBCE reading detected 98 lesions [P0 (67), P1 (23), P2 (8)] (P = 0.0506).

Concordant results (normal SBCE i.e. no findings and/or P0 lesions only) between QVWL and reference reading were observed in 101/106 (95.3%) cases and discordant results in five (4.71%), and 4/5 false negatives with QVWL. With QVBM reading, concordant results (for no findings and/or only P0 lesions) between QVBM and reference reading were observed in 89/106 (84%) cases and discordant results in 17 (16%), and 14/17 false negatives with QVBM.

For QVWL, the sensitivity, specificity, PPV and NPV for P1+P2 lesions (as compared with reference reporting) were 92.3%, 96.3%, 96% and 92.8%, respectively. For QVBM, the above values were 91%, 96%, 96.2% and 90.6%, respectively.

5.3.2 Results - Suspected/known Crohn's disease

Eighty-one (40.5%) patients underwent SBCE for small-bowel evaluation on the basis of a clinical history of suspected or known CD. With QVWL, 71 (45.8%) [<1/4

(62), 1/4-1/2 (3), >1/2 (6)] mucosal ulcers were detected, 68 (43.9%) [<1/4 (51), 1/4-1/2 (9), >1/2 (8)] with QVBM, as compared with 155 [<1/4 (137), 1/4-1/2 (10), >1/2 (8)] ulcers with reference reading, P=0.0003.

		Angioectasias	(N)				Polyps	Total
Type of lesions	P0	Ы	P2	<1/4	1/4 - 1/2	>1/2		
Viewing mode								
Standard view	29	23	8	137	10	8	7	260
QVWL	28	18	8	62	3	9	4	129
QVBM	48	13	2	51	6	8	4	135

Table 5.2: Angioectasias, ulcers and polyps detected with each of the study's viewing modes.

Abbreviations: QVBM, QuickView with Blue Mode; QVWL, QuickView with white light.

Concordant negative results (i.e. no findings/non-specific findings and/or <3 small ulcers) between QVWL and reference reading were observed in 73 (90%) and discordant results in eight (9.9%), 8/8 false negative with QVWL. Concordant negative results between QVBM and reference reading were observed in 73 (90%) and discordant results in eight (9.9%), and 7/8 false negatives with QVBM.

In the suspected CD category (15 patients; 12 mucosal ulcers with reference review of which ulcers <1/4: 10, ulcers>1/4: 2), the overlooked lesions (ulcers<1/4: 6) would have potentially changed the diagnosis in one case. When analysing QVWL and ulcer size (i.e. <1/2, 1/4–1/2 and >1/2 luminal circumference), the sensitivity was 42%, PPV 97% (as compared with reference reporting), increasing to 100% for large ulcers (1/4–1/2 and >1/2).

For QVBM, the sensitivity and PPV were 52% and 91%, respectively, again increasing to 100% for large ulcers (1/4-1/2 and >1/2).

5.3.3 Results - Polyposis syndromes

Ten (5%) patients underwent SBCE for the evaluation of polyposis syndromes or because of a strong clinical suspicion of a primary or a secondary small-bowel mass/tumour lesion. With QVWL and QVBM, four polypoid lesions were detected (the same individual lesions for both modes) compared with seven with standard (reference)review.

5.4 Discussion

Although there is no strict guidance for the best standard/conventional small-bowel CE reading technique and speed, the unique features of small-bowel CE require the reader to be intensely focused and alert (Lo 2006). Nevertheless, lapses in concentration or distractions cannot be prevented in lengthy reading sessions. In most tertiary, high case-volume centres, small-bowel CEs are usually reviewed by examiners who may not be further involved in the patient's management. This requires a quick turnaround time from capsule-to-report (for the non-urgent cases) and reviewer availability/flexibility (Lo 2006). Furthermore, there are clinical settings where a timely report is crucial for further clinical management that is, inpatients with OGIB and patients with severe CD.

Recently, VC has been reported to improve the performance of small-bowel CE. We have shown that BM, a form of VC that is incorporated into the *RAPID®* software, improves the definition of mucosal lesions and possibly increases the detection rate (Krystallis et al. 2011; Spada et al. 2011). The two features, that is, QV and BM should be considered as 'quantitative' and 'qualitative' as they aim to decrease the reviewing time and enhance the detection of small-bowel lesions, respectively. The combination of QV and VC (BM) has not been studied to date.

Consequently, we aimed to evaluate the utility of combining the QV mode with BM and WL. Notably, this is the first study to check the QV reading on version 7 of the RAPID® software. Moreover, a detailed and strict protocol was followed (single reviewer, not more than 10 video reviews/session, low reading speed of 18 fps in a dual mode view on the viewing speed slider and Dual View frame mode for all reviews), whereby we included a large number of SBCEs and did not restrict the study to a single indication to have a realistic representation of everyday clinical scenarios.

In our OGIB group, all P2 lesions were detected with QVWL; therefore, when urgent SBCE analysis is necessary– for further immediate management planning – the QV mode can provide an accurate diagnosis within a few minutes in the majority of cases. Furthermore, in this clinical setting, our study shows that BM

does not confer any additional advantage over WL. QV has a high PPV (all P2 lesions and large ulcers were detected); however, the NPV was just above 90% (for small angioectasias), although this should be interpreted with caution as the clinical relevance of missing such lesions is not necessarily significant on clinical grounds (Frieling 2006; Hindryckx et al. 2008; Maeda et al. 2010).

Conversely, QV showed only 50% sensitivity for small ulcers and aphthae in the known/suspected CD group. In the suspected CD category, lesions that were detected with the reference review and missed by QVWL or QVBM review would have resulted in a different diagnosis in only one case. These results are in agreement with those of other groups who advocate the use of QV solely in the suspected CD group, when multiple and widespread lesions of mucosal inflammation are present (Westerhof et al. 2009).

Moreover, we found that BM, despite excellent results in lesion characterization (Shiotani et al. 2012), does not confer any additional benefit (over WL) in lesion detection in a QV setting. This is not dissimilar to a recently published study from our centre, where BM did not confer any added benefit over WL in Lewis score calculation (Koulaouzidis et al. 2012). Furthermore, this is not in agreement with recently reported data of Abdelaal et al. (2010), although admittedly, the video-reviewing setting was different.

An inherent limitation of this study, similar to previous studies, is that QV has been compared against 'conventional /standard' viewing. Although the initial review was performed by experienced capsule endoscopists and at a low speed for the purpose of regular clinical care, it is not possible to determine whether strict reviewing conditions (similar to those applied by AS in the QVWL/QVBM review) were implemented constantly. Another intrinsic limitation of the present study is the use of a single, less experienced reviewer, for both QV modes (QVWL and QVBM, albeit not in a consecutive manner for each video stream), which increases the risk of interpretation bias. Moreover, although the review was performed in a random order, this has not offset the potential for observer bias. However, it is noteworthy that recent studies have shown that the small-bowel CE detection rate is not necessarily linked to medical background or reviewer experience (Sidhu et al.

2007; Dokoutsidou et al. 2011; Zheng et al. 2012). We should also acknowledge that by including only small-bowel CE with complete small-bowel transit, we have introduced potential applicability limitations.

Furthermore, two generations of PillCam®SB have been used in this study and one should keep in mind the improvement in the field of view from SB1 to SB2 (although this does not alter our results). Lastly, this chapter is based on the number of lesions detected; as it is common to find several 'repetitive' lesions in the same patient, an overestimation of the concordance between the two reading modes may occur. In an attempt to overcome this, we reported the change in the diagnosis of patients with suspected CD.

QV sampling rate (%) N/S N/S High (17) Normal High (17) Normal High (17) N/S 5.15.25 QV reading frame mode speed mode speed mode speed mode speed speed speed speed state (min) N/S 1.44 (median) N/S 1.79 11.6 N/S Single, 25 fps 3.44 (median) N/S 17.9 11.6 N/S	Study	Schmelkin*	Diaz	Appalaneni	Westerhof	Hosoe	Shiotani	Saurin ^b	Shiotani
define frame speed N/S Single, 25 fps N/S N/S N/S N/S ge reading time speed N/S 25,15,5 3 4.4 (median) N/S 17.9 11.6 ge reading time speed N/S N/S N/S Conventional N/S 11.6 speed N/S N/S N/S 4.0 N/S 11.6 version 4.0 N/S N/S 4.0 12.0 12.0 riewers 1 2 2 2 3 3 12.0 riewers 1 2 2 2 3 3 12.0 rases 47 37 N/S 100 45 44 106 ses 1 2 2 2 3 10 N/S N/S sses 4 1 1 1 1 1 1 1 1 sses N/A 1 1 1 1 1 <td>QV sampling rate (%)</td> <td>N/S</td> <td>s/N</td> <td>N/S</td> <td>High (17)</td> <td>Normal</td> <td>High (17)</td> <td>N/S</td> <td>5,15,25,35</td>	QV sampling rate (%)	N/S	s/N	N/S	High (17)	Normal	High (17)	N/S	5,15,25,35
ge reading time N/S 25,15,5 and least reading time A.4 (median) by special read frame N/S A.4 (median) by special read frame N/S N/S A.4 (median) by special read frame speed N/S N/S A.4 (median) by special read frame speed N/S N/S A.4 (median) by special read read speed N/S N/S A.2 (multiview) by speed A.3 (multiview) by speed A.4 (multiview) by speed A.3 (multiview) by speed A.4 (median) by speed A.5 (multiview) by speed A.4 (multiview) by speed A.3 (multiview) by speed A.4 (multiview) by speed A.5 (multiview) by speed A.4 (multiview) by speed	QV reading frame mode speed	N/S	N/S	Single, 25 fps	N/S	s/N	Single 6fps	N/S	Single, N/S
Aversion read frame Speed version N/S N/S Conventional dual view/18 fns speed N/S Conventional nual view/18 fns speed N/S N/S Conventional nual view/18 fns speed N/S N/A N/A <td>Average reading time (min)</td> <td>N/S</td> <td>25,15,5 fns</td> <td>8</td> <td>4.4 (median)</td> <td>S/N</td> <td>17.9</td> <td>11.6</td> <td>S/N</td>	Average reading time (min)	N/S	25,15,5 fns	8	4.4 (median)	S/N	17.9	11.6	S/N
version 4.0 N/S 4.0 5.0 5.0 5.0 5.0 viewers 1 2 2 2 3 3 12 total 4/7 57 50 100 45 44 106 cases 4/7 37 N/S 56 N/S N/S 106 ses N/A 12 N/S 30 N/S N/S N/A osis cases N/A N/S N/S N/S N/S N/A nitivity (%) 100 N/S N/S N/S N/S N/S N/S nitivity (%) 100 N/S N/S N/S N/S N/S N/S nitivity (%) 100 N/S N/S N/S N/S N/S N/S nitivity (%) N/A N/S N/S N/S N/S N/S N/S nitivity (%) N/A N/S N/S N/S N/S N/S </td <td>Comparison read frame mode/ speed</td> <td>S/N</td> <td>N/S</td> <td>N/S</td> <td>Conventional</td> <td>s/N</td> <td>N/S</td> <td>Conventional N/S</td> <td>N/S</td>	Comparison read frame mode/ speed	S/N	N/S	N/S	Conventional	s/N	N/S	Conventional N/S	N/S
iewers 1 2 2 2 3 3 12 total 47 57 50 100 45 44 106 cases 47 37 N/S 56 N/S N/S 106 ses N/A 12 N/S 30 N/S N/S N/A ssis cases N/A N/S N/S 12 14 14 N/A nsitivity (%) 100 N/S N/S N/S N/S N/S 89.2 ecificity (%) 100 N/S N/S N/S N/S 84.7 Hesion (n) N/A N/S 13 N/A 10 8	RAPID version	4.0	N/S	S/N	4.0	5.0	5.0	5.0	6.5
total 47 50 100 45 44 106 cases 47 37 N/S 56 N/S N/S 106 ses N/A 12 N/S 30 N/S N/A 106 sis cases N/A 10 N/S 12 14 14 N/A nsitivity (%) 100 N/S N/S N/S N/S N/S 89.2 ecificity (%) 100 N/S N/S N/S N/S 84.7 I besion (n) N/A N/S 13 N/A 10 8	No reviewers	1	2	2	2	3	3	12	4
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sois cases N/A N/S 12 N/S N/A N/A nsitivity (%) 100 N/S N/S N/S N/S N/S 89.2 ecificity (%) 100 N/S N/S N/S N/S 84.7 A lesion (n) N/A N/S 13 N/A 10 8	CD cases	N/A	12	S/N	30	N/S	S/N	N/A	S/N
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100 N/S N/S N/S 89.2 100 N/S N/S N/S 84.7 N/A N/S 13 N/A 10 8	Other	N/A	10	S/N	12	14	14	N/A	S/N
J 100 N/S N/S N/S N/S 84.7 N/A N/A 13 N/A 10 8	QV sensitivity (%)	100	s/N	S/N	N/S	N/S	N/S	89.2	S/N
N/A N/S 2 13 N/A 10 8	QV specificity (%)	100	s/N	S/N	N/S	N/S	S/N	84.7	S/N
	Missed lesion (n)	N/A	s/N	2	13	N/A	10	8	S/N

Table 5.3: Studies evaluating QuickView to date.

Abbreviations: CD: Crohn's disease; fps: frames per second; N/A: not applicable; N/S: not stated; OGIB: obscure gastrointestinal bleeding (overt + occult); QV: Quick view. * Studies presented only as abstracts, ^b Multi-centre study.

5.5 Conclusion

Our study confirms the safety of QV pre-read in urgent cases, but fails to show any benefit in other clinical scenarios. Although the benefits of QV are outweighed to some extent by a decrease in the overall diagnostic yield, this mode can be used confidently in overt OGIB in an urgent inpatient setting and in outpatients with occult OGIB or suspected CD. As the usefulness of QV may vary, depending on the number of small-bowel lesions, standard review settings are still recommended in all other cases. Furthermore, the present study confirms that BM does not confer any additional advantage in the QV setting.

CHAPTER 6

Evaluation of 4 three-dimensional reconstruction algorithms in capsule endoscopy images and use of enhancement algorithm to suppress reflections in three-dimensional reconstruction

- 6.1 Introduction
- 6.1.2 Tsai's SfS algorithm
- 6.1.3 Ciuti's SfS algorithm
- 6.1.4 Barron's SfS algorithm
- 6.1.5 Torreão's SfS algorithm
- 6.1.6 Highlights removal algorithm
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- 6.2.6 Statistical analysis
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- 6.3.2 Phase 2
- 6.4 Discussion
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6.1 Introduction

Capsule endoscopy has changed our diagnostic approach for small-bowel diseases (Iddan et al. 2000; Eliakim 2013). Although more accurate and of higher diagnostic yield than other modalities (Mata et al. 2008; Koulaouzidis et al. 2013), there are still occasions where pathology is either missed or misinterpreted (Mavrogenis et al. 2011; Hakim et al. 2011; Triantafyllou et al. 2011). Furthermore, reports have shown that 3-D reconstruction can facilitate diagnosis by enhancing textural features of mucosal structures or intestinal abnormalities (Koulaouzidis and Karargyris 2012).

However, accurate 3-D reconstruction of the GI tract requires the use of stereoscopic cameras that can simulate human binocular vision (Kolar et al. 2010). With the current level of technological investment in CE though, i.e. camera size, packaging constraints and power consumption, accurate 3-D imaging of the intestinal lumen in small-bowel CE is still unfeasible (Fisher and Hasler 2012; Koulaouzidis et al. 2013). Three-dimensional reconstruction may be helpful in conjunction with other image-enhancement tools, e.g. virtual chromoendoscopy (FICE and/or colour (blue) mode analysis of CE videos (Koulaouzidis et al. 2013; Koulaouzidis, Rondonotti and Karargyris 2013; Spada et al. 2011).

Therefore, software approaches that offer 3-D representation of conventional monocular 2-D CE frames have been developed (Zhang et al. 1999) and proposed for use in CE (Karargyris et al. 2010). Shape-from-shading (SfS) algorithms recover the 3-D shape from a single monocular image (two-dimensional image). Such approaches, e.g. SfS algorithms, are members of a family of shape-recovery algorithms called shape-from-X techniques (Tsai and Shah 1994). Given a single 2-D image, these algorithms recover the shape of objects using the gradual variation of shading (Zhang et al. 1999; Karargyris et al. 2010). This recovered shape is expressed either with the surface normal (nx, ny, nz) or the surface gradient (p, q). All of the SfS algorithms use a minimization function and constraints on a local or a global scale. Hence, the recovered 3-D shape is an estimate of the real shape of an object and technically not the real physical shape.

Essentially, surface reconstruction with SfS is achieved through a mathematical representation that is inverted in order to recover dense surface distance and normal information by the gradual variation of shading (Karargyris et al. 2010; Koulaouzidis and Karargyris 2012). In the next four paragraphs, the four publicly available SfS algorithms that we use in the clinical experiments are briefly discussed.

6.1.2 Tsai's SfS algorithm

Since images of most surfaces in the real world can be approximated by Lambertian reflectance, the majority of SfS methods use the Lambertian reflectance model (Zhang et al. 1999). Lambertian reflectance is the property that defines an ideal 'matte' or diffusely reflecting surface. The apparent brightness of such a surface to an observer is the same regardless of the observer's angle of view (Tsai and Shah 1994). The important parameters in Lambertian reflectance are albedo and illuminant directions. Commonly, the albedo is assumed to be constant. These constraints make calculations easier. Tsai's algorithm consists of an initial discrete approximation of the surface gradients (p, q), and once incorporated into the Lambertian reflectance equation linear approximations based on Taylor series expansions along points (x, y) produce the depth map Z which is the recovered 3-D shape. The depth Z recovery is based on an iterative algorithm which is a form of the Newton-Raphson method. It converges quadratically when provided with a sufficiently accurate initial approximation and since it operates on a local basis it is highly parallelizable and therefore computationally efficient (Figure 6.1A).

6.1.3 Ciuti's SfS algorithm

The laparoscopic camera was first calibrated to characterize its radiometric response and internal parameters to discover any deviations from the Lambertian reflectance model (Ciuti et al. 2012). They adopted the modeling proposed by Visentini-Scarzanella et al. (Visentini-Scarzanella 2012) where a single light source – instead of two – away from the optical centre is considered. The resulting SFS partial differential equation is characterized with the information from the camera and light calibration procedure and then solved through a Lax-Friedrichs sweeping

scheme (Visentini-Scarzanella 2012). In contrast to the formulation in which the recovery of the albedo relies on robust separation of specular and diffuse components, with additional calibration of the camera, it is possible to recover this scale factor prior to the procedure and dynamically apply it for in-vivo monocular metric structure recovery. They finally retrieve albedo values between consecutive depth-recovered endoscopic images (Figure 6.1B).

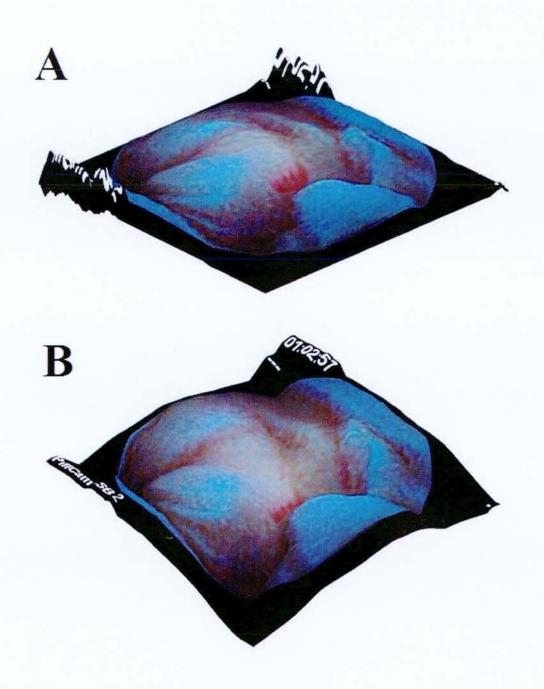


Figure 6.1 (A, B): A) an angioectasias represented with the Tsai's SfS algorithm, and B) the same lesion represented with the Ciuti's SfS algorithm

6.1.4 Barron's SfS algorithm

Barron and Malik (2012) proposed a unified shape recovery SfS algorithm using shape – S(Z,L), illumination – L, and reflectance R from shading of a single image. Colour constancy can be viewed as a subset of the intrinsic images problem: decomposing a single image into its constituent 'images': shape, reflectance and illumination (Barron and Malik 2012). They assume Lambertian reflectance for their modelling. The unknowns Z, R, L are approximated through a minimization function subject to the log-intensity image I = R + S(Z,L). They additionally use a reflectance smoothness model to constraint the minimization function. It is based on a multivariate Gaussian scale mixture (GSM) placed on the differences between each reflectance pixel and its neighbours (Figure 6.2A).

6.1.5 Torreão's SfS algorithm

This SfS algorithm is biologically inspired by being formulated in terms of a model of linear-non-linear neuronal responses (Torreão and Fernandes 2011). The input image to a linear filter was followed by non-linear transformations modelled on the tuning curves of the disparity-selective binocular neurons. More specifically, the linear filter output is next submitted to non-linear transformations, in order to yield the shape estimate. The second non-linear stage was so chosen in order to establish a parallel between our approach and biological stereoscopic processing (**Figure 6.2B**).

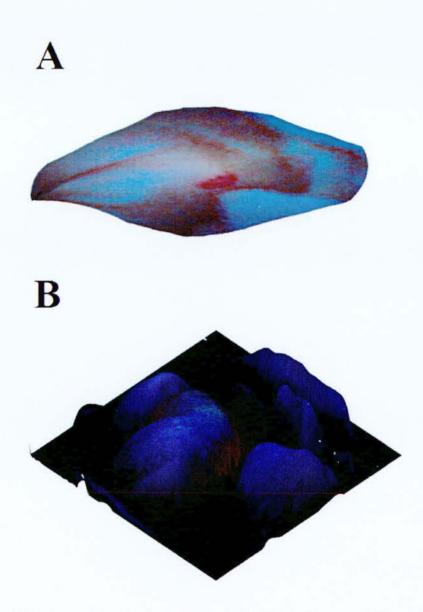


Figure 6.2 (A, B): A) an angioectasias represented with the Barron's SfS algorithm, and B) the same lesion represented with the Torreão's SfS algorithm

6.1.6 Highlights removal algorithm

Light reflections on the surface of the digestive tract are still a significant problem, not only for 3-D representation but also for traditional 2-D CE. When light falls on to a surface, some of the beams are reflected back straight away (specular reflection), while the rest of the beams penetrate it before being reflected (diffuse reflection). As most digestive tract structures/surfaces are dielectric and homogeneous, they display both types of reflections. As mentioned above, most SfS methods work better on images following the Lambertian reflection model. However, the intensity distribution of diffuse reflections approximately follows Lambert's law (Lambert 1760).

Tan and Ikeuchi (2005) proposed a method to separate the two reflection components; diffuse and specular. This method behaves optimally since it does not require colour segmentation as other methods do. Additionally, another advantage is that it runs on two neighbouring pixels minimizing the error of the outcome. Basically, the methodology creates a normalized image containing only the pure specular component of the original image. It also creates a specular-free image out of the normalized picture by using the maximum chromaticity. A logarithmic differentiation of the two images gives the diffuse image, which is the original one with the highlights removed (**Figure 6.3 A, B**).

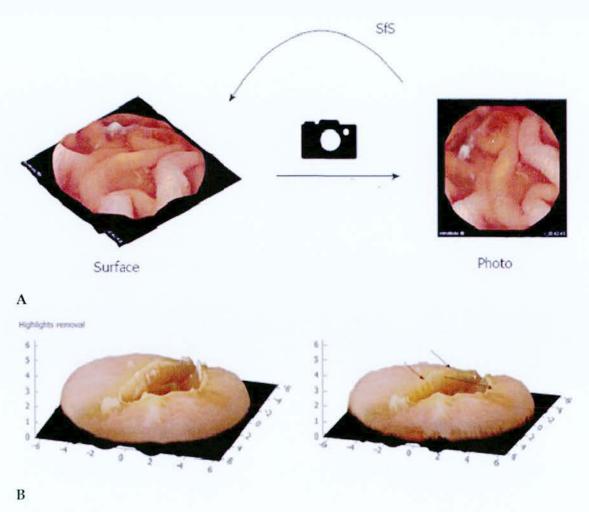


Figure 6.3 (A, B):

A) Shape-from-shading (SfS) principles. Capturing a surface using a camera removes depth information. SfS techniques try to reproduce the missing depth information from a given two-dimensional image.

B) Highlights removal software. Three-dimensional representation image before (left) and after application of highlights removal software (right).

6.1.7 Aims

Currently, there are four publicly available SfS algorithms (Tsai and Shah 1994; Torreão and Fernandes 2011; Barron and Malik 2012; Ciuti et al. 2012). To date, no comparative study using images obtained during clinical small-bowel CE has been performed.

Therefore, this study aims to evaluate the performance of four publicly available SfS algorithms for 3-D representation in CE, by comparing 3-D reconstructed images with their equivalent conventional 2-D images of small-bowel structures/lesions obtained during small-bowel CE. This is in order to identify which of the four algorithms is more helpful in facilitating identification and distinction between lesion and surrounding mucosa. Furthermore, we aim to validate a highlight-suppression algorithm testing its use on to CE images generated by the best-performing 3-D representation algorithm (Tan and Ikeuchi 2005).

6.2 Materials and methods

6.2.1 Phase 1

Between January 2011 and January 2012, 262 small-bowel CE procedures were performed at the Royal Infirmary of Edinburgh (tertiary referral centre for CE for the south-east of Scotland, United Kingdom) in 249 patients (mean age: 52.6 ± 12.1 years). Out of them, 140 were performed with PillCam®SB2 (Given®Imaging Ltd, Yokneam, Israel) and 122 with MiroCam® (IntroMedic®Co, Seoul, South Korea). A total of 54 images (27 obtained with MiroCam® and 27 with PillCam®SB) were selected on the basis of the overall quality, i.e. brightness, absence of air bubbles, debris, or opaque luminal fluid and clarity of findings (lesions or structures). Thereafter, images were classified in the following image groups: (1) vascular lesions i.e. angioectasias (n = 16); (2) inflammatory lesions, i.e. ulcers, erosions, aphthae, cobblestone, fold and/or villous oedema (n = 18); and (3) protruding lesions/structures, i.e. polyp/mass, nodular lymphoid hyperplasia, cluster of focal lymphangiectasias, chylous cysts, and AoV, (n = 20).

6.2.2 Phase 2

For the second phase, a phantom task simulator was created. A stomach ulcer anatomical model (manufacturer: Anatomical Chart Company G200) was used; the stomach model has a red-coloured base ulcer (1/2"diameter and 3/16"depth; Figure 6.4A); the latter was thereafter coloured buttercup yellow using quick-drying spray paint (Tor Coatings®Ltd, UK) and white (using flat white spray from Plasti-Kote®Ltd). A PillCam®SB2 (Given®Imaging Ltd, Yoqneam, Israel) was mounted on a plastic tube and held (with the use of a regular laboratory stand) at 0, 5, 10, 15 and 20 mm from the ulcer base (usual working distance of the CE in vivo, Figure 6.4B). The images were uploaded to a workstation and they were categorized based on distance and ulcer base colour (red, yellow and white). The aim was to check whether the ulcer models appear closer or more distant based on their 3-D representation (Figure 6.5).

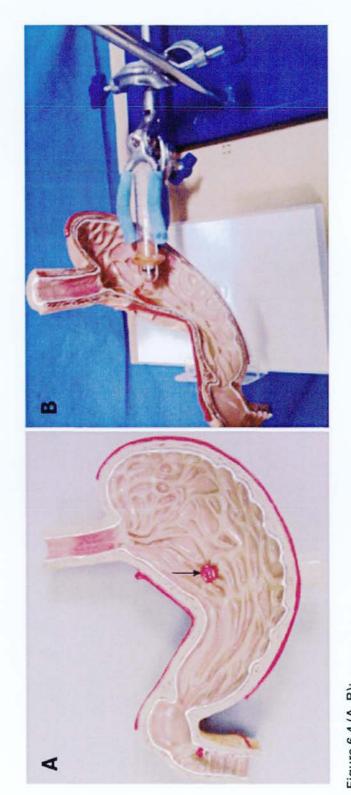


Figure 6.4 (A, B):

A) Phantom model, and B) and task simulator setting.

In A): the arrow points to the gastric ulcer (1/2" diameter and 3/16" depth).

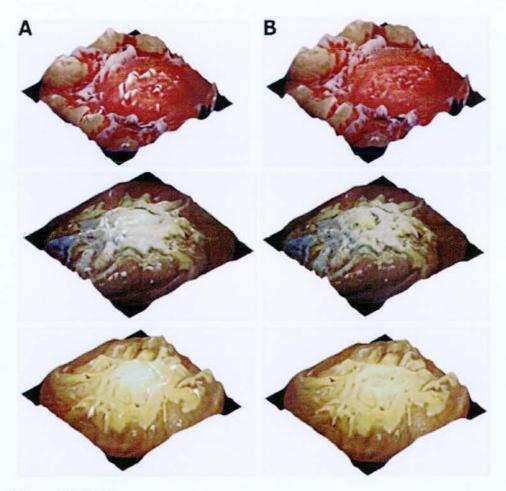


Figure 6.5 (A, B):

Three-dimensional representation of images captured for the 3 models: red, white and yellow.

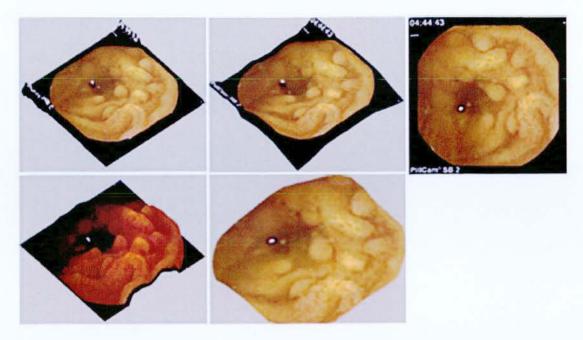
A) Original three-dimensional (3-D) represented images; and

B) The processed 3-D represented images using the highlight-suppression algorithm.

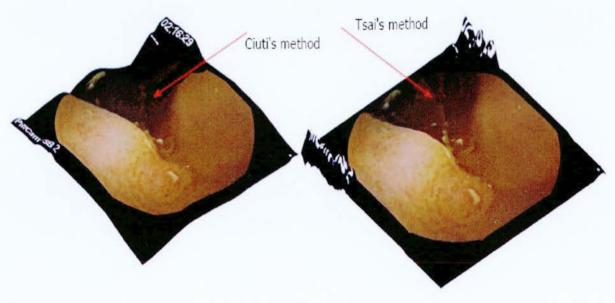
6.2.3 Three-dimensional image representation software

All selected images were reconstructed in 3-D by means of all four SfS algorithms. Three reviewers (ER, GM, AK), with extensive experience in CE and blinded to each other, participated in this study. In order to facilitate the evaluation process, a Mathworks® Matlab program with a graphic user interface (GUI) was developed (Figure: a video presenting the evaluation process is provided as supplementary material via this link: https://dl.dropboxusercontent.com/u/7591304/EvaluationVideo.mov). The program consisted of two windows in which the conventional 2-D small-bowel CE image (Figure: single frame at the right side/window of the GUI screen) and its corresponding 3-D represented images (four, one for each of the four SfS under evaluation) are presented to the reviewer (Figure 6.6 A, left side/window of the GUI screen).

The 3-D SfS representations appeared in random order. The reviewers had the ability and freedom to rotate and zoom in on each of the 3-D represented images. At the bottom of the GUI screen, a single 'task request': 'Choose the 3-D representation you consider most helpful in distinguishing the finding (seen in 2-D) from the surrounding mucosa' appeared. This prompted reviewers to choose one among the four 3-D reconstructed images, each generated by a different 3-D algorithm. After selecting the best SfS representation, the reviewer had to click 'next' to proceed to the next case. This process was repeated until the program reached the last case, after which each separate evaluation was concluded (Figure 6.6B).



A



B

Figure 6.6 (A, B):

- A) For the evaluation phase, a Mathworks©Matlab program with a graphic user interface was developed. The program consists of two windows in which the conventional two-dimensional capsule endoscopy image (single frame at the right side/window of the graphic user interface screen) and its corresponding three-dimensional represented images (four, one for each of the four shape-from-shading under evaluation) were presented to the reviewer.
- B) The two most voted SfS, Ciuti's (left) and Tsai's method (right).

6.2.4 Outcome measures

6.2.4.1 Phase 1

Reviewers were asked to evaluate 54 images. The following subgroup analyses were performed: (1) evaluation of 3-D representation according to the type of finding (vascular vs inflammatory vs protruding); and (2) evaluation according to the system generating the 2-D image (PillCam® vs Mirocam®). Furthermore, interobserver agreement was calculated.

6.2.4.2 Phase 2

SfS algorithms cannot measure the real distance of the camera to the model's surface but they give the relative distance (z) to the black frame background. For each image, the region of interest (ROI) was selected of the ulcer model on the 3-D representation and the average depth (z) for each ROI was calculated.

6.2.5 Ethics consideration

This study was conducted in accordance with United Kingdom research ethics guidelines. After review by the local ethics committee further specific ethical review and approval were not required, as the study was considered an evaluation of previously collected endoscopy images, using data already obtained as part of regular clinical care.

6.2.6 Statistical analysis

For numerical variables, values are presented as mean \pm SD. Where necessary, the Fisher exact test was calculated. A two-tailed P value < 0.05 was considered statistically significant. Inter-observer agreement was calculated using an online kappa calculator (available from http://justusrandolph.net/kappa/), which provides the calculation of Randolph's free-marginal multi-rater kappa (κ), applicable when raters are not forced to assign a certain number of cases to each category. Values of κ can range from -1.0 to 1.0, with -1.0 indicating perfect disagreement below chance, 0.0 indicating agreement equal to chance, and 1.0 indicating perfect agreement above chance. More specifically, the interobesrver

agreement is classified per *K* as poor < 0.20, fair 0.2–0.40, good 0.41–0.60, very good 0.61–0.80 and, excellent 0.81–1.00 (available from http://justusrandolph.net/kappa/). All other statistical analyses were performed using a statistical package, StatsDirect (StatsDirect Ltd, Altrincham, Cheshire, United Kingdom).

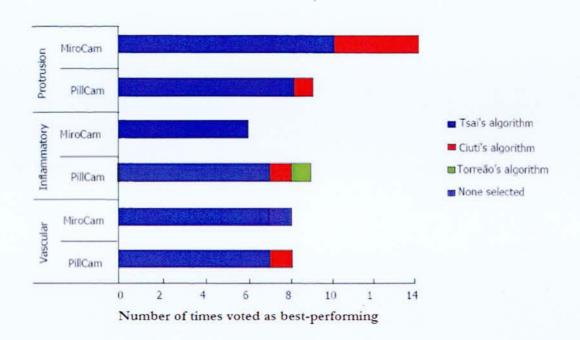
6.3 Results

6.3.1 Phase 1

Of the four SfS algorithms, Tsai's 3-D algorithm outperformed the rest (selected as the best in 45/54 images), followed by Ciuti's (best performing SfS in 7/54 images) and Torreão's (in 1/54 images): there was a single image for which each reviewer selected as best performing a different 3-D representation algorithm. Of note, not once was Barron's 3-D algorithm selected as best performing (**Figure 6.7**). In 26/54 images, Tsai's algorithm was unanimously selected as the best performing 3-D representation SfS software. Tsai's 3-D algorithm superiority was independent of lesion category (protrusion/inflammatory/vascular; P = 0.678) and/or CE system used to obtain the 2-D images (MiroCam®/PillCam®; P = 0.558). Lastly, the interobserver agreement was good (kappa = 0.55).

6.3.2 Phase 2

Since the Tsai's method gave us really satisfying results, we considered improving it by adding a reflectance model transformation as a preprocessing step to make endoscopy images specular free and, therefore, follow the Lambertian reflection model. The results (charts, Figure 6.8) confirm that as the distance of the camera from the model surface increases, so does the relative distance (z) on the 3-D representation. This effect is more evident for the white and yellow ulcer models. However, relative distance does not follow a similar trend for the red-based ulcer model. This is likely to be due to the saturation of the red colour creating variations to the shading: the red colour appears darker or lighter. Finally, from the charts we conclude that the highlight-suppression algorithm improved the quality of the images.



Jakitis mis F and	Vascular		Inflammatory		Protrusion	
SfS method	PillCam*	MiroCam*	PillCam*	MircCam*	PillCam ³	MiroCam*
Tsai	7	7	7	6	8	10
Ciuti	1	0	1	0	1	4
Torreão	0	0	1	0	0	0
Barron	0	0	0	0	0	0
None Selected	0	1	0	0	0	0

Figure 6.7:

Top: Assessment results for the four shape-from-shading algorithms per lesion category. In the Y-axis, lesion categories (protrusion, inflammatory, vascular) and the system (PillCam or MiroCam) used in each case. In the X-axis, the absolute selection numbers.

Bottom: the same results tabulated.

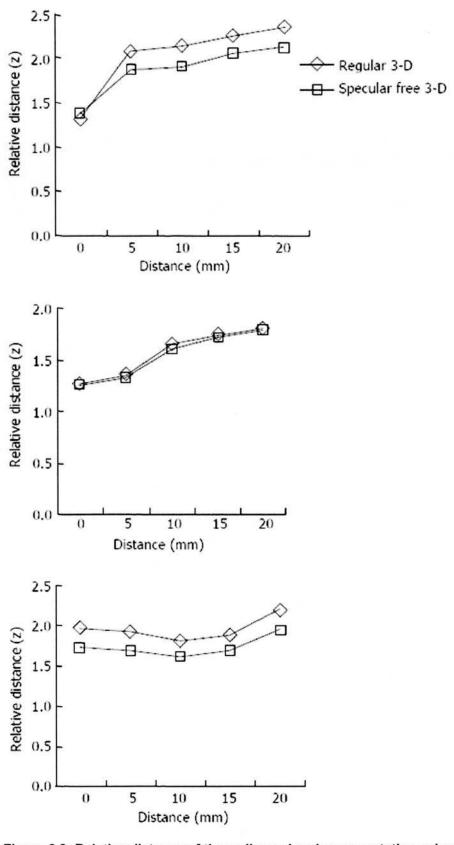


Figure 6.8: Relative distance of three-dimensional representation calculated over images taken from various distances of the capsule from the models.

6.4 Discussion

In the present study, we compared the performance of four publicly available 3-D 'reconstruction' algorithms (SfS software) (Tsai and Shah 1994; Torreão and Fernandes 2011; Barron and Malik 2012; Ciuti et al. 2012), using 54 conventional 2-D CE images. The evaluation criterion was subjective, i.e. the perceived visualization improvement (3-D representations offered over and above the corresponding conventional 2-D images) as ascertained by three experienced CE reviewers. Based on this evaluation, Tsai's algorithm is the 3-D representation model recommended for use in CE. This outcome directly supports Tsai's SfS model theoretical advantages: (1) able to produce good results for round surfaces, which is the case for most digestive tract shapes; and (2) it behaves quite well with bright surfaces (Zhang et al. 1999).

Depth information is an important aspect of human vision; it helps the human brain to analyse and comprehend the surrounding environment. Images captured with conventional (non-stereoscopic) cameras 'discard' the third dimension (depth) as conventional cameras can only save two dimensions (height and width). Therefore, depth information is lost; and moreover, most imaging algorithms perform less efficiently.

To date, engineers have not been able to equip capsule endoscopes with stereoscopic cameras for the following reasons: (1) packaging/space limitations; (2) low-depth resolution of stereoscopic or time-of-flight cameras; and (3) power consumption issues. However, it is almost certain that in the foreseeable future these hardware-related limitations will be overcome (Kolar et al. 2010) and eventually 3-D CE will be a commodity. Nevertheless, until hardware changes are widely implemented, several efforts have been made to convert 2-D images into 3-D images (3-D representation or 'reconstruction') through software and dedicated algorithms.

There are software algorithms that offer a fair trade-off between 2-D images and

hardware-enabled 3-D images. SfS algorithms can be divided into four groups: (1) minimization approaches; (Ciuti et al. 2012; Torreão et al. 2011; Barron and Malik 2012); (2) propagation approaches; (3) local approaches; and (4) linear approaches (Tsai and Shah 1994). It is important to remember that each of the four SfS algorithms evaluated herein utilizes a different approach to recover the shape from a conventional 2-D image. More specifically, Tsai's algorithm (Tsai and Shah 1994) described a repetitive update of the depth using a linear approximation of the reflectance function. Ciuti et al. (2012) used a camera model with perspective projection and a light source close to the surface and away from the optical centre to measure depth. Torreão et al. (2011) applied a linear-non-linear biological model that mimics neuronal responses to estimate shape. Finally, Barron and Malik (2012) proposed a unified model for recovering shape, reflectance and optional illumination while using local smoothness, global scarcity or entropy, and the absolute colour of each pixel. Although Tsai's (Tsai and Shah 1994) method is very straightforward and to an extent simplistic, it provides satisfying results. The algorithm of Ciuti et al. (2012), on the other hand, uses a more advanced model (incorporating a camera model with perspective projection) that makes things in the background appear further back than in Tsai's model (Figure 6.6).

Since, for a given 2-D image, light source and surface shape are not known, these algorithms try to model how the 2-D image was created from the 3-D environment to finally produce an approximation of this 3-D depth. The above modelling has a significant impact on the resulting 3-D representation. During the SfS process additional constraints need to be applied on the surface shape parameters or the light conditions to find the surface characteristics.

6.5 Conclusion

In conclusion, we showed previously that 3-D representation software offers a plausible alternative for 3-D representation of conventional CE images (until optics technology matures enough to allow hardware-enabled 'real' 3-D reconstruction of the GI tract). In the present study we compared four publicly available SfS methods. Three-dimensional reconstruction is attracting interest in CE, especially as newly developed and/or under development CE becomes available, with greater potential due to imager and optics for 3-D software (Fisher and Hasler 2012).

CHAPTER 7

Three-dimensional representation software as imageenhancement tool in small-bowel capsule endoscopy: a feasibility study

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7.1 Introduction

Over the past decade, CE has revolutionized the evaluation of small-bowel diseases (Iddan et al. 2000; Fisher and Hasler 2012). In recent years, research has been carried out to produce 3-D reconstructions of the GI tract in conventional video endoscopy using stereoscopic cameras (Mueller-Richter et al. 2004; Tsutsui et al. 2005): several reports have shown that it can facilitate diagnosis by enhancing mucosal textural features and abnormalities (Bhandari et al. 2004; Taylor et al. 2006). However, due to the current technological limitations of capsule endoscopes (packaging and size constraints and power consumption), hardware-enabled 3-D reconstruction of the intestinal lumen in small-bowel CE is yet to be available. Therefore, a software-based approach (SfS) has been proposed that helps approximate a 3-D representation from monocular 2-D images. These algorithms recover the shape of objects from 2-D images using a gradual variation of shading (Zhang et al. 1999). Eventually, amongst four publicly available SfS algorithms, (Barron and Malik 2012; Visentini-Scarzanella et al. 2012; Torreão and Fernandes 2011; Tsai and Shah 1994) Tsai's method performed better based on preliminary results (see previous chapter).

Therefore, we conducted a two-phase, feasibility study in order to assess:

- 1) the accuracy of 3-D representation, by using CE images from phantom paradigms (Phase 1); and
- 2) whether 3-D representation improves visualization (of surface/textural aspects) of small-intestine structures/lesions, by using of a group of selected SBCE images from clinical practice (**Phase 2**).

7.2 Methods

7.2.1 Phase 1 - Phantom simulator design

For the accuracy assessment of the software, a task simulator was constructed: 2-D images of phantom models were obtained by using CE and compared with their 3-D representation counterparts. Overall, the simulator was designed based on the following principles: (a) to be constructed with readily available materials, e.g. cardboard boxes and stationery office supplies; (b) to allow minimal external light for simulation of clinical CE; and lastly (c) phantom models to be representative of the variety of colours and shapes of structures/lesions encountered in SBCE. A cuboid cardboard box ($12 \times 30 \times 45$ cm) was used to simulate the abdominal wall and allow the placement of CE sensors for video capture. A frame was cut open at the top side of the box to allow insertion of a cardboard cuboid tube ($6 \times 9 \times 42$ cm) which was to act as the main function chamber/bowel simulator.

Furthermore, a 4 × 6 cm rectangular frame was cut open in the lower part the side of the tube facing the open lids of the box. This was done to allow placement of the phantom-model plates on the reviewing surface during CE video capture (**Figure 7.1A**). Finally, following placement of CE sensors, a real-time viewer was used to monitor progress of video/images capture.

7.2.2 Phase 1 – Phantom simulator models

As aforementioned, phantoms were made with commercially available stationery material. Therefore, red-, yellow- and white-coloured, flat-headed drawing pins (Figure 7.1B), as well as blocks of white, red and yellow Pritt® sticky tack (Henkel AG and Co. KGaA, Dusseldorf, Germany) and an ibuprofen tablet (Nurofen® 400mg) were used as phantom models. Phantoms were placed on cardboard panels of equal size in such a way that the model would be either protruding or level with the plate surface.

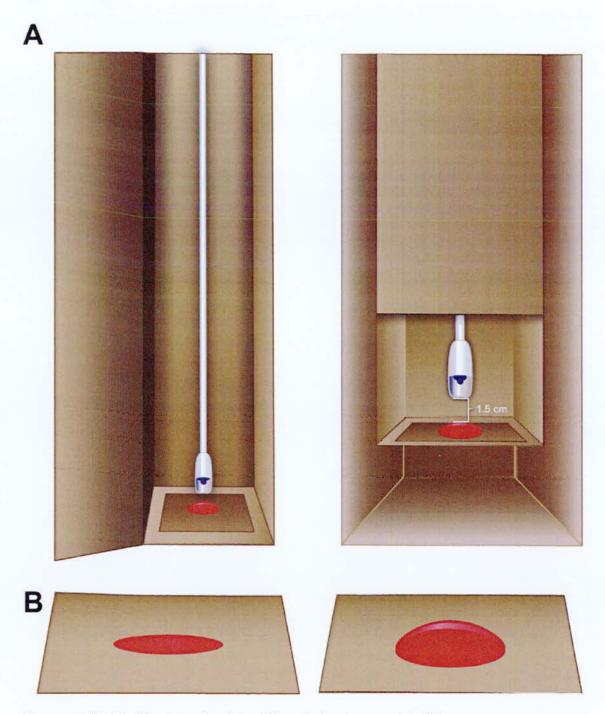


Figure 7.1 (A, B): Phantom simulator (A) and phantom models (B).

7.2.3 Phase 1 – Phantom simulator output

A PillCam®SB2 (Given®Imaging Ltd, Yokneam, Israel) CE was mounted on a small hemispheric plastic cap with Pritt® sticky fixer, and a commercial cotton string was used to suspend the capsule 1.5 cm above the phantom object plates. From the video obtained, 60 two-dimensional images of high quality (20 for each of the 3 colours, i.e. red, yellow and white) were selected by an experienced CE reader (AK), converted into 3-D images and reviewed for evaluation by another investigator (Al.K), who was unaware of the surface type of each image, i.e. if the imaged object was flat or protruding.

7.2.4 Phase 2 - Clinical study, patients

From January 2011 to January 2012, 262 small-bowel CE procedures in 249 patients (67 males/182 females; mean age: 52.6 ±12.1 years) have been performed at the Royal Infirmary of Edinburgh (part of NHS Lothian's University Hospitals Division). Out of those, 140 were performed with PillCam® (Given®Imaging Ltd, Yokneam, Israel) and 122 with MiroCam® (IntroMedic® Co, Seoul, South Korea).

7.2.5 Phase 2 – Clinical study, capsule endoscopy procedure

The technical characteristics of capsules, CE procedure and methodology for review of CE images have been described in detail previously (Koulaouzidis et al. 2012; Metzger et al. 2009). In essence, SBCE was performed with PillCam®SB2 and MiroCam® capsule endoscopes using an established, for-our-unit procedure protocol, i.e. strict liquid diet the day prior to the test, combined with purge (2 l polyethylene glycol; Moviprep®, Norgine Ltd, Middlesex, UK) and overnight fast. The capsule is ingested with 100 mg of anti-foam (Simeticone) and 5 mg of liquid prokinetic suspension (domperidone), unless in exceptional circumstances. The patients are allowed to drink clear fluids after two hours and consume a light meal/snack after four hours. Written informed consent was obtained from all patients prior to the procedure as part of their regular clinical care.

7.2.6 Phase 2 – Images selection and images groups

An experienced small-bowel CE provider (SD), familiar with both aforementioned SBCE systems, selected and de-identified a group of images by reviewing the thumbnails of all 262 videos. Images were selected on the basis of their overall quality, i.e. brightness, no bubbles and/or luminal debris or opaque luminal fluid and findings (lesions or structures) clarity. An expert CE reviewer (ER) acted as second selector. Eventually, only images for which there was complete agreement between the two reviewers in terms of image quality, colour and type of depicted finding, were included.

Therefore, a total of 192 small-bowel CE images (84 obtained with PillCam®SB2 / 108 obtained with MiroCam®), covering a wider spectrum of findings seen in SBCE, entered 3-D reconstruction. These images were classified as per:

- 1. Predominant colour of the depicted structure/lesion into 4 image-groups: red, white, mixed (red+white) and a group with lesion colour similar to that of the surrounding mucosa;
- 2. Surface morphology of the depicted structure/lesion into the following groups:
- a) convex surface morphology, i.e. polyp/neoplastic, chylous cysts, nodular lymphoid hyperplasia (NLH), fold oedema, and AoV (n = 67);
- b) flat or concave surface morphology, i.e. mucosal ulcer, erosion, aphthae, villous oedema and angioectasias (n = 103); and
- c) combi-surface morphology, i.e. cobblestone and lymphangiectasias (n = 22).
- 3. Diagnostic category into the following groups:
- a) vascular, i.e. angioectasias; (n = 50);
- b) inflammatory, i.e. ulcers, erosions, aphthae, cobblestone, fold/villous oedema; (n = 73); and
- c) luminal protrusion i.e. polyp/neoplastic, NLH, cluster of focal lymphangiectasias, chylous cysts, and AoV; (n = 69), (Table 7.1).

4. Lastly, each diagnosis was examined separately.

7.2.7 Three-dimensional image-representation software

Three-dimensional visualization software was developed in Mathworks®Matlab; it can process a 576 × 576 image in less than 2 seconds. The software allows a reviewer to load capsule endoscopy images from a folder. Then, the software processes each image and exports its corresponding 3-D represented image in a proprietary format of Matlab® (.fig extension). For the evaluation process, another Matlab® program with a user interface was devised. The program consists of two windows in which the conventional 2-D small-bowel CE image and its corresponding 3-D represented image are given (Figure 7.2). The reviewer can rotate and zoom in on the 3-D images. At the bottom of the screen, a single question regarding the efficiency of the 3-D representation is given. Five possible answers to choose from are also presented. After selecting the desired answer the reviewer clicks next to proceed to the next case. This process is performed until the program reaches the last case after which each separate evaluation is concluded.

7.2.8 Raters and outcome measures

Seven reviewers – each with substantial experience in GI endoscopy, but variable experience in the interpretation of CE images – participated in **Phase 2**. Reviewers were unaware of each other's evaluations. Each of the 3-D representation images were scored for textural enhancement of the depicted finding and therefore categorized as improved/non-improved. To evaluate whether the 3-D representation tool improves visualization of small-bowel CE images, reviewers were asked to compare each 3-D represented image with a corresponding 2-D counterpart and to rate it according to the following scale:

- +2 or definitely improved;
- +1 or somewhat improved;

0 or no different/equivalent to conventional 2-D image;

-1 or somewhat worse; and

-2 or definitely worse.

Thereafter, reviewers' scores were tallied and the average score for each image was calculated (Imagawa et al. 2011). To simplify analysis the data are presented in three categories:

1) *improved* if average score ≥ 1;

2) same if average score was 0.99 to -0.99; and

3) worse if average score ≤ -1.

The following subgroup analyses were performed: evaluation of 3-D representation according to groups described above, i.e. predominant colour of depicted structure, surface morphology, diagnostic category and diagnosis; the equipment generating the 2-D image (PillCam® vs Mirocam®); and the CE experience of raters. Inter-observer agreement was calculated for each image group (vascular, inflammatory and protuberant).

Furthermore, reviewers were advised to leave each 3-D image at an angle most consistent with their grading so that mean angles for right/left and up/down (for each image group) could be calculated.

7.2.9 Ethics consideration

This study was conducted in accordance with UK research ethics guidelines. After review by the local ethics committee, further specific ethical review and approval were not required, as the study was considered an evaluation of previously collected images, using data already obtained as part of regular patient care.

7.2.10 Statistical analysis

For numerical variables, values are expressed as mean (\pm standard deviation, SD). The *t*-test for continuous variables and the chi-square (χ^2) test for categorical variables were used. A two-tailed *P* value <0.05 was considered statistically significant. Pearson's agreement correlation was used for phase 1 of this study. For phase 2, inter-observer agreement was measured by free-marginal multi-rater kappa statistics (Viera, Garrett 2005) using an online Kappa Calculator, available at http://justusrandolph.net/kappa/; (accessed November 24, 2012). A sample size of 192 images provides a margin of error of 7.04% (as calculated by an online sample size calculator, available at http://www.raosoft.com/samplesize.html). *Kappa* < 0.4 was considered as slight agreement whereas between 0.41–0.6 as moderate, 0.61–0.80 substantial, and 0.81–1.00 as excellent agreement. All other statistical analyses were performed using a statistical package, StatsDirect® (StatsDirect Ltd, Altrincham, Cheshire, UK).

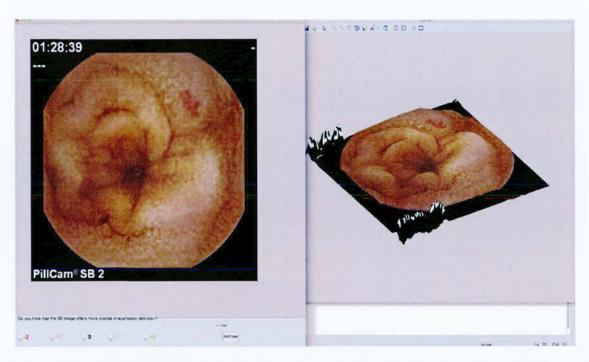


Figure 7.2: The 3-D image representation software evaluation interface in a $\mathsf{Matlab}^{\scriptscriptstyle \oplus}$ environment.

7.3 Results

7.3.1 Phase 1 - results

Overall, phantom experiments showed that the SfS algorithm was 90%, 70% and 45% (P=0.14) accurate in interpreting the protruding or non-protruding surface nature of red, yellow and white phantom models, respectively (**Figure 7.3**). Sensitivity and specificity of the above evaluation was 80% and 100% for red-coloured objects; 81.3% and 25% for yellow-coloured objects; 100% and 21.3% for white-coloured objects. Lastly, Pearson's correlation was 0.93, 0.63 and 0.35 for red, yellow and white, respectively.

7.3.2 Phase 2 – selected CE images

The number of images selected for each category, according to the SBCE system used, and the type of findings is tabulated in **Table 1**. Overall, there was no statistically significant difference in the number of images included per diagnostic category for vascular, inflammatory and protruding structures/lesions, (P = 1.0, 0.359, 0.435, respectively).

7.3.3 Phase 2 – image evaluation and sub-analysis

For the entire image group (n = 192) and all (n = 7) reviewers, 51/192 (27.6%) was evaluated as improved (better) with 3-D representation and 141/192 (73.4%) as equivalent to their 2-D counterparts. Sub-analysis per predominant colour revealed that 3-D representation improved red, white, mixed and lesions with colour similar to the surrounding mucosa in 53.7% (29/54), 21.8% (12/55), 17.3% (5/29), and 9.2% (5/54) of cases, (P < 0.0001).

Diagnostic category	N	Small-bowel CE PillCam® - MiroCam®	P value
VASCULAR (n=50)		25-25	1.0
Angioectasias	50	25-25	
INFLAMMATORY (n= 79)		28-45	0.36
Mucosal cobblestone	9	4-5	
Mucosal breaks/aphthae	21	11-10	
Mucosal ulcers	25	7-18	
Mucosal fold/Villous oedema	18	6-12	
PROTRUDING (n= 69)		31-38	0.43
Lymphomas	3	0-3	
Polyps	10	5-5	
Chylous cysts	11	5-6	
Lymphangiectasias	13	8-5	
Lymphoid hyperplasia	15	5-10	
AoV	17	8-9	

Table 7.1: Evaluated images in total and per small-bowel CE system used (PillCam®-MiroCam®).

Abbreviations: AoV: ampulla of Vater; N: number; CE: small-bowel CE.

Sub-analysis per surface morphology showed that 3-D representation was felt to improve evaluation in 14/67 (20.9%) of convex findings, 33/103 (32%) of flat/concave findings and 4/22 (18.2%) of combi-surface morphology findings, P = 0.1929.

- Sub-analysis per diagnostic category; 56% (28/50) of vascular, 23.2% (16/69) of protruding, and 9.6% (7/73) of inflammatory lesions were evaluated as showing enhanced textural features on 3-D representation (Figures 7.4-6, Table 7.2).
- Sub-analysis per diagnosis revealed that evaluation of angioectasias with 3-D representation showed improved visualization in 56% (28/50); chylous cysts 36.36% (4/11); polyps/neoplastic lesions 30.76% (4/13); LNH 26.6% (4/15); mucosal cobblestone 22.2% (2/9); lymphangiectasias 15.38% (2/13); AoV 11.76% (2/17); mucosal ulcers/erosions/aphthae 8.69% (4/46); and villous/fold oedema 5.55% (1/18), (P <0.0001).</p>
- o Sub-analysis per SBCE system revealed that 3-D representation led to enhanced visualization in 20.2% (17/84) of images obtained with PillCam® and 31.5 % (34/108) of images captured by Mirocam®, P = 0.099.
- o Sub-analysis per CE reviewer experience (for the entire image series); there was statistically significant difference between the rating from experienced CE and non-CE readers (77/192 vs 51/192, P <0.007). For both evaluators' sub-groups though, no image was perceived as worse than its 2-D equivalent. The results of the comparison between CE and non-CE readers according to type of lesion and SBCE equipment generating the 2-D images are summarized in **Table 7.3**. Inter-observer agreement was at <0.4 for the entire group of images, as well as when each diagnostic category was examined separately. The *kappa* statistics for all raters, CE readers and non-CE readers is presented in **Table 7.4**.

n/N (%)	
34/108 (31.5)	
17/84 (20.2)	
28/50 (56.0)	
16/69 (23.2)	
7/73 (9.6)	
29/54 (53.7)	
12/55 (21.8)	
5/29 (17.3)	
5/54 (9.2)	
51/192 (26.6)	
	34/108 (31.5) 17/84 (20.2) 28/50 (56.0) 16/69 (23.2) 7/73 (9.6) 29/54 (53.7) 12/55 (21.8) 5/29 (17.3) 5/54 (9.2)

Table 7.2: Image enhancement with the three-dimensional image representation software, as per small-bowel capsule endoscope system, image group and colour of structure/finding.

CE readers (%)	Non-CE readers (%)	P value
38/50 (76.0)	24/50 (48.0)	0.007
31/69 (44.9)	12/69 (17.4)	0.008
8/73 (10.9)	15/73 (20.5)	0.172
77/192 (40.1)	51/192 (26.6)	0.006
	38/50 (76.0) 31/69 (44.9) 8/73 (10.9)	38/50 (76.0) 24/50 (48.0) 31/69 (44.9) 12/69 (17.4) 8/73 (10.9) 15/73 (20.5)

Table 7.3: Sub-groups analyses performed for capsule endoscopy and non-capsule endoscopy readers. Abbreviations: CE, capsule endoscopy.

Raters groups	All images	Diagnostic	Category	
		Vascular	Inflammatory	Protuberant
All readers (n=7)	0.182	0.163	0.193	0.185
CE readers (n=3)	0.164	0.358	0.115	0.082
Non-CE readers (n=4)	0.301	0.3	0.318	0.29

Table 7.4: Inter-observer agreement for all reviewers (and per CE reviewing experience groups) for all images and per diagnostic category. Abbreviations: CE, capsule endoscopy.

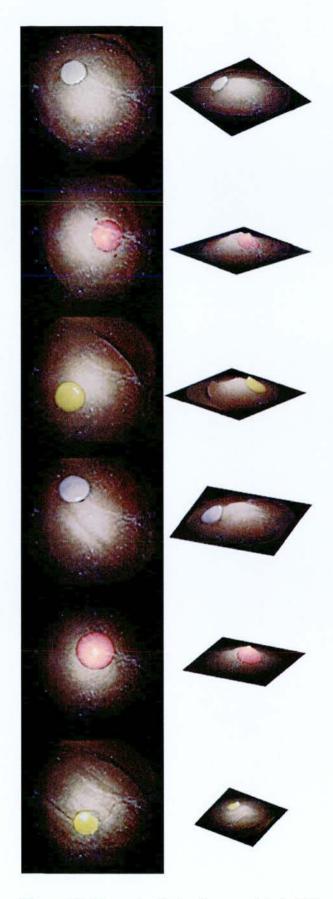
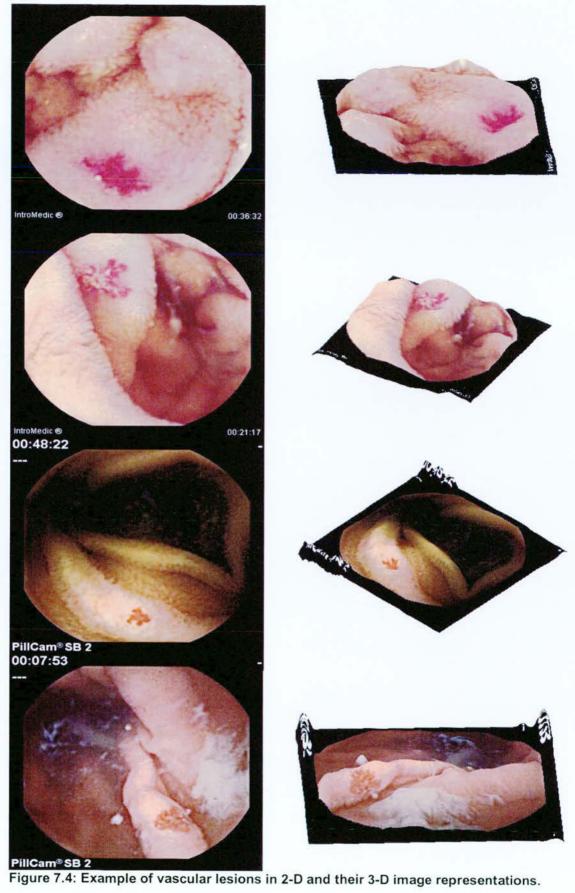


Figure 7.3 Example of phantom models in 2-D and their 3-D image representations.



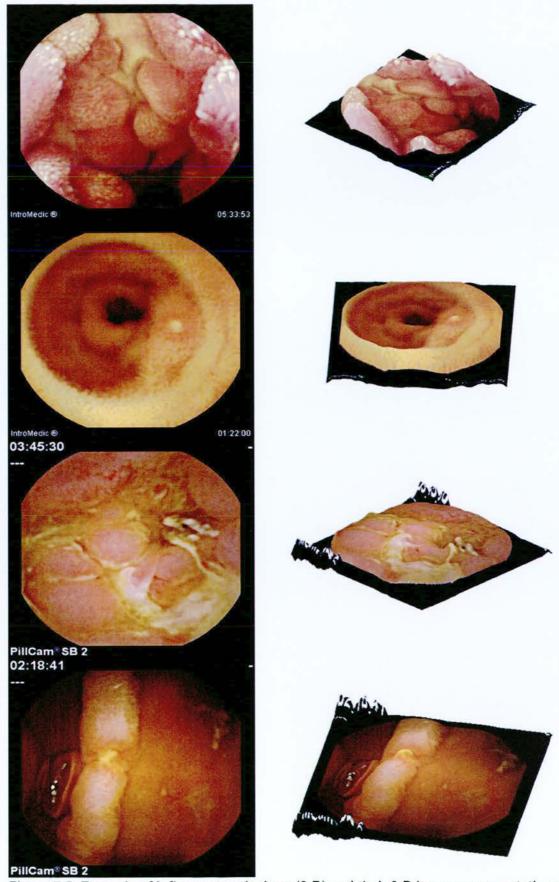


Figure 7.5: Example of inflammatory lesions (2-D) and their 3-D image representations

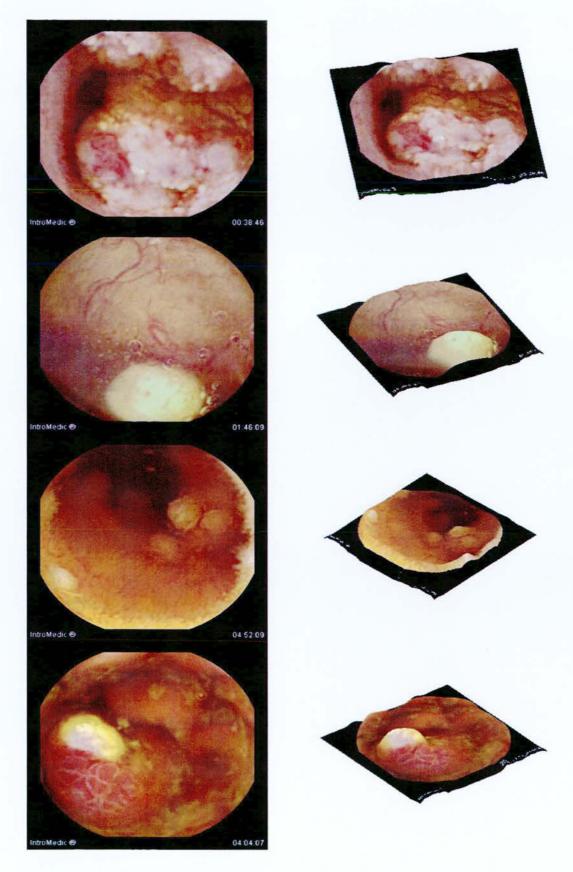


Figure 7.6: Example of protruding structures/lesions in 2-D and their 3-D image representation.

7.4 Discussion

Hardware-based reconstruction is based on stereoscopic vision, where multiple image sensors are used to provide the necessary information for depth retrieval. Stereoscopic approaches utilize at least two images – of the same target – at two different angles of view. Hence, a typical 3-D imaging system comprises two independent cameras, each camera contributing one viewpoint. However, inclusion of two cameras within a CE device to create a stereo-image can be unwieldy (Fisher and Hasler 2012). Therefore, a couple of important 3-D hardware-enabled endoscopy technologies have been proposed (Kolar et al. 2009), presenting a system that can give – in real time – both 3-D and texture information using an infrared projector and a CMOS camera; the major disadvantages of this system are its size and power consumption. Lately, thera are promising reports for endoscopic 3-D imaging that uses a single lens system. This technique creates two viewpoints in a single-lens camera by placing a bipartite filter at the limiting aperture, but this is still to be incorporated in a small-bowel CE device.

Therefore, in the current absence of a hardware-enabled 3-D reconstruction Karargyris et al. (2011), recently proposed the use of a 3-D software-enabled technique (SfS) for CE videos. The algorithm is very fast and 'behaves' reasonably well with specular textures (Koulaouzidis and Karargyris 2012). Eventually, all SfS techniques, such as the linear method of Tsai, take a single 2-D input signal, i.e. a conventional small-bowel CE image and through a series of mathematical transformations (energy minimization) produce a corresponding 3-D representation image. Strictly from a mathematical point of view, since 3-D represented images are derived from monocular 2-D conventional CE images, only visualization changes. Essentially, this means that the image information does not change.

In order to assess the usefulness of this 3-D representation approach in small-bowel CE, we conducted a feasibility study including (a) a task simulator and (b) a clinical part. In the latter, we included reviewers from a wider endoscopic audience and not only CE readers. Moreover, the clinical small-bowel CE images we selected cover a wide range of findings in CE, and they were categorised as per group/type of finding and type of small-bowel CE system used to produce the 2-D image.

Overall, the simulator showed that 3-D representation software gives a 90%, 70% and 45% accuracy when it comes to predicting the protruding, or not, nature of red, yellow and white phantom models, respectively. Furthermore, the clinical study showed that in using 3-D representation software in images obtained from small-bowel CE, about a quarter (26%) of them present enhanced visualization features, as compared to their 2-D conventional counterparts. This effect is independent of the type of small-bowel CE system used (see **Table7.2**).

Having observed increased accuracy of the 3-D software for red-coloured phantoms and less so for yellow- and white-coloured, it is not surprising that major improvement is observed for vascular lesions (56%), whereas moderate (23%) and low (<10%) is noted for inflammatory and protruding findings, respectively. Recently, it has been reported that vascular lesions represent the majority of smallbowel pathology identified by means of capsule endoscopy and account for about 50% of small-bowel CE diagnostic yield in patients with obscure GI bleeding (Liao et al. 2010). An improved visualization using 3-D reconstruction was shown only for vascular lesions. It is of course to an extent inopportune that findings presenting better delineation with 3-D enhancement, i.e. angioectasias, are those most easy to recognize using a standard visualization. This is likely to be due to the fact that vascular lesions, even those of small size, present a clear margin, a well-defined lesion border and a definite colour difference with the surrounding mucosa. One could argue that regularly implementing this image-enhancement tool in smallbowel CE could lead to improved vascular lesion detection. Furthermore, perhaps it would be clinically relevant to further investigate whether 3-D representation may provide a classification of such lesions in order to identify those at higher risk of bleeding (Spada et al. 2011).

The most difficult lesions to be visualized and categorized are flat/concave lesions and/or neoplastic lesions where the improvement of 3-D reconstruction seems to be marginal. One might expect that a 3-D representation would perform best in enhancing differences between flat and protruding lesions; certainly, the results of the task simulator were reassuring in this regard. This has not become evident though in our second-stage clinical assessment. A plausible explanation is that real-life protruding small-bowel structures or lesions are not necessarily entirely, or

solely, red and more likely to have mixed colouring or be similar to that of the surrounding mucosa (e.g. AoV, small-bowel polyps or masses etc.). Furthermore, lack of insufflation in SBCE often causes a protruding lesion to appear only in part in the video frames as a 'fold between folds', i.e. not as a defined luminal protrusion. Even for experienced CE readers, protruding lesions often represent a significant diagnostic challenge, particularly when the distinction between masses and bulges is at stake (Girelli et al. 2011). Nevertheless, readers with CE experience noted a significantly higher improvement as compared to non-CE readers (44.9% vs 17.4%).

Interestingly, when we analysed the evaluation results based on the assessor's SBCE experience, it became obvious that physicians experienced in CE review, i.e. assessors most used to 2-D SBCE images of small-bowel pathology, described a significantly higher image improvement with the use of the 3-D enhancement tool, $38/50 \text{ vs } 24/50 \ (P=0.007) \text{ and } 31/69 \text{ vs } 12/69 \ (P=0.008),$ for angioectasias and protruding findings, respectively. Conversely, in the inflammatory lesions image group, both CE and non-CE readers agreed that 3-D offered only a limited textural/feature enhancement with 8/73 vs 15/73 respectively, P=0.172. These results may simply reflect familiarity with SBCE reviewing software and/or image manipulation or merely enthusiasm bias. In that respect, we believe that including a diverse group of GI endoscopists – all with advanced image-interpretation skills but variable experience in CE images interpretation – provides a more balanced evaluation of this enhancement tool.

The present study has few limitations: firstly, in order to test the performance of the 3-D software, we selected high-clarity small-bowel CE images; hence, we do not know if our results can be reproduced with images obtained in everyday SCBE practice, where the presence of intraluminal debris or opaque fluid can affect the overall visibility and 3-D representation of small-bowel findings. Secondly, the heterogeneous group of raters/assessors could be considered by some as a potential limitation of this evaluation. Thirdly, although we attempted a subgroup analysis per type of small-bowel CE system, raters where not blinded to the brand of small-bowel CE used to obtain the 2-D image, as eventually the two small-bowel CE systems produce images with different characteristics. Furthermore, some inherant

limitations of the software should be taken into account, i.e. many objects in the real world are dielectric and homogeneous, hence displaying dual reflections. In fact, this might be responsible for the only fair inter-observer agreement of this study. Most digestive structures fall into this category. Therefore, when the light beams fall on to such an object, some of them reflect back immediately, creating the specular reflection; the rest firstly penetrate the object and then reflect, creating the diffuse reflection. This phenomenon creates highlights, which distort the outcome of any 3-D image representation.

7.5 Conclusion

Until optics technology matures enough to allow a hardware-enabled 3-D reconstruction of the GI tract (Barkhoudarian et al. 2013; Kolar et al. 2010), 3-D representation software offers a plausible alternative for 3-D representation of conventional CE images. The present study, the first of its kind, examines the potential usefulness of 3-D representation based on subjection evaluation by experienced CE reviewers. However, further analysis of the clinical validity of 3-D on diagnostic accuracy is needed; therefore, the main aim of the following chapter is to evaluate the effect of 3-D software application on diagnostic accuracy.

CHAPTER 8

Revisiting the 'mass or bulge' question in small-bowel capsule endoscopy with the help of three-dimensional reconstruction software.

- 8.1 Introduction
- 8.2 Materials and methods
- 8.2.1 Phase 1 choosing the optimal angle for 3-D video reconstruction
- 8.2.2 Phase 2 evaluation of 3-D videos review
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- 8.2.5 Ethics consideration
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- 8.3.1 Phase 1 choosing the optimal angle for 3-D reconstruction
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- 8.4 Discussion
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8.1 Introduction

Since its introduction in clinical practice in 2001, small-bowel CE has become a prime mode for the evaluation of the small-bowel in several clinical settings such as OGIB and CD (Wang et al. 2013). In this context, small-bowel CE has a high DY and a positive impact on cost-effectiveness and patient management (Marmo et al. 2007; Gerson 2012). The commonest small-bowel findings, i.e. angioectasias, ulcers and/or luminal stenosis, are easy to recognize and they are rarely missed (Lewis et al. 2005). Conversely, large small-bowel protruding lesions, e.g. small-bowel mass lesions can be missed by CE; hence the value of a negative small-bowel CE in excluding sinister small-bowel pathology remains unclear (Chong et al. 2006; Baichi et al. 2007; Postgate et al. 2008; Lewis et al. 2008; Zagorowicz et al. 2013). Furthermore, those of us who routinely read SBCE studies will attest that luminal protrusions in SBCE are a common finding.

Luminal protrusions with changes in colour (erythema) and signs of mucosal disruption (exudates, erosions and ulcers) are highly suggestive of a neoplastic process; in the majority of cases though, the CE appearance of mass lesions is not dissimilar to that of innocent mucosal bulges (MB). MB are defined as round, smooth, large-based luminal protrusions with ill-defined boundaries, resulting either from loop angulations and/or impression from adjacent loops/structures (Girelli and Porta 2008; Mergener et al. 2007). They are benign endoscopic findings of no clinical significance (Wang et al. 2013; Islam et al. 2013). Therefore, an accurate distinction between masses and MB is crucial, as missing a tumour can eventually jeopardize a curative resection and patient prognosis; on the other hand, misclassifying an innocent small-bowel MB as a neoplastic mass may lead to unnecessary, invasive and – most of the time – expensive procedures.

Therefore, software tools, e.g. FICE, Blue Mode and/or SBI have been developed to assist capsule reviewers with the, so called, 'difficult' to characterize small-bowel lesions (Koulaouzidis et al. 2013). Furthermore, research has been recently carried out to produce 3-D reconstruction of the GI tract using stereoscopic vision methods

(Kolar et al. 2010). However, as aforementioned (chapters 6 and 7), due to technological limitations, i.e. packaging in capsule-size endoscopes and powerconsumption constraints, hardware-enabled 3-D reconstruction of the intestinal lumen is yet to be available (Karargyris and Bourbakis 2011; Koulaouzidis and Karargyris 2012). Over the last few years, software that enables 3-D representation/approximation (SfS) from monocular 2-D small-bowel CE images has been developed. This software recovers the shape of objects from 2-D images using gradual variation of shading (Tsai and). In the previous chapter, it is evident that the application of such software in CE leads to improved visualization/image enhancement for a significant proportion of vascular and protruding small-bowel lesions (Koulaouzidis et al. 2013). However, this reconstruction has been applied only to still images, not to video segments, and it is not clear whether the subjective enhancement is associated with a clear clinical impact; furthermore, the majority of studies performed thus far were focusing more on technical aspects, i.e., quality of images/visualization (Fan et al. 2010; Prasath et al. 2012; Koulaouzidis et al. 2013) than on clinical issues, i.e. reaching a diagnosis (Ciaccio et al. 2013).

In this two-phase study, we aimed to evaluate whether coupling the standard 2-D (s2-D) video clips with a 3-D reconstruction enhanced the performance of small-bowel CE readers (with different levels of CE experience) in distinguishing masses from innocent MB.

8.2 Materials and methods

8.2.1 Phase 1 – choosing the optimal angle for 3-D video reconstruction

PillCam®SB2 (Given®Imaging Ltd, Yoqneam, Israel) captures two 2-D fps. These images are displayed in sequence, as the relevant proprietary software (*RAPID®*) generates a video that gives the impression of movement of the capsule through the small-bowel. In order to recreate 3-D video clips for the purpose of this study, short 2-D video segments were selected and 'broken down' into the frames that constituted them. Individual frames were 3-D reconstructed and recompressed to relevant 3-D videos. For this task, dedicated 3-D visualization software was developed in a Mathworks®Matlab environment. It should be noted that when a single image is reconstructed in 3-D, the user can manipulate the viewing angle and rotate at 360°degrees and zoom in/out, whereas there is no freedom to rotate the viewing angle of all the 3-D images stitched together in a 3-D video. For this reason, before proceeding with the main evaluation, it was necessary to decide which is the optimal viewing angle for 3-D reconstruction of individual frames before they are stitched back again into a 3-D video.

To select the best angle for reconstruction, 10 three-minute-long, 2-D small-bowel CE videos (containing about 360 frames each), depicting small-bowel luminal protrusions (small-bowel cancer 1; polyps 3; bulging 4 and AoV: 2) were selected by an expert small-bowel CE reviewer (GM), de-identified and stored in a folder for further processing. Using the aforementioned software, for each standard s2-D video clip, a corresponding 3-D clip was reconstructed at 25°, 35°, 45°, 55°, 65°, 75°, and 85° degrees. This resulted in a total of 70 short 3-D video clips (**Figure 8.1**).

Three experienced small-bowel CE reviewers (AK, SD, ER), all with extensive experience in small-bowel CE and blinded to each other (but aware of the finding depicted in each video-clip), reviewed the clips in random order. Prompted by the question:

'Is this 3-D reconstructed video clip helpful in facilitating the elevated lesion/structure from the surrounding mucosa in the clip?'

they were asked to assign a number between 1 (not helpful) and 5 (very helpful), for each of the seven different angles of 3-D reconstruction of each 2-D video. Thereafter, the scores were tallied (the maximum score for each group of ten 3-D reconstructed videos – at a certain angle – was 50); the 3-D reconstruction angle with the higher score was used for the rest of the 3-D video reconstructions in phase 2 of this study.

8.2.2 Phase 2 - evaluation of 3-D video reviews

8.2.2.1 Video selection

For phase 2 of this study, three gastroenterologists experts in small-bowel CE (CG, MS, LF) selected and de-identified short (5 min) video clips (from an equal number of SBCE examinations performed in two centres CG and LF – Ospedale Busto Arsizio, Milano; MS – Ospedale San Carlo Borromeo, Milan, Italy) containing either masses or MB. If obvious endoscopic markers of possible malignancy (i.e. mucosal disruption, surface ulceration, active bleeding) were identified, the videos were excluded. All small-bowel CE examinations were performed with the capsule system used in the first phase of the study. Small-bowel CE was carried out after an overnight fast and bowel cleansing by 2 1 of polyethylene glycol (PEG) solution, taken the afternoon prior to the small-bowel CE investigation. As per manufacturer protocol, liquids are allowed two hours into the study and a light meal four hours following the ingestion of the capsule.

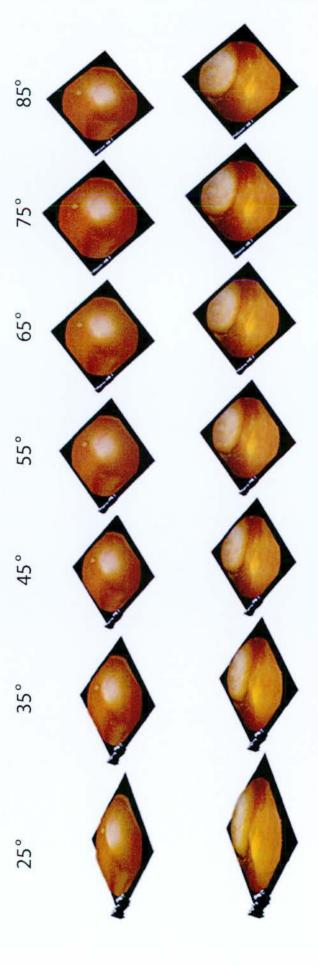


Figure 8.1: Two 2-D small-bowel CE frames reconstructed in 3D using the SfS algorithm at the 7 angles (25°, 35°, 45°, 55°, 65°, 75°, and 85° degrees). Abbreviations: 2-D, two-dimensional; CE, capsule endoscopy; 3-D, three-dimensional; SfS, shape-from-shading.

8.2.2.2 Video evaluation

Videos clips were de-identified, encoded to ensure blind review and stored in a dedicated Dropbox[™] folder. The Matlab® software reconstructed the 3-D videos at the optimal 3-D viewing angle (as per the first phase of the study). These videos were uploaded to the shared folder on Dropbox[™]. The folder was shared among the reviewers for easier access.

Two small-bowel CE readers groups were involved in the evaluation: a group of small-bowel CE experts (n = 3; all >1,000 small-bowel CE reviews; more than 10 years of experience), and a group of novice readers (n =3; competent in conventional digestive endoscopy, familiar with the SBCE system, who received training on CE for the purpose of this study, but not completed >10 SBCE reviews, nor working with SBCE in routine clinical practice) (Rajan et al. 2013). To avoid any possible 'referral bias' in evaluating video clips, the readers were unaware of the clinical indication to small-bowel CE.

All readers, blind to each other and in a random order, reviewed first the s2-D small-bowel CE videos (provided to them in avi. format) and then 5–7 days later, in order to minimize the 'recall' bias, the 'combined' 2-D+3-D video clips (Figure 8.2). In the 'combined' 2-D+3-D view the reader was able to visualize side to side the 2-D and the reconstructed 3-D video of the same patient; he/she was free to visualize them in sequence or at the same time and to repeat the visualization several times. For each case, the diagnosis (mass or MB) reached after s2-D and 2-D+3-D review – by each individual reader and group – was compared with that of the reference standard (RS) (Figure 8.3).

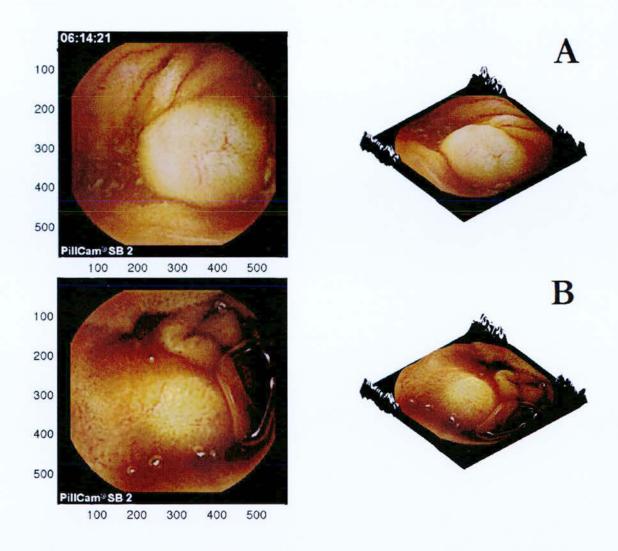


Figure 8.2: Two small-bowel CE frames depicting a mass (A) and bulging (B) with their corresponding 55° 3-D reconstruction. Abbreviations: CE, small-bowel capsule endoscopy; 3-D, three-dimensional.

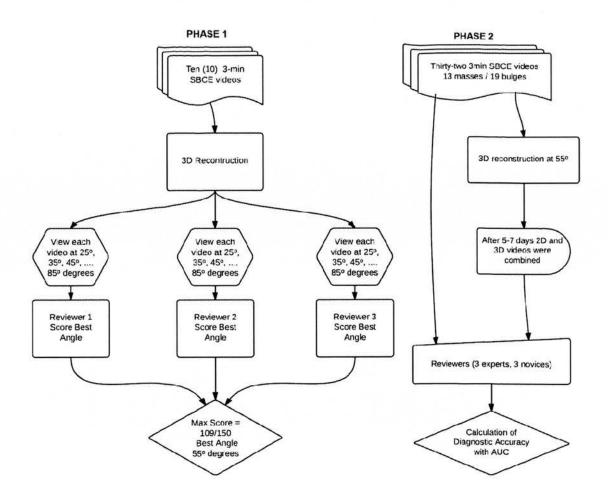


Figure 8.3: Flowchart of study phase 1 (left side) and phase 2 (right side).

8.2.3 Reference standard

In our study, the presence of a small-bowel mass has to be confirmed by histology (reference standard for positive diagnosis) or excluded after a complete diagnostic work-up and clinical follow-up (reference standard for negative diagnosis). For these purposes all the included patients received an individualized diagnostic work-up including computed tomography enterography (CTE), and/or magnetic resonance enterography (MRE), and/or antegrade or retrograde double-balloon enteroscopy, and/or surgical exploration, as necessary. If after the diagnostic work-up no mass was found, patients were clinically followed-up for a period of six months prior to medical discharge, and the finding identified by small-bowel CE was therefore defined as an innocent MB (Figure 8.3).

8.2.4 Statistics

Individual and per-reader group (experts/novices) sensitivity, specificity, positive and negative likelihood ratios (LR) were calculated for each of the reviewers. Diagnostic accuracy [true positive (TP) + true negatives (TN)/TP + false positive (FP) + false negative (FN) + TN)] and precision (TP/TP+FP) were also calculated. In addition, individual and summative receiver-operating characteristics (ROC) analysis was undertaken. The ROC curve is initially constructed by plotting the sensitivity and the false positivity (1-specificity) for each reviewer. The ROC curve is then constructed to fit these points. The area under the ROC curve (AUC) is then calculated. An AUC close to 1.0 signifies that the test has near perfect discrimination and AUC close to 0.5 suggests poor discrimination (Harrell et al. 1996). The AUC comparison was performed by comparing the square of their standardized difference to the quartiles of the chi-square distribution. The analyses were performed with stata 13 (© Copyright 1996–2013 StataCorp LP, Texas, USA) using the function roccomp as described in detail elsewhere (Hanley et al. 1983; DeLong et al. 1988).

Inter-observer agreement, for each group and each reviewing session, was measured by the kappa statistic using the Randolph's free-marginal multi-rater kappa; κ (Randolph 2005). In 1981, Brennan and Prediger suggested using free-marginal κ when raters are not forced to assign a certain number of cases to each category and using fixed-marginal κ when they are (Brennan and Prediger 1981). A negative value represents agreement worse than chance, whereas values in the range of 0 to 0.25, 0.25–0.50, 0.50–0.75 and 0.75–1.00 represent poor, fair, good and near perfect agreement, respectively (Landis and Koch 1977).

8.2.5 Ethics consideration

This study was conducted in accordance with established research ethics guidelines. After review by the local ethics committee, further specific ethical review and approval were not required, as the study was considered an evaluation of previously collected endoscopy images, using data already obtained as part of regular clinical care. Patients gave their written, informed consent for the studies undertaken a part of clinical workup.

8.3 Results

8.3.1 Phase 1 – choosing the optimal angle for 3-D reconstruction

The 3-D video reconstruction at 55° obtained the highest score from each of the three experts individually (38/50, 28/50 and 33/50 respectively) as well as summative (109/150) and mean score (3.7/5). Scores obtained by the three expert readers are tabulated in **Table 8.1**.

3-D viewing angle	Expert 1	Expert 2	Expert 3	Summative score	mean
Videos reconstructed at 25° degrees	11/50	13/50	23/50	47/150	1.6
Videos reconstructed at 35° degrees	18/50	16/50	19/50	53/150	1.8
Videos reconstructed at 45° degrees	27/50	21/50	25/50	73/150	2.4
Videos reconstructed at 55° degrees	38/50	38/50	33/50	109/150	3.7
Videos reconstructed at 65° degrees	36/50	29/50	32/50	97/150	3.2
Videos reconstructed at 75° degrees	23/50	37/50	32/50	92/150	3.0
Videos reconstructed at 85° degrees	15/50	31/50	29/50	75/150	2.5

Table 8.1: Summative and mean score for 3-D reconstructed videos according the angle of view. Abbreviation: 3-D, three-dimensional.

8.3.2 Phase 2 – Distinguishing between mass and bulge (with 3-D review)

Thirty-two short videos were selected (25 contributed by CG and LF; 8 by MS). Thirteen of them were classified by the RS as depicting masses and 19 MBs. More specifically 6 neuroendocrine tumours, 5 gastrointestinal stromal tumours and 2 adenocarcinomas were finally diagnosed.

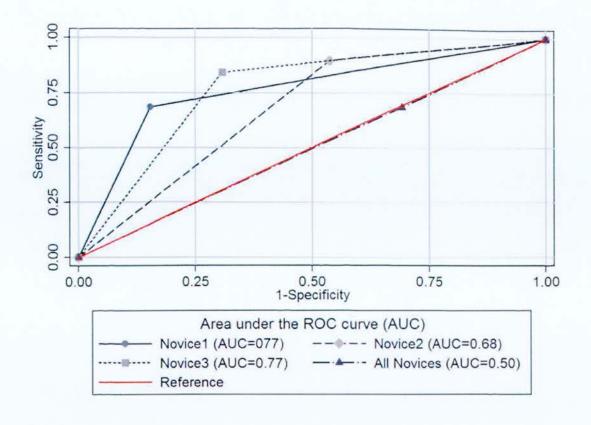
The sensitivity, specificity, positive and negative LR for individual reviewers is presented in **Table 8.2**. In the 2-D video reviews, the summative diagnostic accuracy/precision for experts and novices were 0.87/0.65 and 0.79/0.5, respectively. In 'combined' 2-D+3-D video reviews, the relevant values for experts and novices were 0.81/0.52 and 0.87/0.79, respectively.

The summative AUC for the expert and novice groups with s2-D review was 0.74 and 0.5, respectively (P = 0.0053). The summative AUC for the expert and novice groups with 'combined 2-D+3-D' review was 0.70 and 0.57, respectively (P = 0.1846). Comparing the 2-D and the 2-D+3-D video reviews, no statistical difference in the AUC was observed among experts (P = 0.245), while a significant improvement was observed among novices (P = 0.049). The AUC for each of the two CE reviewers groups with 2-D and 2-D+3-D (as well as the summative ROCs) are showed in details in **Figure 8.4** and **Table 8.3**.

In 2-D review, the inter-observer agreement (κ) of experts and novices was 0.71 and 0.54, respectively. In 2-D+3-D review, the κ value for experts and novices was 0.58 for both groups.

REVIEWERS	REVIEWERS Sens (%) [95%CI]	5%CI]	Spec (%) [95%CI]	%ci]	(+)LR [95%CI]	F	(-)LR [95%CI]	(CI)
	s2-D	2-D+3-D	s2-D	2-D+3-D	s2-D	2-D+3-D	s2-D	2-D+3-D
Expert 1	83 [70;96]	100 [90.6;100]	90 [79.6;100]	84 [71.3;96.7]	8.3 [3.4;960]	6.3 [3.2;30.3]	0.2 [0.0;0.4]	0 [0;0:1]
Expert 2	83 [70;96]	100 [90.6,100]	90 [79.6;100]	63 [46.3;79.9]	8.3 [3.4;960]	2.7 [1.7;5.0]	0.2 [0.0;0.4]	0 [0;0.2]
Expert 3	83 [70;96]	92 [82.6;100]	85 [72.6;97.4]	79 [64.9;93.1]	5.5 [2.6;36.9]	4.4 [2.4;14.5]	0.2 [0.0;0.4]	0.1 [0;0.3]
Novice 1	85 [72.6;97.4]	[53;85]	68 [52.8;84]	84 [71.3;96.7]	2.7 [1.5;6.1]	4.3 [1.8;25.8]	0.2 [0.0;0.5]	0.4 [0.2;0.7]
Novice 2	69 [53;85]	64 [47.4;80.6]	84 [71.2;96.7]	100 [90.6;100]	4.3 [1.8;25.8]	640 [5;806]	0.4 [0.2;0.7]	0.4 [0.2;0.6]
Novice 3	46 [28.7;63.3]	46 [28.7;63.3]	89 [78.1;99.8]	89 [78.1;99.8]	4.2 [1.3;316.5]	4.2 [1.3;316.5]	0.6 [0.4;0.9]	0.6[0.4;0.9]

Table 8.2: Performances (sensitivity, specificity, likelihood ratio positive and negative) of novices and experts in reading 2-D and 2-D+3-D reconstructed videos. Abbreviations: Sens, sensitivity; Spec, specificity; LR, likelihood ratio; s2-D: standard two-dimensional; 3-D: threereconstructed videos. dimensional.



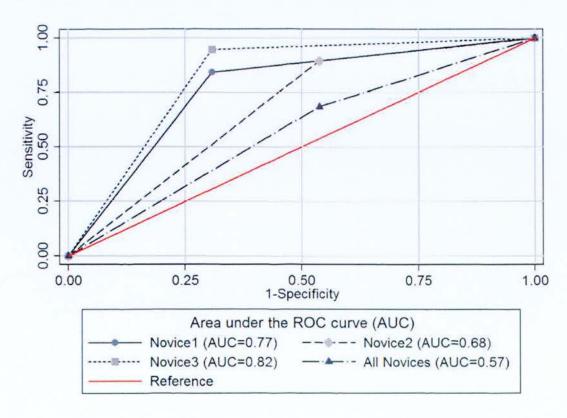


Figure 8.4 A: ROC curves for novices reading with 2-D (top figure) and 2-D+3-D videos (bottom figure). Abbreviations: ROC, receiver operating characteristics; 2-D, two-dimensional; 3-D, three-dimensional.

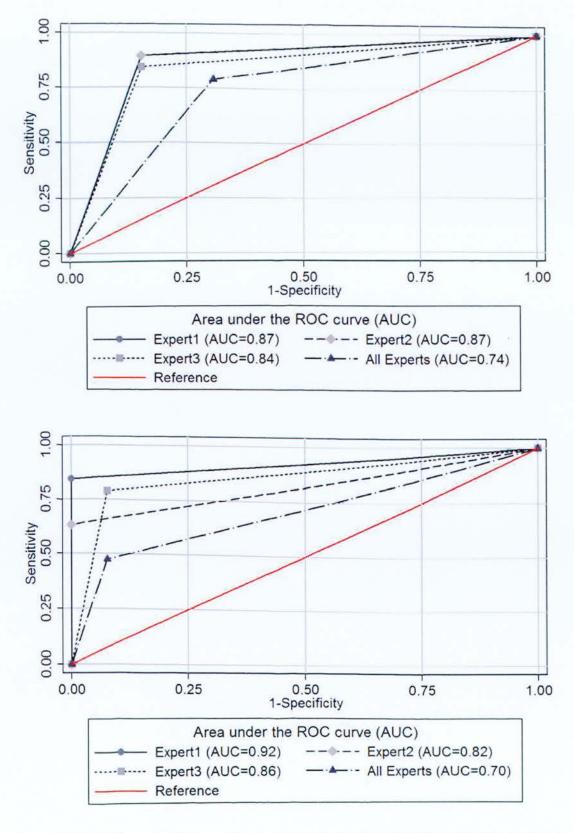


Figure 8.4 B: ROC curves for experts reading with 2-D (top figure) and 2-D+3-D videos (bottom figure). Abbreviations: ROC, receiver operating characteristics; 2-D, two-dimensional; 3-D, three-dimensional.

Туре	Group	AUC	[95% CI]	SE
2 -D	Expert 1	0.87	0.746 - 0.995	.06
	Expert 2	0.87	0.746 - 0.996	.06
	Expert 3	0.84	0.712 - 0.976	.07
	All experts	0.74	0.580 - 0.902	.08
2-D+3- D	Expert 1	0.92	0.837 - 1.0	.04
J	Expert 2	0.82	0.704 - 0.923	.06
	Expert 3	0.86	0.736 - 0.977	.06
	All experts	0.70	0.561 - 0.836	.07
2 -D	Novice 1	0.77	0.617 - 0.913	.08
	Novice 2	0.68	0.520 - 0.836	.08
	Novice 3	0.77	0.612 - 0.923	.08
	All novices	0.50	0.327 - 0.665	.09
2-D+3- D	novice1	0.77	0.612 - 0.923	.08
<u> </u>	novice2	0.68	0.520 - 0.836	.08
	novice3	0.82	0.679 - 0.960	.07
	all novices	0.57	0.396 - 0.750	.09

Table 8.3: Area under the ROC curve (AUC) of novices and experts in reading 2-D and 2-D+3-D reconstructed videos. Abbreviations: 2-D, two-dimensional; 3-D, three-dimensional; CI, confidence interval; SE, standard error.

8.4 Discussion

The present study confirms that the distinction between masses and bulges, in the s2-D small-bowel CE videos, remains a challenging task (even for expert CE readers); nevertheless, as expected, experienced readers perform better than novices. Noteworthy is that the addition of 3-D reconstructed video clips to the s2-D small-bowel CE reading software does not improve the performance of experts, while it significantly improves the performance of novice readers.

Small-bowel CE is an effective method of evaluating the small-bowel mucosa and it has been proved to have a higher DY when compared to other diagnostic techniques for the study of the small-bowel (Wang et al. 2013; Koulaouzidis et al. 2013). Since the advent of wireless CE, the small-bowel tumour detection rate has risen to 2-9% in those presenting with OGIB (Rondonotti et al. 2008). The greatest increase was seen in carcinoid tumours, followed by lymphomas and adenocarcinomas (Rondonotti et al. 2008; Islam et al. 2013). Nevertheless, several studies showed that SBCE can miss large (often sinister) protruding mucosal lesions (Postgate et al. 2008; Zagorowicz et al. 2013). The presence of a 'mass' can be the result of several processes, e.g. mucosal disruption by underlying pathology, a lesion with intact overlying intact mucosa (either due to submucosal or extramural/extrinsic origin) and/or false positive findings from bowel contraction, loop angulation or even intussusception (Mergener et al. 2007; Girelli and Porta 2008). Moreover, it has been shown that both the inter-observer agreement and the detection rate of significant findings are low, regardless of the readers' experience (Rondonotti et al. 2012; Zheng et al. 2012). A plausible explanation is that in conventional endoscopy, air insufflation (together with the ability to probe and/or take biopsies) are helpful in distinguishing between masses and innocent MB, whereas in CE this 'luxury' is lacking. Furthermore, a small-bowel lesion can be depicted only in a few frames and/or a mass may only be seen tangentially and it cannot be biopsied or probed (Wang et al. 2013; Islam et al. 2013).

False-positive findings are not uncommon either, therefore, the differentiation between masses and bulges in SBCE is still challenging (Islam et al. 2013). This is

clearly demonstrated by the performance of expert reviewers in evaluating s2-D video clips, where the summative diagnostic accuracy is high, albeit <90%. Furthermore, about 15% of cases are wrongly classified; interestingly, in 9% of cases a mass is classified as a MB, 'preventing' further work-up and eventually altering the prognosis of a potentially curable malignancy (Rondonotti et al. 2008). This is even more evident in the novices group, with a significant lower accuracy and AUC than the experts, confirming that experience seems to be a key factor in CE, influencing the correct evaluation of difficult findings.

To overcome the aforementioned confounders, a couple of novel indices/scoring systems (aiming to discriminate a mucosal bulge from a mass on CE) have been developed. Shyung et al. (2009) reported a score composed of five parameters, i.e. bleeding, mucosal disruption, irregular surface, colour and the presence of white villi. Small-bowel mass lesion is probable with a score ≥4, while a score of ≤2 indicates a low probability of a sinister lesion (Mergener et al. 2007; Shyung et al. 2009). However, this index takes into account 'high-risk' features such as bleeding, mucosal disruption and irregular mucosal surface, i.e. clear endoscopic markers of malignancy, adopted in the consensus statement (2006/2007) of a panel of international experts in capsule endoscopy as helpful discriminators (Mergener et al. 2007). More recently, Girelli and Porta noted that a smooth, round, protruding 'mass' exhibits the following characteristics when it is associated with the innocent MB: (1) an ill-defined boundary with the surrounding mucosa, (2) a diameter larger than its height, (3) no visible lumen in the frames in which it appears, and (4) an image lasting less than 10 minutes (Girelli and Porta 2008; Islam et al. 2013). Based on this observation, in a subsequent study, Girelli et al. proposed the Smooth Protruding Index on Capsule Endoscopy (SPICE) score (Girelli et al. 2011). A SPICE score of >2 has 83% sensitivity and 89% specificity for tumours (Girelli et al. 2011). Other attempts to differentiate tumours on CE include an automated scale that uses wavelet-based analysis in CE images; this has a reported 95% sensitivity and specificity (Kobayashi et al. 2012). Conversely, FICE offers no benefit in this setting over the standard reviewing mode (Kobayashi et al. 2012; Duque et al. 2012).

Therefore, we thought that software offering 3-D reconstruction – hence emphasizing certain endoscopy features such as the perception of depth and volume differences between the objects – could allow resolution of diagnostic dilemmas in such a setting. Furthermore, to the best of our knowledge, all previous studies on 3-D reconstruction were performed with individual frames/images (Fan et al. 2010; Prasath et al. 2012; Koulaouzidis et al. 2013; Ciaccio et al. 2013). The majority of these studies focused on technical issues (i.e. image quality, visualization) rather than on clear clinical issues (Fan et al. 2010; Prasath et al. 2012; Koulaouzidis et al. 2013). It is well known that in CE the video component is as crucial in the final intepretation (MB flattens with peristalsis) as cautious reviewing of still frames. Our data suggest that this new system does not have any impact in discriminating masses from bulges (when expert readers are involved). One can argue that the level of expertise of those involved in this study (experts> 1000 small-bowel CE reviews, longer than 10 years of clinical experience) negatively biased the contribution of the new software in this subgroup.

Furthermore, the fact that they are used to working with the s2-D software can explain why the introduction of the new feature might be challenging (Prasad and Cifu 2011). On the other hand, we selected novices who were already familiar with the s2-D and received training similar to that proposed by the American Society of Gastrointestinal Endoscopy (Rajan et al. 2013), but were at the beginning of using CE. Therefore, our results suggest that, although the new software cannot substitute clinical and small-bowel CE experience (even after the 3-D reconstruction novices' performance was poorer than those of experts) it may be helpful in the training phase by – potentially – shortening the learning curve.

This study has some limitations including small sample size (a consequence of the relative rarity of small-bowel tumours) and the inflexibility of the selected video clips review (short video clips in .avi format – it was not possible to modify review speed or change the angle of view). In addition, we decided to include only patients whose diagnosis was confirmed by a widely accepted 'hard' RS. Consequently, we selected cases by excluding all those with endoscopic high-risk 'stigmata' of mass lesions. However, the time for follow-up of six months may be seen as not adequate

for a complete assessment of this group.

Another possible limitation is a bias introduced by the combined evaluation of the 3-D reconstruction and the s2-D, instead of the 3-D reconstruction alone, of which we were fully aware. Nevertheless, we decided to combine 2-D with 3-D as the reconstruction of an eight-hour-long video in 3-D would require considerable time and resources. We aimed to simulate a clinical scenario, similar to that of other advanced endoscopic features (i.e. NBI, iSCAN, FICE), where the reader evaluates the video in the s2-D mode and applies the new feature (in our study, 3-D reconstruction) to a region of interest. The first phase of the study was performed to overcome issues with image angle of view. However, we cannot be certain that the angle chosen for 3-D applies to all lesions depicted in this current study. Nevertheless, this means that there are areas of future research in the use of 3-D alone or in combination with other software tools (Iakovidis et al. 2006).

8.5 Conclusion

The results of the present study confirm that the distinction between masses and MB in SBCE is still a challenging task even for experienced readers. In this situation, review experience seems to have a primary role. The addition of 3-D reconstruction to the s2-D video reading software significantly improves the performance of novice SBCE readers in distinguishing masses from MB, thus potentially shortening their learning curve. Further studies are needed to test the feasibility of 3-D reconstruction in clinical practice and to evaluate the impact on the reviewing process in terms of both time and DY.

CHAPTER 9

Conclusions and future directions

Optimal DY in small-bowel CE requires not only optimal visualization of the smallbowel mucosal surface and lumen, but also complete capsule transits through the entire small-bowel, i.e. total enteroscopy. Therefore, it is expected that decreasing GTT and SBTT will allow any capsule model to successfully reach the caecum by the end of its battery life (currently an average of 10-12 hours should be considered). The results of the conducted meta-analysis show that the use of prokinetics - and specifically that of metoclopramide with purgative and/or RTV - in small-bowel CE improves CR. The issue of improving CR in small-bowel CE is still contentious; although it is anticipated that in the foreseeable future the use of newer capsule endoscopes with extended battery life will improve both CR and - potentially - DY, there is a constant interest in standardizing the small-bowel CE procedure. This can only be seen, though, as a race against an ever-evolving technology. Historically, the CR of SBCE has been reported at a low 80% rate. Recently published national guidelines for the use of bowel preparation before video CE state that the use of prokinetics in small-bowel CE is not recommended. However, in chapter 2 a rigorous meta-analysis shows that, the 'smart', selective and judicious use (before as well as during small-bowel CE) of prokinetics in combination with other modalities, such as real time and/or purge, in improving the CR of SBCE.

Reading SBCE has certain limitations; firstly, the DY is usually dependent on the experience of the reader. Secondly, the uncontrolled capsule movement does not allow visualization of the entire small-bowel mucosa. However, the main limitation is that an accurate complete review of the generated lengthy video streams is time-consuming. Although there is no strict guidance for the best standard/conventional SBCE reading technique and speed, the unique features of SBCE require the reader to be intensely focused and alert. QV pre-read in urgent cases, but fails to show any benefit in other clinical scenarios. Although the benefits of QV are outweighed to some extent by a decrease in the overall diagnostic yield, this mode can be used

confidently in overt OGIB in an urgent inpatient setting and in outpatients with occult OGIB or suspected CD. As the usefulness of QV may vary, depending on the number of small-bowel lesions, standard review settings are still recommended in all other cases. Furthermore, the present study confirms that BM does not confer any additional advantage in the QV setting.

Apart from BM, the use of FICE in CE is limited. Its use improved the visualization/definition of mucosal aphthae/ulcers but made no difference to any other lesion groups. Conversely, BM improved most of the images (overall image enhancement 83%), with a range between 73.3% and 100%, in different lesion groups. BM filter showed promising results and its use as the main viewing mode, especially in cases of obscure GI bleeding, should be further examined in regard to feasibility and in connection with the DY.

An improved visualization using 3-D reconstruction was showed only for vascular lesions. The most difficult lesions to be visualized and categorized are flat/concave lesions and/or neoplastic lesions where the improvement of 3-D reconstruction seems to be marginal. One might expect that a 3-D representation would perform best in enhancing differences between flat and protruding lesions; this was not evident. A plausible explanation for this is that lack of insufflation in CE often causes a protruding lesion to appear only in part in the video frames as a 'fold between folds', i.e. not as a defined luminal protrusion. Until optics technology matures enough to allow a hardware-enabled 3-D reconstruction of the GI tract, 3-D representation software offers a plausible alternative for 3-D representation of conventional CE images.

Furthermore, the validity of this software is in improving decision making in the clinical scenario that is mass or bulge. The distinction between masses and MB in SBCE is still a challenging task even for experienced readers. In this situation, review experience seems to have a primary role. The addition of 3-D reconstruction to the s2-D video reading software significantly improves the performance of novice SBCE readers in distinguishing masses from MB, thus potentially shortening their learning curve. Further studies are needed to test the feasibility of 3-D

reconstruction in clinical practice and to evaluate the impact on the reviewing process in terms of both time and DY.

An area of future research remains open for the software tested in this thesis as well for other developments (software or hardware). However, it should not be forgotten that true 3-D capability requires dual video images, although the inclusion of two cameras within the shell of a capsule endoscopy might be unwieldy at present.

References

Anonymous. 2007. FDA Announces Discontinued Marketing of GI Drug, Zelnorm, for Safety Reasons. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm1088 79.htm

Anonymous. Available from: Available from: http://justusrandolph.net/kappa/

Anonymous. Available from: http://en.wikipedia.org/wiki/Lambertian_reflectance

Abdelaal UM, Morita E, Nouda S, Kuramoto T, Miyaji K, Fukui H, Tsuda Y, Fukuda A, Murano M, Tokioka S, Umegaki E, Higuchi K. 2010. W1594: new method for better detection and visualization of vascular and non-vascular lesions of small-bowel by using blue mode viewing: capsule endoscopy study [abstract]. Gastrointest Endosc 71(5):AB367.

Almeida N, Figueiredo P, Freire P, Lopes S, Lérias C, Gouveia H, Leitão MC. 2010. The effect of metoclopramide in capsule enteroscopy. Dig Dis Sci 55(1):153-57.

Aparicio JR, Martínez J, Casellas JA. 2009. Right lateral position does not affect gastric transit times of video capsule endoscopy: a prospective study. Gastrointest Endosc 69(1):34-37.

Apostolopoulos P, Kalantzis C, Gralnek IM, Liatsos C, Tsironis C, Kalantzis N. 2008. Clinical trial: effectiveness of chewing-gum in accelerating capsule endoscopy transit time--a prospective randomized, controlled pilot study. Aliment Pharmacol Ther 28(4):405-11.

Appalaneni V, Glenn T, Hoffman BJ. 2007. Video capsule endoscopy: accuracy of QuickView [abstract]. Gastrointest Endosc 65(5):AB313.

Appleyard M, Fireman Z, Glukhovsky A, Jacob H, Shreiver R, Kadirkamanathan S, Lavy A, Lewkowicz S, Scapa E, Shofti R, Swain P, Zaretsky A. 2000. A randomized trial comparing wireless capsule endoscopy with push enteroscopy for the detection of small-bowel lesions. Gastroenterology 119(6):1431-38.

Baichi MM, Arifuddin RM, Mantry PS. 2007. Small-bowel masses found and missed on capsule endoscopy for obscure bleeding. Scand J Gastroenterol 42(9):1127-32.

Barkhoudarian G, Del Carmen Becerra Romero A, Laws ER. 2013. Evaluation of the three-dimensional endoscope in transsphenoidal surgery. Neurosurgery 73(1 Suppl Operative):ons 74-8.

Barron JT, Malik J. Colour constancy, intrinsic images, and shape estimation. 2012. Fitzgibbon Andrew, Lazebnik Svetlana, Perona Pietro, Sato Yoichi, Schmid Cordelia (Eds.), Proceedings of the 12th European conference on Computer Vision – Volume Part IV (ECCV'12), Vol. Part IV, Springer-Verlag, Berlin, Heidelberg, pp. 57-70.

Belsey J, Crosta C, Epstein O, Fischbach W, Layer P, Parente F, Halphen M. 2012. Meta-analysis: efficacy of small-bowel preparation for small-bowel video capsule endoscopy. Curr Med Res Opin 28(12):1883-90.

Bhandari S, Shim CS, Kim JH, Jung IS, Cho JY, Lee JS, Lee MS, Kim BS. 2004. Usefulness of three-dimensional, multidetector row CT (virtual gastroscopy and multiplanar reconstruction) in the evaluation of gastric cancer: a comparison with conventional endoscopy, EUS, and histopathology. Gastrointest Endosc 59(6):619-26.

Blais F. 2004. Review of 20 years of range sensor development. J Electron Imaging 13(1):231-40.

Brennan RL, Prediger DJ. 1981. Coefficient Kappa: Some Uses, Misuses, and Alternatives. Educational and Psychological Measurement 41(3):687-99.

Buscaglia JM, Kapoor S, Clarke JO, Bucobo JC, Giday SA, Magno P, Yong E, Mullin GE. 2008. Enhanced diagnostic yield with prolonged small-bowel transit time during capsule endoscopy. Int J Med Sci 5(6):303-08.

Butterly L, Robinson CM, Anderson JC, Weiss JE, Goodrich M, Onega TL, Amos CI, Beach ML. 2014. Serrated and adenomatous polyp detection increases with longer withdrawal time: results from the New Hampshire Colonoscopy Registry. Am J Gastroenterol 109(3):417-26.

Caddy GR, Moran L, Chong AK, Miller AM, Taylor AC, Desmond PV. 2006. The effect of erythromycin on video capsule endoscopy intestinal-transit time. Gastrointest Endosc 63(2):262-66.

Camilleri M. 2011. New treatment options for chronic constipation: mechanisms, efficacy and safety. Can J Gastroenterol 25 Suppl B:29B-35B.

Cass OW. 2006. Is half-knowledge worse than ignorance? Gastrointest Endosc 64(4):542-43.

Chong AK, Chin BW, Meredith CG. 2006. Clinically significant small-bowel pathology identified by double-balloon enteroscopy but missed by capsule endoscopy. Gastrointest Endosc 64(3):445-49.

Ciaccio EJ, Tennyson CA, Bhagat G, Lewis SK, Green PH. 2013. Use of shape-from-shading to estimate three-dimensional architecture in the small intestinal lumen of celiac and control patients. Comput Methods Programs Biomed 111(3):676-84.

Ciaccio EJ, Tennyson CA, Bhagat G, Lewis SK, Green PH. 2013. Implementation of a polling protocol for predicting celiac disease in videocapsule analysis. World J Gastrointest Endosc 5(7):313-22.

Champion MC, Hartnett M, Yen M. 1986. Domperidone, a new dopamine antagonist. CMAJ 135(5):457-61.

Ciuti G, Visentini-Scarzanella M, Dore A, Menciassi A, Dario P, Guang-Zhong Y. 2012. Intra-operative monocular 3-D reconstruction for image-guided navigation in active locomotion capsule endoscopy. Biomedical Robotics and Biomechatronics (BioRob); 4th IEEE RAS and EMBS International Conference June 2012:768-74.

Clarke JO, Giday SA, Magno P, Shin EJ, Buscaglia JM, Jagannath SB, Mullin GE. 2008. How good is capsule endoscopy for detection of periampullary lesions? Results of a tertiary-referral center. Gastrointest Endosc 68(2):267-72.

Crook DW, Knuesel PR, Froehlich JM, Eigenmann F, Unterweger M, Beer HJ, Kubik-Huch RA. 2009. Comparison of magnetic resonance enterography and video capsule endoscopy in evaluating small-bowel disease. Eur J Gastroenterol Hepatol 21(1):54-65.

Davison C. Reader extender of capsule endoscopy. 2006. Tech Gastrointest Endosc 8(1):188-93.

de Franchis R, Rondonotti E, Villa F. 2007. Capsule endoscopy – state of the art. Dig Dis 25(3): 249-51.

DeLong ER, DeLong DM, Clarke-Pearson DL. 1988. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. Biometrics 44(3):837-45.

DerSimonian R, Laird N. 1986. Meta-analysis in clinical trials. Control Clin Trials 7(3):177-88.

Diaz AP, Viso LM, Asanza CG, Arregui EC, Fernandez-Pacheco PM. 2006. Evaluation of Quickview® System and Suspected Blood Indicator Test from of Given M2A Plus® Capsule Endoscopy Software in the Clinical Setting [abstract]. Gastrointest Endosc 63(5):AB227.

Dionisio PM, Gurudu SR, Leighton JA, Leontiadis GI, Fleischer DE, Hara AK, Heigh RI, Shiff AD, Sharma VK. 2010. Capsule endoscopy has a significantly higher diagnostic yield in patients with suspected and established small-bowel Crohn's disease: a meta-analysis. Am J Gastroenterol 105(6):1240-48.

Dokoutsidou H, Karagiannis S, Giannakoulopoulou E, Galanis P, Kyriakos N, Liatsos C, Faiss S, Mavrogiannis C. 2011. A study comparing an endoscopy nurse and an endoscopy physician in capsule endoscopy interpretation. Eur J Gastroenterol Hepatol 23(2):166-70.

Drew K, McAlindon ME, Sanders DS, Sidhu R. 2013. The nurse endoscopist: moving ahead with time. Gastroenterol Nurs 36(3):209-13.

Duque G, Almeida N, Figueiredo P, Monsanto P, Lopes S, Freire P, Ferreira M, Carvalho R, Gouveia H, Sofia C. 2012. Virtual chromoendoscopy can be a useful software tool in capsule endoscopy. Rev Esp Enferm Dig 104(5):231-36.

East JE, Tan EK, Bergman JJ, Saunders BP, Tekkis PP. 2008. Meta-analysis: narrow band imaging for lesion characterization in the colon, oesophagus, duodenal ampulla and lung. Aliment Pharmacol Ther 28(7):854-67.

Eliakim R. 2013. Video capsule endoscopy of the small-bowel. Curr Opin Gastroenterol 29(2):133-39.

Enns R. 2007. Transit times in capsule endoscopy: are all patients the same? Dig Liver Dis 39(6):581-83.

Fan Y, Meng MQ, Li B. 2010. 3-D reconstruction of wireless capsule endoscopy images. Conf Proc IEEE Eng Med Biol Soc 2010:5149-52.

Fatima H, Rex DK, Rothstein R, Rahmani E, Nehme O, Dewitt J, Helper D, Toor A, Bensen S. 2008. Cecal insertion and withdrawal times with wide-angle versus standard colonoscopes: a randomized controlled trial. Clin Gastroenterol Hepatol 6(1):109-14.

Filip D. 2013. Self-stabilising capsule endoscopy for early detection and biopsy of colonic polyps. Thesis submitted to the faculty of Graduate Studies (Department of Electrical and Computer engineering) for the degree of Doctor of Philosophy; pp 1-25.

Fischer D, Schreiber R, Levi D, Eliakim R. 2004. Capsule endoscopy: the localization system. Gastrointest Endosc Clin N Am 14(1):25-31.

Fisher LR, Hasler WL. 2012. New vision in video capsule endoscopy: current status and future directions. Nat Rev Gastroenterol and Hepatol 9(27):392-405.

Frieling T. 2006. The clinical impact of capsule endoscopy: to believe or not to believe. Eur J Gastroenterol Hepatol 18(8):873-74.

Fu Y, Zhang DW, Liu H, Meng MQH. 2012. 3-D shape recovery of luminal wall from WCE image. Proceedings of the Automation and Logistics (ICAL) 2012; IEEE International Conference on; 2012 Aug 15-17; Zhengzhou, China. Automation and Logistics (ICAL), pp.300-03.

Gerson LB. 2012. Small-bowel endoscopy: cost-effectiveness of the different approaches. Best Pract Res Clin Gastroenterol 26(3):325-35.

Girelli CM, Porta P. 2008. Bulge or mass? A diagnostic dilemma of capsule endoscopy. Endoscopy 40(8):703-4.

Girelli CM, Porta P, Colombo E, Lesinigo E, Bernasconi G. 2011. Development of a novel index to discriminate bulge from mass on small-bowel capsule endoscopy. Gastrointest Endosc 74(5):1067-74.

Gono K, Obi T, Yamaguchi M, Ohyama N, Machida H, Sano Y, Yoshida S, Hamamoto Y, Endo T. 2004. Appearance of enhanced tissue features in narrow-band endoscopic imaging. J Biomed Opt 9(3):568-77.

Gralnek IM, Defranchis R, Seidman E, Leighton JA, Legnani P, Lewis BS. 2008. Development of a capsule endoscopy scoring index for small-bowel mucosal inflammatory change. Aliment Pharmacol Thep 27(2):146-54.

Gupta A, Postgate AJ, Burling D, Ilangovan R, Marshall M, Phillips RK, Clark SK, Fraser CH. 2010. A prospective study of MR enterography versus capsule endoscopy for the surveillance of adult patients with Peutz-Jeghers syndrome. AJR Am J Roentgenol 195(1):108-16.

Hakim FA, Alexander JA, Huprich JE, Grover M, Enders FT. 2011. CT-enterography may identify small-bowel tumours not detected by capsule endoscopy: eight years' experience at Mayo Clinic Rochester. Dig Dis Sci 56(10):2914-19.

Haneishi H, Hasegawa T, Hosoi A, Yokoyama Y, Tsumura N, Miyake Y. 2000. System design for accurately estimating the spectral reflectance of art paintings. Appl Opt 39(35):6621-32.

Hanley JA, McNeil BJ. 1983. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 148(3): 839-43.

Hara AK, Leighton JA, Heigh RI, Sharma VK, Silva AC, De Petris G, Hentz JG, Fleischer DE. 2006. Crohn disease of the small-bowel: preliminary comparison among CT enterography, capsule endoscopy, small-bowel follow-through, and ileoscopy. Radiology 238(1):128-34.

Harrell FE Jr, Lee KL, Mark DB. 1996. Tutorial in biostatistics multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 15(4):361-87.

Harris RJ, Bradburn M, Deeks J, Harbord RM, Altman D, Steichen T, Sterne J. 2007. METAN: Stata module for fixed and random effects meta-analysis. Boston College Department of Economics, Statistical Software Components series.

Hayden JA, Côté P, Bombardier C. 2006. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 144(6):427-37.

Higgins JP, Thompson SG, Deeks JJ, Altman DG. 2003. Measuring inconsistency in meta-analyses. BMJ 327(7414):557-60.

Hindryckx P, Botelberge T, De Vos M, De Looze D. 2008. Clinical impact of capsule endoscopy on further strategy and long-term clinical outcome in patients with obscure bleeding. Gastrointest Endosc 68(1):98-104.

Höög CM, Bark LÅ, Arkani J, Gorsetman J, Broström O, Sjöqvist U. 2012. Capsule retentions and incomplete capsule endoscopy examinations: an analysis of 2300 examinations. Gastroenterol Res Pract 2012:518718.

Hooks SB 3rd, Rutland TJ, Di Palma JA. Lubiprostone neither decreases gastric and small-bowel transit time nor improves visualization of small-bowel for

capsule endoscopy: a double-blind, placebo-controlled study. Gastrointest Endosc 70(5):942-46.

Hosoe N, Rey JF, Imaeda H, Bessho R, Ichikawa R, Ida Y, Naganuma M, Kanai T, Hibi T, Ogata H. 2012. Evaluations of capsule endoscopy software in reducing the reading time and the rate of false negatives by inexperienced endoscopists. Clin Res Hepatol Gastroenterol 36(1):66-71.

Hosono K, Endo H, Sakai E, Sekino Y, Uchiyama T, Watanabe S, Iida H, Sakamoto Y, Koide T, Takahashi H, Yoneda M, Tokoro C, Abe Y, Inamori M, Kobayashi N, Kubota K, Nakajima A. 2011. Optimal approach for small-bowel capsule endoscopy using polyethylene glycol and metoclopramide with the assistance of a real-time viewer. Digestion 84(2):119-25.

Iakovidis DK, Maroulis DE, Karkanis SA. 2006. An Intelligent System for Automatic Detection of Gastrointestinal Adenomas in Video Endoscopy. Computers in Biology and Medicine 36(10):1084-1103.

Iaquinto G, Fornasarig M, Quaia M, Giardullo N, D'Onofrio V, Iaquinto S, Di Bella S, Cannizzaro R. 2008. Capsule endoscopy is useful and safe for small-bowel surveillance in familial adenomatous polyposis. Gastrointest Endosc 67(1):61-67.

Ida Y, Hosoe N, Imaeda H, Bessho R, Ichikawa R, Naganuma M, Kanai T, Hibi T,Ogata H. 2012. Effects of the oral administration of mosapride citrate on capsule endoscopy completion rate. Gut Liver 6(3):339-43.

Iddan G, Meron G, Glukhovsky A, Swain P. 2000. Wireless capsule endoscopy. Nature 405(6785):417.

Iddan GJ, Swain CP. 2004. History and development of capsule endoscopy. Gastrointest Endosc Clin N Am 14(1):1-9.

Imagawa H, Oka S, Tanaka S, Noda I, Higashiyama M, Sanomura Y, Shishido T, Yoshida S, Chayama K. 2011. Improved visibility of lesions of the small intestine via capsule endoscopy with computed virtual chromoendoscopy. Gastrointest Endosc;73(2):299-306.

Islam RS, Leighton JA, Pasha SF. 2013. Evaluation and management of small-bowel tumours in the era of deep enteroscopy. Gastrointest Endosc Dec 21. [Epub ahead of print]

Iwamoto J, Mizokami Y, Shimokobe K, Ito M, Hirayama T, Saito Y, Honda A, Ikegami T, Matsuzaki Y. 2010. The effect of metoclopramide in capsule endoscopy. Hepatogastroenterology 57(104):1356-59.

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17(1):1-12.

Jang BI, Lee SH, Moon JS, Cheung DY, Lee IS, Kim JO, Cheon JH, Park CH, Byeon JS, Park YS, Shim KN, Kim YS, Kim KJ, Lee KJ, Ryu JK, Chang DK, Chun HJ, Choi MG. 2010. Inter-observer agreement on the interpretation of capsule endoscopy findings based on capsule endoscopy structured terminology: a multicenter study by the Korean Gut Image Study Group. Scand J Gastroenterol 45(3):370-74.

Jensen MD, Nathan T, Kjeldsen J. 2010. Inter-observer agreement for detection of small-bowel Crohn's disease with capsule endoscopy. Scand J Gastroenterol 45(7-8):878-84.

Kaffes AJ. 2009. Achieving total enteroscopy with capsule endoscopy in all patients: are we stretching the limits of technology? Gastrointest Endosc 69(1):81-83.

Karagiannis S, Dücker C, Dautel P, Strubenhoff J, Faiss S. 2010. Identification of the duodenal papilla by colon capsule endoscope. Z Gastroenterol 48(7):753-55

Karargyris A, Bourbakis N. 2011. Three-dimensional reconstruction of the digestive wall in capsule endoscopy videos using elastic video interpolation. IEEE Trans Med Imaging 30(4):957-71.

Karargyris A, Karargyris O, Bourbakis N. 2010. 3-D Representation of the Digestive Tract Surface in Wireless Capsule Endoscopy Videos; BIBE; May 31-Jun 3; Philadelphia, United States. New Jersey: IEEE International Conference on Bioinformatics and BioEngineering. In: Proceedings of the 2010 IEEE xplore; pp. 279-80.

Karargyris A, Rondonotti E, Mandelli G, Koulaouzidis A. 2013. Evaluation of 4 three-dimensional representation algorithms in capsule endoscopy images. World J Gastroenterol 19(44):8028-33.

Katsinelos P, Kountouras J, Chatzimavroudis G, Zavos C, Pilpilidis I, Fasoulas K, Paroutoglou G. 2009. Wireless capsule endoscopy in detecting small-intestinal polyps in familial adenomatous polyposis. World J Gastroenterol 15(48):6075-79.

Kobayashi Y, Watabe H, Yamada A, Hirata Y, Yamaji Y, Yoshida H, Koike K. 2012. Efficacy of flexible spectral imaging colour enhancement on the detection of small intestinal diseases by capsule endoscopy. J Dig Dis 13(12):614-20.

Kolar A, Romain O, Ayoub J, Faura D, Viateur S, Granado B, Graba T. 2009. A system for an accurate 3-D reconstruction in video endoscopy capsule. EURASIP Journal on Embedded Systems. 2009:716317.

Kolar A, Romain O, Ayoub J, Viateur S, Granado B. 2010. Prototype of video endoscopic capsule with 3-D imaging capabilities. IEEE Trans Biomed Circuits Syst 4(4):239-49.

Kong H, Kim YS, Hyun JJ, Cho YJ, Keum B, Jeen YT, Lee HS, Chun HJ, Um SH, Lee SW, Choi JH, Kim CD, Ryu HS, Hyun JH. 2006. Limited ability of capsule endoscopy to detect normally positioned duodenal papilla. Gastrointest Endosc 64(4):538-41.

Kopylov U, Papageorgiou NP, Nadler M, Eliakim R, Ben-Horin S. 2012. Head or tail: the orientation of the small-bowel capsule endoscope movement in the small-bowel. Dig Dis Sci 57(3):694-98.

Korniski R, Bae SY, Shearn M, Manohara H, Shahinian H. 2011. 3-D imaging with a single-aperture 3-mm objective lens: concept, fabrication, and test. R. Koshel J G. Gregory GG (Eds.), SPIE Proceedings Vol. 8129 – Novel Optical Systems Design and Optimization XIV, Vol. 812904, SPIE, Bellingham, WA, USA, pp. 11.

Koulaouzidis A. 2012. Upper oesophageal images and Z-line detection with 2 different small-bowel capsule systems. World J Gastroenterol 18(41):6003-04.

Koulaouzidis A, Douglas S. 2009. Capsule endoscopy in clinical practice: concise up-to-date overview. Clin Exp Gastroenterol 2:111-16.

Koulaouzidis A, Douglas S, Plevris JN. 2012. Heads or tail orientation in small-bowel capsule endoscopy: 2 capsule models with 2 reviewers. Dig Dis Sci 57(4):1102-3.

Koulaouzidis A, Douglas S, Plevris JN. 2011. Identification of the ampulla of Vater during oesophageal capsule endoscopy: two heads and viewing speed make a difference. Eur J Gastroenterol Hepatol 23(4):361.

Koulaouzidis A, Douglas S, Plevris JN. 2012. Blue mode does not offer any benefit over white light when calculating Lewis score in small-bowel capsule endoscopy. World J Gastrointest Endosc 4(2):33-37.

Koulaouzidis A, Karargyris A. 2012. Three-dimensional image reconstruction in capsule endoscopy. World J Gastroenterol 18(31):4086-90.

Koulaouzidis A, Karargyris A. 2013. Application of 3-D-Representation Algorithms in Small-Bowel Capsule Endoscopy. Glob J Gastroenterol Hepatol 1(2):2-3.

Koulaouzidis A, Karargyris A, Rondonotti E, Noble CL, Douglas S, Alexandridis E, Zahid AM, Bathgate AJ, Trimble KC, Plevris JN. 2013. Three-dimensional representation software as image enhancement tool in small-bowel capsule endoscopy: a feasibility study. Dig Liver Dis 45(11):909-14.

Koulaouzidis A, Rondonotti E, Giannakou A, Plevris JN. 2012. Diagnostic yield of small-bowel capsule endoscopy in patients with iron-deficiency anemia: a systematic review. Gastrointest Endosc 76(5):983-92.

Koulaouzidis A, Rondonotti E, Karargyris A. 2013. Small-bowel capsule endoscopy: a ten-point contemporary review. World J Gastroenterol 19(24):3726-46.

Koulaouzidis A, Yung DE, Lam JH, Douglas S, Plevris JN. 2012. The use of small-bowel capsule endoscopy in iron-deficiency anemia alone; be aware of the young anemic patient. Scand J Gastroenterol 47(8-9):1094-1100.

Krystallis C, Koulaouzidis A, Douglas S, Plevris JN. 2011. Chromoendoscopy in small-bowel capsule endoscopy: Blue mode or Fuji Intelligent Colour Enhancement? Dig Liver Dis 43(12):953-57.

Ladas SD, Triantafyllou K, Spada C, Riccioni ME, Rey JF, Niv Y, Delvaux M, de Franchis R, Costamagna G; ESGE Clinical Guidelines Committee. 2010. European Society of Gastrointestinal Endoscopy (ESGE): recommendations (2009) on clinical use of video capsule endoscopy to investigate small-bowel, esophagealand colonic diseases. Endoscopy 42(3):220-27.

Lambert JH. Photometria Sive de Mensura de Gratibus Luminis, Colourum et Umbrae. Augsberg, Germany: Eberhard Klett, 1760.

Landis JR, Koch GG. 1977. The measurement of observer agreement for categorical data. Biometrics 33(1):159-74.

Lee HS, Lee KG, Kim J, Hyun JJ, Kim ES, Park SC, Park S, Keum B, Seo YS, Tae Y. 2010. Comparison of PillCam SB and SB2 – Study of normally positioned ampulla of Vater detection. Gastrointest Endosc 71(5):AB370-1.

Leighton JA, Triester SL, Sharma VK. 2006. Capsule endoscopy: a meta-analysis for use with obscure gastrointestinal bleeding and Crohn's disease. Gastrointest Endosc Clin N Am 16(2):229-50.

Leontiadis GI, Molloy-Bland M, Moayyedi P, Howden CW. 2013. Effect of comorbidity on mortality in patients with peptic ulcer bleeding: systematic review and meta-analysis. Am J Gastroenterol 108(3):331-45.

Leung WK, Chan FK, Fung SS, Wong MY, Sung JJ. 2005. Effect of oral erythromycin on gastric and small-bowel transit time of capsule endoscopy. World J Gastroenterol 11(31):4865-68.

Lewis BS. 2004. How to read wireless capsule endoscopic images: tips of the trade. Gastrointest Endosc Clin N Am 14(1):11-16.

Lewis BS, Eisen GM, Friedman S. 2005. A pooled analysis to evaluate results of capsule endoscopy trials. Endoscopy 37(10):960-65.

Liao Z, Gao R, Xu C, Li ZS. 2010. Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. Gastrointest Endosc 71(2):280-86.

Liao Z, Li F, Li ZS. 2008. Right lateral position improves complete examination rate of capsule endoscope: a prospective randomized, controlled trial. Endoscopy 40(6):483-87.

Lo SK. 2006. How should we do capsule reading? Tech Gastrointest Endosc 8(4):145-47.

Maeda M, Kanke K, Terano A, Hiraishi H. 2010. Management of obscure gastrointestinal bleeding based on the classification of capsule endoscopic bleeding findings. Dig Endosc 22(3):174-79.

Mang T, Kolligs FT, Schaefer C, Reiser MF, Graser A. 2011. Comparison of diagnostic accuracy and interpretation times for a standard and an advanced 3-D visualization technique in CT colonography. Eur Radiol 21(3):653-62.

Mantel N, Haenszel W. 1959. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22(4):719-48.

Marmo R, Rotondano G, Piscopo R, Bianco MA, Cipolletta L. 2005. Meta-analysis: capsule enteroscopy vs conventional modalities in diagnosis of small-bowel diseases. Aliment Pharmacol Ther 22(7):595-604.

Marmo R, Rotondano G, Rondonotti E, de Franchis R, D'Incà R, Vettorato MG, Costamagna G, Riccioni ME, Spada C, D'Angella R, Milazzo G, Faraone A, Rizzetto M, Barbon V, Occhipinti P, Saettone S, Iaquinto G, Rossini FP; Club Italiano Capsula Endoscopica - CICE. 2007. Capsule enteroscopy vs other diagnostic procedures in diagnosing obscure gastrointestinal bleeding: a cost-effectiveness study. Eur J Gastroenterol Hepatol 19(7):535-42.

Mata A, Llach J, Bordas JM. 2008. Wireless capsule endoscopy. World J Gastroenterol 14(13):1969-71.

Mathus-Vliegen E, Pellisé M, Heresbach D, Fischbach W, Dixon T, Belsey J, Parente F, Rio-Tinto R, Brown A, Toth E, Crosta C, Layer P, Epstein O, Boustiere C. 2013. Consensus guidelines for the use of bowel preparation prior to colonic diagnostic procedures: colonoscopy and small-bowel video capsule endoscopy. Curr Med Res Opin 29(8):931-45.

Mavrogenis G, Coumaros D, Renard C, Bellocq JP, Defta D, Charneau D, Leroy J. 2011. Jejunal gastrointestinal stromal tumour missed by three capsule endoscopies. Endoscopy 43(8):735-36.

McKenna MT, Wang S, Nguyen TB, Burns JE, Petrick N, Summers RM. 2012. Strategies for improved interpretation of computer-aided detections for CT colonography utilizing distributed human intelligence. Med Image Anal 16(6):1280-92.

Mergener K, Ponchon T, Gralnek I, Pennazio M, Gay G, Selby W, Seidman EG, Cellier C, Murray J, de Franchis R, Rösch T, Lewis BS. 2007. Literature review and recommendations for clinical application of small-bowel capsule endoscopy, based on a panel discussion by international experts. Consensus statements for small-bowel capsule endoscopy, 2006/2007. Endoscopy 39(10):895-909.

Metzger YC, Adler SN, Shitrit AB, Koslowsky B, Bjarnason I. 2009. Comparison of a new PillCam[™] SB2 video capsule versus the standard PillCam[™] SB for detection of small-bowel disease. Rep Med Imaging 2:7-11.

Moayyedi P. 2004. Meta-analysis: Can we mix apples and oranges? Am J Gastroenterol 99(12):2297-301.

Mouri R, Yoshida S, Tanaka S, Oka S, Yoshihara M, Chayama K. 2009. Evaluation and validation of computed virtual chromoendoscopy in early gastric cancer. Gastrointest Endosc 69(6):1052-58.

Mueller-Richter U, Limberger A, Weber P, Ruprecht KW, Spitzer W, Schilling M. 2004. Possibilities and limitations of current stereo-endoscopy. Surg Endosc 18(6):942-47.

Nakaji K, Suzumura S, Fujita A, Kumamoto M, Nakae Y. 2011. Effectiveness of Daikenchuto, a Traditional Japanese Herbal Medicine, in Accelerating Capsule Endoscopy Transit Time-A Prospective Pilot Study. New Techniques in Gastrointestinal Endoscopy, Prof. Oliviu Pascu (Ed.), ISBN: 978-953-307-777-2, InTech, DOI: 10.5772/22599. Available from: http://cdn.intechopen.com/pdfs-wm/21086.pdf

Nakamura M, Ohmiya N, Shirai O, Takenaka H, Kenji, Morishima, Miyahara R, Ando T, Watanabe O, Kawashima H, Itoh A, Hirooka Y, Niwa Y, Goto H. 2009. Advance of video capsule endoscopy and the detection of anatomic landmarks. Hepatogastroenterology 56(96):1600-05.

Neumann H, Fry LC, Bellutti M, Malfertheiner P, Mönkemüller K. 2009. Double-balloon enteroscopy-assisted virtual chromoendoscopy for small-bowel disorders: a case series. Endoscopy 41(5):468-71.

Niv E, Bonger I, Barkay O, Halpern Z, Mahajna E, Depsames R, Kopelman Y, Fireman Z. 2008. Effect of erythromycin on image quality and transit time of capsule endoscopy: a two-center study. World J Gastroenterol 14(16):2561-65.

Niv Y. 2008. Efficiency of bowel preparation for capsule endoscopy examination: a meta-analysis. World J Gastroenterol 14(9):1313-17.

Osawa H, Yamamoto H, Yamada N, Yoshizawa M, Sunada K, Kita H, Ajibe H, Satoh K, Sugano K. 2009. Diagnosis of endoscopic Barrett's esophagus by transnasal flexible spectral imaging colour enhancement. J Gastroenterol 44(11):1125-32.

Park S, Chun HJ, Keum B, Seo YS, Kim YS, Jeen YT, Lee HS, Um SH, Kim CD, Ryu HS. 2012. Capsule endoscopy to detect normally positioned duodenal papilla: performance comparison of SB and SB2. Gastroenterol Res Pract 2012:202935.

Park SC, Keum B, Hyun JJ, Seo YS, Kim YS, Jeen YT, Chun HJ, Um SH, Kim CD, Ryu HS. 2010. A novel cleansing score system for capsule endoscopy. World J Gastroenterol 16(7):875-80.

Parra-Blanco A, Jiménez A, Rembacken B, González N, Nicolás-Pérez D, Gimeno-García AZ, Carrillo-Palau M, Matsuda T, Quintero. 2009. Validation of Fuji non

intelligent chromoendoscopy with high definition endoscopes in colonoscopy. World J Gastroenterol 15(42):5266-73.

Pickhardt PJ, Schumacher C, Kim DH. 2009. Polyp detection at 3-dimensional endoluminal computed tomography colonography: sensitivity of one-way fly-through at 120 degrees field-of-view angle. <u>J Comput Assist Tomogr</u> 33(4):631-5.

Pohl J, Aschmoneit I, Schuhmann S, Ell C. 2010. Computed image modification for enhancement of small-bowel surface structures at video capsule endoscopy. Endoscopy 42(6):490-92.

Pohl J, May A, Rabenstein T, Pech O, Ell C. 2007. Computed virtual chromoendoscopy: a new tool for enhancing tissue surface structure. Endoscopy 39(1):80-83.

Pohl J, Nguyen-Tat M, Pech O, May A, Rabenstein T, Ell C. 2008. Computed virtual chromoendoscopy for classification of small colourectal lesions: a prospective comparative study. Am J Gastroenterol 103(3):562-69.

Pohl J, Lotterer E, Balzer C, Sackmann M, Schmidt KD, Gossner L, Schaab C, Frieling T, Medve M, Mayer G, Nguyen-Tat M, Ell C. 2009. Computed virtual chromoendoscopy versus standard colonoscopy with targeted indigocarmine chromoscopy: a randomised multicentre trial. Gut 58(1):73-78.

Postgate A, Despott E, Burling D, Gupta A, Phillips R, O'Beirne J, Patch D, Fraser C. 2008. Significant small-bowel lesions detected by alternative diagnostic modalities after negative capsule endoscopy. Gastrointest Endosc 68(6):1209-14.

Postgate A, Tekkis P, Patterson N, Fitzpatrick A, Bassett P, Fraser C. 2009. Are bowel purgatives and prokinetics useful for small-bowel capsule endoscopy? A prospective randomized controlled study. Gastrointest Endosc 69(6):1120-28.

Prasad V, Cifu A. 2011. Medical reversal: why we must raise the bar before adopting new technologies. Yale J Biol Med 84(4):471-78.

Prasath VBS, Figueiredo IN, Figueiredo PN, Palaniappan K. 2012. Mucosal region detection and 3-D reconstruction in wireless capsule endoscopy videos using active contours. Conf Proc IEEE Eng Med Biol Soc 2012:4014-17.

Rajan E, Iyer PG, Oxentenko AS, Pardi DS, Alexander JA, Baron TH, Bruining DH, Hansel SL, Larson MV, Murray JA, Debritto J, Dierkhising RA, Gostout CJ. 2013. Training in small-bowel capsule endoscopy: assessing and defining competency. Gastrointest Endosc 78(4):617-22.

Rajan EA, Pais SA, Degregorio BT, Adler DG, Al-Haddad M, Bakis G, Coyle WJ, Davila RE, Dimaio CJ, Enestvedt BK, Jorgensen J, Lee LS, Mullady DK, Obstein KL, Sedlack RE, Tierney WM, Faulx AL; ASGE Training Committee 2011-2012. 2013. Small-bowel endoscopy core curriculum. Gastrointest Endosc 77(1):1-6.

Rokkas T, Papaxoinis K, Triantafyllou K, Pistiolas D, Ladas SD. 2009. Does purgative preparation influence the diagnostic yield of small-bowel video capsule endoscopy?: A meta-analysis. Am J Gastroenterol 104(1):219-27.

Rondonotti E, Marmo R, Petracchini M, de Franchis R, Pennazio M. 2013. The American Society for Gastrointestinal Endoscopy (ASGE) diagnostic algorithm for obscure gastrointestinal bleeding: eight burning questions from everyday clinical practice. Dig Liver Dis 45(3):179-85.

Rondonotti E, Pennazio M, Toth E, Menchen P, Riccioni ME, De Palma GD, Scotto F, De Looze D, Pachofsky T, Tacheci I, Havelund T, Couto G, Trifan A, Kofokotsios A, Cannizzaro R, Perez-Quadrado E, de Franchis R; European Capsule Endoscopy Group; Italian Club for Capsule Endoscopy (CICE); Iberian Group for Capsule Endoscopy. 2008. Small-bowel neoplasms in patients undergoing video capsule endoscopy: a multicenter European study. Endoscopy 40(6):488-95.

Rondonotti E, Soncini M, Girelli C, Ballardini G, Bianchi G, Brunati S, Centenara L, Cesari P, Cortelezzi C, Curioni S, Gozzini C, Gullotta R, Lazzaroni M, Maino M, Mandelli G, Mantovani N, Morandi E, Pansoni C, Piubello W, Putignano R, Schalling R, Tatarella M, Villa F, Vitagliano P, Russo A, Conte D, Masci E, de Franchis R; AIGO, SIED and SIGE Lombardia. 2010. Small-bowel capsule endoscopy in clinical practice: a multicenter 7-year survey. Eur J Gastroenterol Hepatol 22(11):1380-86.

Rondonotti E, Soncini M, Girelli CM, Russo A, Ballardini G, Bianchi G, Cantù P, Centenara L, Cesari P, Cortelezzi CC, Gozzini C, Lupinacci G, Maino M, Mandelli G, Mantovani N, Moneghini D, Morandi E, Putignano R, Schalling R, Tatarella M, Vitagliano P, Villa F, Zatelli S, Conte D, Masci E, de Franchis R; AIGO, SIED and SIGE Lombardia. 2012. Can we improve the detection rate and interobserver agreement in capsule endoscopy? Dig Liver Dis 44(12):1006-11.

Ross A, Mehdizadeh S, Tokar J, Leighton JA, Kamal A, Chen A, Schembre D, Chen G, Binmoeller K, Kozarek R, Waxman I, Dye C, Gerson L, Harrison ME, Haluszka O, Lo S, Semrad C. 2008. Double balloon enteroscopy detects small-bowel mass lesions missed by capsule endoscopy. Dig Dis Sci 53(8):2140-43.

Saurin JC, Delvaux M, Gaudin JL, Fassler I, Villarejo J, Vahedi K, Bitoun A, Canard JM, Souquet JC, Ponchon T, Florent C, Gay G. 2003. Diagnostic value of endoscopic capsule in patients with obscure digestive bleeding: blinded comparison with video push-enteroscopy. Endoscopy 35(7):576-84.

Saurin JC, Lapalus MG, Cholet F, D'Halluin PN, Filoche B, Gaudric M, Sacher-Huvelin S, Savalle C, Frederic M, Lamarre PA, Ben Soussan E; French Society of Digestive Endoscopy (SFED). The French Society of Digestive Endoscopy (SFED). 2012. Can we shorten the small-bowel capsule reading time with the 'Quick-view' image detection system? Dig Liver Dis 44(6):477-81.

Schmelkin I. 2006. RAPID® 4 quickview v4 has 100% negative and positive predictive values. In: The 5th international conference of capsule endoscopy, editor. Boca Raton, FL: ICCE; pp. 89-90.

Schwarzberg MN. 2005. Pro-kinetic medications as aids in imaging the small-bowel by video-capsule. Med Hypotheses 64(3):602-07.

Selby W. 2005. Complete small-bowel transit in patients undergoing capsule endoscopy: determining factors and improvement with metoclopramide. Gastrointest Endosc 61(1):80-85.

Selby WS, Prakoso E. 2011. The inability to visualize the ampulla of Vater is an inherent limitation of capsule endoscopy. Eur J Gastroenterol Hepatol 23(1):101-03.

Selby WS, Prakoso E. 2011. Reply to: identification of the ampulla of Vater during oesophageal capsule endoscopy: two heads and viewing speed make a difference. Eur J Gastroenterol Hepatol 23(4):362.

Shibuya T, Mori H, Takeda T, Konishi M, Fukuo Y, Matsumoto K, Beppu K, Sakamoto N, Osada T, Nagahara A, Otaka M, Ogihara T, Watanabe S. 2012. The relationship between physical activity level and completion rate of small-bowel examination in patients undergoing capsule endoscopy. Intern Med 51(9):997-1001.

Shiotani A, Honda K, Kawakami M, Kimura Y, Yamanaka Y, Fujita M, Matsumoto H, Tarumi K, Manabe N, Haruma K. 2012. Analysis of small-bowel capsule endoscopy reading by using Quickview mode: training assistants for reading may produce a high diagnostic yield and save time for physicians. J Clin Gastroenterol 46(10):e92-5.

Shiotani A, Honda K, Kawakami M, Murao T, Matsumoto H, Tarumi K, Kusunoki H, Hata J, Haruma K. 2011. Evaluation of RAPID(®) 5 Access software for examination of capsule endoscopies and reading of the capsule by an endoscopy nurse. J Gastroenterol 46(2):138-42.

Shiotani A, Honda K, Kawakami M, Nishi R, Murao T, Ishii M, Matsumoto H, Kusunoki H, Hata J, Haruma K. 2011. Use of an external real-time image viewer coupled with prespecified actions enhanced the complete examinations for capsule endoscopy. J Gastroenterol Hepatol 26(8):1270-74.

Shyung LR, Lin SC, Shih SC, Chang WH, Chu CH, Wang TE. 2009. Proposed scoring system to determine small-bowel mass lesions using capsule endoscopy. J Formos Med Assoc 108(7):533-38.

Sidhu R, McAlindon ME, Drew K, Hardcastle S, Cameron IC, Sanders DS. 2012. Evaluating the role of small-bowel endoscopy in clinical practice: the largest single-centre experience. Eur J Gastroenterol Hepatol 24(5):513-19.

Sidhu R, Sanders DS, Kapur K, Marshall L, Hurlstone DP, McAlindon ME. 2007. Capsule endoscopy: is there a role for nurses as physician extenders? Gastroenterol Nurs 30(1):45-48.

Sidhu R, Sanders DS, Morris AJ, McAlindon ME. 2008. Guidelines on small-bowel enteroscopy and capsule endoscopy in adults. Gut 57(1):125-36.

Solad Y, Wang C, Laine L, Deng Y, Schwartz H, Ciarleglio MM, Aslanian HR. 2014. Influence of Colonoscopy Quality Measures on Patients' Colonoscopist Selection. Am J Gastroenterol Jul 29. doi: 10.1038/ajg.2014.201. [Epub ahead of print]

Song ZQ, Gu F, Yao W, Li J, Zhou LY, Lin SR. 2010. [Evaluation of capsule endoscopy on the diagnosis of gastrointestinal diseases]. [Article in Chinese]. Beijing Da Xue Xue Bao 42(5):539-42.

Song HJ, Moon JS, Do JH, Cha IH, Yang CH, Choi MG, Jeen YT, Kim HJ; Korean Gut Image Study Group. 2013. Guidelines for bowel preparation before video capsule endoscopy. Clin Endosc 46(2):147-54.

Spada C, Hassan C, Costamagna G. 2011. Virtual chromoendoscopy: will it play a role in capsule endoscopy. Dig Liver Dis 43(12):927-28.

Spyrou E, Iakovidis DK. 2014. Video-based measurements for wireless capsule endoscope tracking. Meas Sci Technol 25(1):015002.

Sterne JA, Egger M. 2001. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol 54(10):1046-55.

Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. 2000. Methods for Meta-Analysis in Medical Research. Chichester, England: John Wiley and Sons Ltd

Swain P. At a watershed? Technical developments in wireless capsule endoscopy. 2010. J Dig Dis 11(5):259-65.

Tan RT, Ikeuchi K. 2005. Separating reflection components of textured surfaces using a single image. Pattern Analysis and Machine Intelligence, IEEE Transactions on 27(2):178-93.

Taylor SA, Halligan S, Slater A, Goh V, Burling DN, Roddie ME, Honeyfield L, McQuillan J, Amin H, Dehmeshki J. 2006. Polyp detection with CT colonography: primary 3-D endoluminal analysis versus primary 2-D transverse analysis with computer-assisted reader software. Radiology 239(3):759-67.

Than TD, Alici G, Zhou H, Li W. 2012. A review of localization systems for robotic endoscopic capsules. IEEE Trans Biomed Eng 59(9):2387-99.

Togashi K, Osawa H, Koinuma K, Hayashi Y, Miyata T, Sunada K, Nokubi M, Horie H, Yamamoto H. 2009. A comparison of conventional endoscopy, chromoendoscopy, and the optimal-band imaging system for the differentiation of neoplastic and non-neoplastic colonic polyps. Gastrointest Endosc 69(3 Pt 2):734-41.

Torreão JRA, Fernandes JL. 2011. Linear-nonlinear neuronal model for shape from shading. Pattern Recognition Letters 32(9):1223-39.

Triantafyllou K, Papadopoulos AA, Kalantzis N, Ladas SD. 2009. Diabetes mellitus is a risk factor for incomplete small-bowel capsule endoscopy. Gastrointest Endosc 69(7):1408-09.

Triantafyllou K, Papanikolaou IS, Papaxoinis K, Ladas SD. 2011. Two cameras detect more lesions in the small-bowel than one. World J Gastroenterol 17(11):1462-67.

Triester SL, Leighton JA, Leontiadis GI, Fleischer DE, Hara AK, Heigh RI, Shiff AD, Sharma VK. 2005. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with obscure gastrointestinal bleeding. Am J Gastroenterol 100(11):2407-18.

Tsai PS, Shah M. 1994. Shape from shading using linear approximation. Comput Vis Image 12(2):487-98.

Tsutsui A, Okamura S, Muguruma N, Tsujigami K, Ichikawa S, Ito S, Umino K. 2005. Three-dimensional reconstruction of endosonographic images of gastric lesions: preliminary experience. J Clin Ultrasound 33(3):112-8.

Viera AJ, Garrett JM. 2005. Understanding interobserver agreement: the kappa statistic. Fam Med;37(5):360-63.

Villa F, Signorelli C, Rondonotti E, de Franchis R. 2006. Preparations and prokinetics. Gastrointest Endosc Clin N Am 16(2):211-20.

Visentini-Scarzanella M, Stoyanov D, Yang GZ. 2012. Metric depth recovery from monocular images using Shape-from-Shading and specularities. Image Processing (ICIP), 2012 19th IEEE International Conference on; 2012 Sept. 30-Oct. 3; pp.25-28.

Wang A, Banerjee S, Barth BA, Bhat YM, Chauhan S, Gottlieb KT, Konda V, Maple JT, Murad F, Pfau PR, Pleskow DK, Siddiqui UD, Tokar JL, Rodriguez SA; ASGE Technology Committee. 2013. Wireless capsule endoscopy. Gastrointest Endosc 78(6):805-15.

Ward ST, Mohammed MA, Walt R, Valori R, Ismail T, Dunckley P. 2014. An analysis of the learning curve to achieve competency at colonoscopy using the JETS database. Gut Jan 27. doi: 10.1136/gutjnl-2013-305973. [Epub ahead of print]

Warrens MJ. 2010. Inequalities between multi-rater kappas. Adv Data Anal Classif 4(4):271-86.

Wei W, Ge ZZ, Lu H, Gao YJ, Hu YB, Xiao SD. 2007. Effect of mosapride on gastrointestinal transit time and diagnostic yield of capsule endoscopy. J Gastroenterol Hepatol 22(10):1605-08.

Westerhof J, Koornstra JJ, Hoedemaker RA, Sluiter WJ, Kleibeuker JH, Weersma RK. 2012. Diagnostic yield of small-bowel capsule endoscopy depends on the small-bowel transit time. World J Gastroenterol 18(13):1502-07.

Westerhof J, Koornstra JJ, Hoedemaker RA, Sluiter WJ, Kleibeuker JH, Weersma RK. 2012. Diagnostic yield of small-bowel capsule endoscopy depends on the small-bowel transit time. World J Gastroenterol 18(13):1502-07.

Westerhof J, Koornstra JJ, Weersma RK. 2009. Can we reduce capsule endoscopy reading times? Gastrointest Endosc 69(3 Pt 1):497-502.

Westerhof J, Weersma RK, Koornstra JJ. 2009. Risk factors for incomplete small-bowel capsule endoscopy. Gastrointest Endosc 69(1):74-80.

Wijeratne R, Condon D. 2006. Ampulla of Vater is infrequently visualised by capsule endoscopy. Gastrointest Endosc 63(5):AB172.

Wong RF, Tuteja AK, Haslem DS, Pappas L, Szabo A, Ogara MM, DiSario JA. 2006. Video capsule endoscopy compared with standard endoscopy for the evaluation of small-bowel polyps in persons with familial adenomatous polyposis (with video). Gastrointest Endosc 64(4):530-37.

Woods SP, Constandinou TG. 2011. Towards a micropositioning system for targeted drug delivery in wireless capsule endoscopy. Conf Proc IEEE Eng Med Biol Soc 2011:7372-75.

Woods SP, Constandinou TG. 2013. Wireless capsule endoscope for targeted drug delivery: mechanics and design considerations. IEEE Trans Biomed Eng 60(4):945-53.

Wu L, Cao Y, Liao C, Huang J, Gao F. 2011. Systematic review and meta-analysis of randomized controlled trials of Simethicone for gastrointestinal endoscopic visibility. Scand J Gastroenterol 46(2):227-35.

Wysowski DK, Corken A, Gallo-Torres H, Talarico L, Rodriguez EM. 2001. Postmarketing reports of QT prolongation and ventricular arrhythmia in association with cisapride and Food and Drug Administration regulatory actions. Am J Gastroenterol 96(6):1698-703.

Xiong GY, Wang M, Yang LH, et al. 2012. Relationship between gastric transit time and complete examination rate of the capsule endoscopy examinations. Shijie Huaren Xiaohua Zazhi 20:2318-21.

Yazici C, Losurdo J, Brown MD, Oosterveen S, Rahimi R, Keshavarzian A, Bozorgnia L, Mutlu E. 2012. Inpatient capsule endoscopy leads to frequent incomplete small-bowel examinations. World J Gastroenterol 18(36):5051-57.

Yoshida S, Chayama K. 2011. Improved visibility of lesions of the small intestine via capsule endoscopy with computed virtual chromoendoscopy. Gastrointest Endosc 73(2):299-306.

Yoshida N, Naito Y, Kugai M, Inoue K, Uchiyama K, Takagi T, Ishikawa T, Handa O, Konishi H, Wakabayashi N, Kokura S, Yagi N, Morimoto Y, Yanagisawa A,Yoshikawa T. 2010. Efficacy of magnifying endoscopy with flexible spectral imaging colour enhancement in the diagnosis of colourectal tumours. J Gastroenterol 46(1):65-72.

Zagorowicz ES, Pietrzak AM, Wronska E, Pachlewski J, Rutkowski P, Kraszewska E, Regula J. 2013. Small-bowel tumours detected and missed during capsule endoscopy: Single center experience. World J Gastroenterol 19(47):9043-48.

Zhang R, Tsai PS, Cryer JE, Shah M. 1999. Shape from shading: a survey. IEEE Transactions on Pattern Analysis and Machine Intelligence 21(8): 690-706.

Zhang JS, Ye LP, Zhang JL, Wang CY, Chen JY. 2011. Intramuscular injection of metoclopramide decreases the gastric transit time and does not increase the complete examination rate of capsule endoscopy: a prospective randomized controlled trial. Hepatogastroenterology 58(110-111):1618-21.

Zheng Y, Hawkins L, Wolff J, Goloubeva O, Goldberg E. 2012. Detection of lesions during capsule endoscopy: physician performance is disappointing. Am J Gastroenterol 107(4):554-60.

Appendix 1

The capsule procedure protocol of our unit

Strict liquid diet the day prior to the test, small-bowel purge (2 litres polyethylene glycol; Moviprep®) with overnight fast. The capsule is ingested with 40–100 mg of anti-foam (Simeticone, Infacol®) and Domperidone (usual dose 5 mg of liquid prokinetic), unless stated otherwise. Prior to 2008, some patients – based on clinical judgement, were given Metoclopramide.

The patients are allowed to drink clear fluids after 2 hours and consume a light meal/ snack after 4 hours.

Appendix 2

The work described in this thesis has resulted in the following publications:

- **I. Koulaouzidis A**, Iakovidis DK, Karargyris A, Plevris JN. Optimising lesion detection in small-bowel capsule endoscopy: from present problems to future solutions. Expert Rev Gastroenterol Hepatol. 2014; in press
- **II. Koulaouzidis A**, Plevris JN. Detection of the ampulla of Vater in small-bowel capsule endoscopy: experience with two different systems. J Dig Dis. 2012;13(12):621-7.
- **III. Koulaouzidis A**, Giannakou A, Yung DE, Dabos KJ, Plevris JN. Do prokinetics influence the completion rate in small-bowel capsule endoscopy? A systematic review and meta-analysis. Curr Med Res Opin. 2013 S;29(9):1171-85.
- IV. Dabos KJ, Giannakou A, Koulaouzidis A. Chewing gum and completion rate in small-bowel capsule endoscopy: meta-analyzing the data. Gastrointest Endosc. 2014;79(6):1032-4.
- **V.** Krystallis C, **Koulaouzidis A**, Douglas S, Plevris JN. Chromoendoscopy in small-bowel capsule endoscopy: Blue mode or Fuji Intelligent Colour Enhancement? Dig Liver Dis. 2011;43(12):953-7.
- VI. Koulaouzidis A, Smirnidis A, Douglas S, Plevris JN. QuickView in small-bowel capsule endoscopy is useful in certain clinical settings, but QuickView with Blue Mode is of no additional benefit. Eur J Gastroenterol Hepatol. 2012;24(9):1099-104.
- VII. Karargyris A, Rondonotti E, Mandelli G, Koulaouzidis A. Evaluation of 4 three-dimensional representation algorithms in capsule endoscopy images. World J Gastroenterol. 2013;19(44):8028-33.
- **VIII. Koulaouzidis A**, Karargyris A. Use of enhancement algorithm to suppress reflections in 3-D reconstructed capsule endoscopy images. World J Gastrointest Endosc. 2013;5(9):465-7.
- **IX. Koulaouzidis A**, Karargyris A, Rondonotti E, Noble CL, Douglas S, Alexandridis E, Zahid AM, Bathgate AJ, Trimble KC, Plevris JN. Three-dimensional representation software as image enhancement tool in small-bowel capsule endoscopy: a feasibility study. Dig Liver Dis. 2013;45(11):909-14.
- **X**. Rondonotti E, **Koulaouzidis A**, Karargyris A, Giannakou A, Fini L, Soncini M, Pennazio M, Douglas S, Shams A, Lachlan N, Zahid A, Mandelli G, Girelli C. Utility of 3-dimensional image reconstruction in the diagnosis of small-bowel masses in capsule endoscopy (with video). Gastrointest Endosc. ;80(4):642-51.

EXPERT REVIEWS

Optimizing lesion detection in small-bowel capsule endoscopy: from present problems to future solutions

Expert Rev. Gastroenterol. Hepatol. Early online, 1-19 (2014)

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This review presents issues pertaining to lesion detection in small-bowel capsule endoscopy (SBCE). The use of prokinetics, chromoendoscopy, diagnostic yield indicators, localization issues and the use of 3D reconstruction are presented. The authors also review the current status (and future expectations) in automatic lesion detection software development. Automatic lesion detection and reporting, and development of an accurate lesion localization system are the main software challenges of our time. The 'smart', selective and judicious use (before as well as during SBCE) of prokinetics in combination with other modalities (such as real time and/or purge) improves the completion rate of SBCE. The tracking of the capsule within the body is important for the localization of abnormal findings and planning of further therapeutic interventions. Currently, localization is based on transit time. Recently proposed software and hardware solutions are proposed herein. Moreover, the feasibility of software-based 3D representation (attempt for 3D reconstruction) is examined.

Keyworbs: 3D reconstruction • capsule endoscopy • diagnostic yield • FICE • innovation • lesion detection • small bowel • software

It has become customary - dare to say almost cliché - for every review paper on capsule endoscopy (CE) to start with a statement along those lines: the advent of wireless capsule endoscopy has revolutionized the investigation pathways for the small bowel [1]. Admittedly, since its official introduction in clinical practice (2000) [2], CE has drastically changed clinical decision-making by restructuring our diagnostic approaches and increasing the diagnostic yield (DY). A wealth of evidence has confirmed the validity of the use of CE in obscure gastrointestinal bleeding (OGIB) - the latter accounts for 60-70% of all small-bowel CE examinations world-wide - and Crohn's disease (CD), known and/or suspected [3]. Other clinical indications, although less common, are celiac disease, small-bowel polyposis syndromes and/or clinical or radiological suspicion of small-bowel neoplasia [4-8]. To date, more than 2 million capsules have been ingested worldwide and >3000 PubMed-listed publications have appeared in the medical literature [1].

However, 'nothing endures but change' [9] and every disruptive technology, such as CE, brings new solutions together with new challenges [10]. For instance, CE approaches an almost 'physiological or airless endoscopy' [9.11.12]. Often, in digestive endoscopy, air insufflation (especially over-insufflation) leads to imaging difficulties as it can make lesion edges difficult to detect [11]. Conversely, the capsule moves passively — propelled by bowel peristalsis — and images the intestinal mucosa in a collapsed state [13]. All commercially available CE devices are constructed following the same baseline principles.

To begin with, the shape and volume of any CE device is sufficiently small to allow it to pass through the main anatomical sphincters (cricopharyngeous, lower esophageal sphincter, pylorus and ileocecal valve) without becoming an obstruction risk [13]. Nevertheless, it is this same small size — in conjunction with the peristaltic movements of the small bowel — the 'Achilles tendon' of the capsule,

predisposing the CE to rotate (or tumble) within the smallbowel lumen. This frequently results in deficient luminal and/ or mucosal coverage [14]. The tumbling movements of the capsule (oblique-forward, oblique-reverse, perpendicular movements) often result in temporary visual interference that may render the images unsuitable for diagnostic purposes [15]. Furthermore, it is already known that even expert reviewers have a limited ability to recognize the vector of capsule movement in the small-bowel lumen or through anatomical sphincters [16-18].

The capsules' sheath is made of disposable and biocompatible plastic material, resistant to digestive fluids (in order to seal and protect its internal components in the hostile 'milieu' of the GI tract); the capsule weighs between 3.3 and 6 g (depending on the CE model) (Table 1) [1]. The internal compartment of any CE device includes a complementary metal oxide semiconductor (CMOS) imager or a high-resolution charge coupled device (CCD)-based chip camera, a short focal-length (hemispheric) and compact multi-element lens, a white-light illumination system - provided by four to six light-emitting diodes (LEDs) -, two silver oxide batteries and a transmitter. At first, it seemed that CMOS had advantages (as compared with CCD) of lower cost and power consumption (requires about 1% of the energy of CCD), improved foveal activity (the ability to select images at different sites on the chip), for them to be built relatively and integrated on production lines with computer chips, but they had the disadvantage of inferior

The imager, which has no shutter, operates by taking still frames in a dark environment intermittently illuminated by LEDs throughout the capsule passage. Capsule endoscopes offer an 8× magnification, and a minimum size of lesion detection in the range of 0.1-0.2 mm. The CE device is activated by its removal from a magnetic holder. Depending on the manufacturer, the operating time of capsules can vary between 8 and 15 h (TABLE 1) [1]. Commercially available small-bowel CE models can acquire and transmit between 0.5 and 16 frames per second (fps) [1]. This results to a total of 50,000-120,000 transmitted images that are 'stitched' and converted to a continuous video that gives the illusion of continuous digital video stream recording without gaps. Two fps is, of course, much lower than current standard television frame rates. Standard progressive frame rates have been 24 fps for sound motion pictures since the 1920s [9]. Furthermore, PAL and SECAM television is 25 fps and for NTSC television 30 fps. High-definition television systems use standards of 50 or 60 fps. These rates reduce the perception of flicker by the human eye [9].

In our center, we have experience with two small-bowel CE systems. Hence, in the next few paragraphs, we will briefly describe the technical characteristics and specifications of these two systems.

PillCam®SB

The first commercially available CE device (mouth-to-anus; M2A®) was developed by Given® Imaging Ltd (Yoqueam, Israel) and it was approved (for clinical use in humans) in Europe and the USA in August 2000. Initially, its battery life was about 6 h. The first generation of PillCamSB (essentially a renamed M2A) was released in 2001, while the second generation of PillCamSB was released in 2007 (PillCamSB2). The latest commercial small-bowel PillCamSB CE model (Pill-CamSB3) was released in 2013 [7.15]. PillCamSB2, which is still used in most centers, measures 11 × 26 mm and weighs <4 g [1,4]. It contains a miniature color video CMOS camera with four illuminating LEDs, two batteries, a radiofrequency (RF) transmitter and an antenna. Images are captured at a rate of 2 fps for PillCamSB2 or 4 fps for PillCam SB2-4, while the battery life is between 8 h (PillCamSB) and 12 h (PillCamSB2ex) (TABLE 1) [4].

Due to increased field of view (156°), PillCam SB2 has a broader mucosal coverage, as compared with 140° of its predecessor, and an effective visibility distance of 30 mm [19]. The image resolution of PillCam SB is 256 × 256 pixels. Advanced optics and bautomatic automatic light control provide optimal image quality and illumination. Therefore, at a reference working distance of 4.5 mm, the coverage mucosal area of PillCam SB2 is 1100 mm² as compared with 500 mm² of its predecessor [19].

The proprietary reading software of Given Imaging Ltd is the RAPID TM Reader and through repeated developments it has now reached its eighth version. This software interface provides single, dual or quadruple window video review as well as additional diagnostic features and study reviewing aids. It contains an improved user interface similar to the ribbon toolbar concept used in Microsoft® products, the Lewis Score calculator, the Fujinon Intelligent Colour Enhancement (FICE), the suspected blood indicator [1], QuickView (QV), a thumbnail comparison feature, backward compatibility with studies from previous RAPIDTM software versions and an improved progress indicator/localization guide.

MiroCam®

MiroCam (which stands for Micro Intelligent Robotic Object Camera) has been developed by the intelligent Microsystem center established by the Korea Ministry of Science & Technology in Seoul, South Korea, which was renamed to IntroMedic Co Ltd in 2006 [15]. The company's small-bowel CE device passed the European medical standards and received certification (CE mark) in 2007; it also received the US FDA approval in May 2011 [3.8]. MiroCam (currently version 2, version 3 to be released in 2014), utilizes a novel transmission technology, the electric field propagation. This technology uses the capsule itself to generate an electrical field and the human body as a conductive medium for data transmission, in the so-called human body communication. Perhaps this, in conjunction with the set array of sensors, is the main reason for the persistent failure of this CE model to capture upper esophageal and gastroesophageal junction (Z-line) images [20].

Specifications of the MiroCam CE device include a size of 10.8 × 24.5 mm, a weight of 3.4 g, a field of view of 170°

Capsule endoscopy	Company, country	75 C	lmage sensor	Transmission Frames per second	Frames per second	Dimensions (mm)		Weight Battery (g) life (h)	Reviewing software	Optical enhancements
PillCam [®] SB2	Given [®] Imaging, Israel	156	CMOS	Radiofrequency	2-4	11 × 26	3,45	9->11.5	RAPID™v8	Blue mode; FICE 1, 2, 3
MiroCam ²⁰ v2	IntroMedic® Co., Korea	170	CMOS	Electric field propagation	3	ø11 × 24	3.2	12	MiroView* v2	ALICE; color mode
EndoCapsule*	Olympus© Co., Japan	145	CCD	Radiofrequency	2	ø11 × 26	3.45	10	OLYMPUS®WS-1	Contrast imaging
owow.	Chongding Jinshan Science & Technology Co., China	140	CCD	Radiofrequency	2 (variable) 13 × 27.9	13 × 27.9	o	∞	OMOM® workstation	N/A
CapsoCam*SV	CapsoVision** Inc., USA	360	NA	On- board – EPROM flash	16 (4 per camera)	11 × 31	N/A	15	CapsoView*	NA

(150° of the first model), a resolution of 102,400 (320 × 320) pixels and an image capture rate of 3 fps (Table 1) [1]. Illumination is provided by six LEDs. As a power-saving method, it incorporates two external electrodes and a single skin electrode for electric data conduction across the human body. Hence, it avoids the need for RF and allows for a long battery life without any need for image compression and a safer use in a significant minority of patients, that is, those with implantable pacemakers or in situ defibrillator devices [21,22]. Furthermore, MiroCam remains the smallest commercially available smallbowel CE device. The extra available space (10% free internal space) could be used for additional internal components, such as different sensors or stabilizing components for advanced CE. The two systems have been repeatedly checked in head-to-head trials and have been shown to have at least equivalent capability in detecting small-bowel disease [1.23].

MiroView™

MiroView v2.0, the proprietary reading software of IntroMedic® Co Ltd, offers a variety of tools and functions to aid reporting process. For instance, the function Range View displays a range of images to readily identify landmarks in the GI tract. In this mode, the side bar images will move one image per second, while the center images will display images per user selection, that is, 15 fps. Another function, the Map-View, which is similar to Given Imaging Ltd color bar but uses different technology and patent, displays a range of thumbnail images to readily identify landmarks in the GI tract. Furthermore, the Express View eliminates similar images and the Range View can be used to identify landmarks and disease pathologies by viewing a total of nine images before and after the main image. In the image-enhancement field, MiroView offers the ALICE and color mode functions. Admittedly, they have not attracted clinicians' attention or any clinical studies to date.

Diagnosis, DY & expertise in CE

Essentially, DY in CE is the combination of lesion detection and lesion interpretation. CE procedure is not operatordependent and does not require the same technical skills as conventional GI endoscopy [11,24]. Indeed, capsule administration and swallowing requires only a couple of minutes and no special skills - apart from obtaining an informed consent [25] - on behalf of the healthcare professional. Therefore, accurate diagnosis and expertise with CE lies purely in the ability of an individual reviewer to read and interpret the CE findings [26]. Of note is that key indicators of expert interpretation (of any type of medical images) are consistent, accurate and efficient diagnostic performance, which requires not only formal and dedicated training, but also a certain degree of talent, aptitude and motivation [27].

So, in the end, despite great technologic advances, it boils down to the CE reviewer and the act of observation [11]. Hence, vigilance is especially necessary when the task is long and monotonous [11,28]. As CE is a by and large a visual

modality, it would seem that in order to optimize training, an understanding of how visual perception and skills develop and change as a function of experience would be beneficial [27,29,30]. Nonetheless, although the latter is bound to improve with experience, recent studies showed that the lesion detection is not improving with the numbers of CE reviews [31].

There are certain reasons behind that. First, the average CE video footage reading time varies between 30 and 120 min depending on the small-bowel transit, quality of images and the experience of the reader [11,28,32]. Second, a small-bowel lesion may only be visible in just a few or even just a single frame [33]. Not surprisingly, most physicians familiar with CE review are concerned that lesions could easily be missed when fast reviewing rates are applied [11]. Therefore, at a consensus conference of CE users (International Conference of Capsule Endoscopy) in 2002, it was agreed that 15 images per second is the fastest acceptable rate for CE review [11,34]. Conversely, Fleischer [35] argued that the time required to read the studies (60-90 min) does not make economic or practical sense [11.35]. Indeed, periods greater than 50 min increase the stress to the observer no matter what the cue or event rate is [1136]. Third, it has been demonstrated that search patterns are somewhat unique to the individual and tend neither to be uniform in image coverage nor to alter with experience [27].

Although relevant work has been performed in other specialties, for example, radiology and pathology, where it has been shown that specialty experts generally adopt similar visual search strategies [27], similar research experience in CE is lacking (apart from experts' opinion papers). Nevertheless, we know from colonoscopy quality-improvement studies that prolonging scope withdrawal time is associated with increased adenoma detection rate [37,38]. Therefore, the current notion is that large amount of visual information, for instance, CE footage, requires focused and undivided attention for careful evaluation by the CE reviewer [32,39].

However, going (at low reviewing speed) through a rather monotonous video recording, in a room with deemed lights, is the perfect way for someone to become hypnotized [32]. To date, only limited data address errors in CE lesion detection [11,32,33]. As such, there is still significant heterogeneity in reviewing modes and interpretation sessions timing and length, lesion detection rates and reviewer competency, detect and interpret capsule endoscopy [33,40,41]. Furthermore, there is also limited published data concerning optimizing operator performance for interpretation of capsule endoscopy [33,42].

One proposed strategy to reduce CE reading times would be to use trained non-physician readers (e.g., endoscopy assistants/ scientists) to pre-read the CE footage [24,43], (TABLE 2) [24,43-54]. However, training pre-readers is time consuming, not standardized and may not be feasible during regular business hours [44]. Furthermore, the majority of studies in this field attempt to prove non-inferiority lesion detection (by physicians' extenders or specialty nurses) instead of focusing on lesion interpretation. The lack of an homogenous approach (viewing speed and/or mode) in CE review seems to account for some of the reported

discrepancies in DY and inter-observer agreement on CE videos interpretation [33,41,55]. In the majority of these studies, however, the gold standard was the physician's detection rate, a reference 'shaky' enough as recent studies have shown [31]. Interestingly, there are currently no standardized, validated training tools for capsule endoscopy. Couple of attempts by Postgate et al. have not found wider acceptance [42,49].

Another approach is to use to special software programs to select significant images for subsequent viewing [1,47]. In light of all that, several attempts have been made to develop technical software features, in order to make CE video analysis easier and shorter (without jeopardizing its accuracy or in other words its DY). The first software feature designed for this purpose was the suspected blood indicator, an automatic system able to pick up, in a completely automatic fashion, frames containing several red pixels and, therefore (theoretically) to detect blood and or other red-colored lesions such as big angioectasias. Nevertheless, the accuracy profile of this tool is suboptimal and, at the present time, it can be used only as supportive/adjunct tool in CE reporting [1].

In a single-center prospective study, gastroenterology fellows were trained in capsule endoscopy using a structured program devised by the American Society of Gastrointestinal Endoscopy and subsequently evaluated using a newly developed formalized assessment tool called the Capsule Competency Test [26,56]. The capsule competency test score obtained by staff capsule endoscopists was considered the gold standard; achievement of a score that was 90% of that achieved by staff members was taken as optimal competence. Of 39 fellows involved in the study, the mean scores for trainees with <10, 11–20 and 21–35 capsule endoscopy interpretations were 79, 79 and 85%, respectively. Hence, the authors suggest that fellows need to perform at least 20 supervised capsule endoscopies before they can be certified as adequately trained [26,56,57].

Localization of capsule & lesion

Capsules do not provide localization information while traversing the GI tract [14,58]. The tracking of the capsule within the body is important for the localization of abnormal findings and planning of further therapeutic interventions. Currently, localization is based on transit time. Once the pylorus and cecum are identified, the location of a lesion in the small intestine is an estimate based on the time from one of these two points [58]. The output of these localization modules is a graphic trajectory of the capsule while it moves along the intestinal lumen [8.59]. This method uses signal strength analysis from aerial antennae attached to the patient's abdomen has been validated on healthy volunteers against fluoroscopy [59].

However, this technique has been criticized for its inability to definitively localize small bowel lesions, mainly because it is prone to inaccuracy due to differences in small-bowel transit time or variant anatomy [58]. The average position error reported for this technique is 3.77 cm, with a maximum error reaching 11.4 cm [39.58.59]. Most commercially available software packages provide a 2D tracking application of the capsule

of origin Bossa et al. Italy (2006) Brock et al. USA (2012) Dokoutsidou et al. Greece (2011) Drew et al. (2013) UK Fernández- Spain	rigin studies	Physicians	Name and Address of the Owner, where the Owner, which is the Owner, where the Owner, which is the Owner,	The same of the last of the la					
et al. sidou et al. t al. (2013)			Non- physicians	Physicians	Non- physicians	measure/s	agreement		
. et al. (2013)	39	1 (GI)	RGN	n/s	n/s	Lesion	Kappa = 77–85%	High to excellent I/A	[52]
sidou et al. t al. (2013)	220	2	RGN	n/s	None	Lesion	£6 → 85%	Physicians	Ŧ.
	re 102	1 (GI)	RGN	Experienced	>50 supervised CE reviews	Lesion	70-100%	Consensus of 2, no RS	145
	95	Physician	RGN	>2000	>200	Lesion	99% agreement in thumbnails	Panel of 2 experts	124
(2008)	50	1 (GI)	PE × 2 (RGN, resident)	experienced	rVs	Lesion	79% GI physician 86% RGN 80% resident	Consensus of 4, no RS	[20]
(2009) Leursen et al. Denmark	nark 30 × 2 (reviews)	-	RGN	None	None	Lesion detection	Dr. 48 — 62% RGN: 89 — 62%	Endoscopist, Given Imaging Review Service	[165]
Levinthal et al. USA (2003)	20	-	RGN			Lesion	93% of lesions detected by Dr	VA, no RS	[49]
Niv & Niv (2005) Israel	20	-	RGN	n/s	n/a	Lesion	i/a of 97% for significant lesions	GI was the gold standard	[53]
Postgate et al. UK (2008)	12, 22	2	RGN	None (prior to training)	None (prior to training)	Lesion	Improved with training for all	CE trainer	[113]
Riphaus et al. Germany (2009)	any 48	-	RGN	n/s	Experienced (n/s)	Lesion	94% of lesions detected by Dr	VA, no RS	14
Shiotani et al. Japan (2011)	44	2	RGN	>250 >100	Expert (n/s)	Lesion	No difference between readers	VA, no RS	<u>£</u>
Shiotani et al. Japan (2012)	100 (images) QuickView	3	RGN	1 250–350	150	Lesion	RGN 87% Physician 84% Physicians 63%	Selected	9+1
Sidhu et al. UK (2007)	20	1 (GI)	RGN	Experienced	None	Lesion	RGN identified all relevant findings	Another GI physician	[5]

route. More recently, 30 healthy volunteers swallowed a CE (EndoCapsule; Olympus, Japan) and then underwent five sets of anteroposterior and lateral radiographs every 30 min while the software calculated the position of the capsule. Average error (and standard deviation) among the 3D coordinates was X, 2.00 cm (1.64); Y, 2.64 cm (2.39) and Z, 2.51 cm (1.83). The average total spatial error among all measurements was 13.26 cm³ (22.72) [60].

On the other hand, an innovative capsule-based platform, motility monitoring system (MTS2) by Motilis Medica SA, Lausanne, Switzerland enables monitoring of regional transit time and a more accurate recording of capsule position. Furthermore, in the research domain two main approaches have been explored to retrieve positional information: magnetic field strength-based methods and electromagnetic wave-based methods [14,58].

In magnetic field strength-based methods, a permanent magnet is incorporated in the capsule, while an external array of magnetic sensors is placed outside the patient's body. As the capsule (with the incorporated magnet) moves, its magnetic flux changes in magnitude and direction and the external sensors can measure these magnetic signals. In electromagnetic wave-based methods, different electromagnetic waves have been utilized with lower position information accuracy. To date, only radio (RF) waves, visible waves, x-ray and gamma ray have been explored in literature because of their high penetrability through human tissue [14.58].

In order to improve lesion localization in small-bowel CE, we proposed a modified capsule which could incorporate localization and – theoretically – stabilization capabilities. This conceptual design consists of a capsule fitted with protruding wheels attached to a spring mechanism. This would act as a miniature odometer, leading to more accurate lesion localization information in relation to duodenal entry. Furthermore, this capsule could allow video stabilization as any erratic, nonforward movement through the gut is minimized [14.61.62].

In 2014, a software capsule localization approach was also presented [63]. This approach is based solely on a video analysis methodology for visual odometry. It includes automatic detection and tracking of points of interest, in consecutive CE video frames and application of a motion estimation model to calculate the displacement and the rotation of the capsule in the GI tract. Unlike the wheel odometry, visual odometry is not affected by wheel slip in uneven terrain or other adverse conditions. It has been demonstrated that it can provide more accurate measurements, with relative position error ranging from 0.1 to 2% [64]. Challenges with respect to its application in CE include coping with intestine deformability and motility, and coping with the presence of intestinal content.

DY & indicators

CE has advantages and disadvantages compared with other diagnostic modalities that evaluate the small intestine. The main advantage of CE is that it is a non-invasive technique with little or no side effects or complications [3]. Perhaps one the main disadvantages of CE is that its diagnostic accuracy is

difficult to determine due to a lack of an adequate 'gold standard'. Therefore, in the early days of CE, the term diagnostic accuracy has been substituted with the term DY. Due to the unique and intriguing nature of CE, DY is defined as the likelihood that a test or procedure will provide the information needed to establish a diagnosis [65].

In CE, the DY is influenced by several factors, integral to the capabilities of the capsule device (e.g., CE device technological specifications, quality and percentage of intestinal mucosal coverage), the challenging 'environment' of the small bowel and reviewer's performance. To date, human studies have compared different methods of small-bowel examination, reporting their comparative DY [1]. The true negative diagnostic rate was defined as the number of cases in which both methods of examination were negative. This is certainly only an approximation of a true yield. Historically, the DY of CE varies between 38 and 83% [66,67].

One method to determine and – at a second stage attempt to improve the DY of any diagnostic procedure – is to use markers (at least some of which are in a difficult position to be seen) that are present in every intestine and confirmed to be there with another test. This was first done in 2000, by Appleyard et al. [67]. who sewed glass beads into the intestines of dogs and then performed capsule endoscopy and push enteroscopy. The sensitivities were 64 and 37%, respectively. Another solution (more applicable to humans) is to look for an anatomical finding, that is, surrogate marker present in everyone [68.69]. Therefore, over the last few years, clinical researchers have highlighted the use of markers (some are in a position where they are difficult to spot), which are present in the intestine as quality assurance indicators in small-bowel CE [69].

The major duodenal papilla, or ampulla of Vater (AoV), which is present in all individuals who have not undergone duodenal resection and is located on the posteromedial aspect of the duodenal sweep, 8–10 cm distal to the pylorus, is a reasonable candidate marker. It is difficult to see, as the translucent dome of the propelled CE tends to point toward the outer aspect of sharply angulated bowel loops. On the other hand, choosing the AoV as the marker and extrapolating the results of the detection to polyp lesions may not be completely reliable [1,69,70].

The factors that make the AoV difficult to observe, such as the location, size/lumen protrusion and capsule transit speed in this intestinal segment, are only part of the reason why small-bowel lesions such as polyps may be missed in the small-bowel CE examination [69,70]. Misinterpretation of a mass for a bulge is an area of immense research and another potential pitfall of the CE reader, no matter what the experience level is [5,10,33,71]. Moreover, the notion that 'we can only see what the small intestine offers through its own aiming and propulsion of the video capsule' has never been more contemporary [69]. Indeed, with the advent of panoramic/side-viewing CE, it has become evident that the AoV is not seen in vast majority (as it was expected) and that the panoramic views (at least at present) are not panacea in CE [KOULAOUZIDIS A, BARTZIS L, PLEVRIS JN. ABSTRACT IN UEGW 2014, UNPUBLISHED DATA] [72]. Maneuverer ability and external

The issue of prokinetics in small-bowel capsule

Maximum DY in small-bowel CE requires not only optimal visualization of the intestinal mucosal surface, but also complete capsule transit through the entire small bowel [75,76]. Currently, one of the major limitations of small-bowel CE is the high rate of incomplete examinations, that is, the percentage of cases in which the capsule does not reach the cecum by the end of the recording period and/or exhaustion of capsule's battery life. Recent systematic reviews showed that the completion rate (CR) of small-bowel CE varies between 81.3 and 83.5% (for retrospective and prospective studies, respectively) [1.66]. If complete enteroscopy is not achieved, concerns remain over missed small-bowel pathology [77]. This could lead to repeated or new investigations increasing healthcare costs.

Risk factors for incomplete CE include intestinal dysmotility (e.g., prior small-bowel surgery, diabetes mellitus), immobility/ hospitalization, patient's age, moderate or poor bowel cleansing and a delayed gastric transit time >45 min [78-81]. Furthermore, the presence of small intestinal debris, chyme, biliary secretions and/or air bubbles can interfere with the visualization quality and potentially affect the DY. However, reducing small-bowel transit time may influence the DY of CE. With colonoscopy, the detection rate of neoplastic lesions is higher when the time to withdraw the colonoscope is longer [82]. It is conceivable that a similar principle also applies for small-bowel CE.

Therefore, it is expected that decreasing gastric transit time and small-bowel transit time will allow a capsule to successfully reach the cecum by the end of its battery life. To this end, a variety of prokinetic agents has been used. Metoclopramide remains the most commonly administered prokinetic [1,5,83]. Domperidone, an antidopaminergic agent, on the other hand has not been widely used in small-bowel capsule endoscopy and the evidence base is limited [1,5,84]. Unlike metoclopramide, it does not readily cross the blood-brain barrier; hence it lacks extrapyramidal adverse effects [84,85]. Recently, few studies evaluated the use of metoclopramide, erythromycin, mosapride, lubiprostone, daikenchuto or even postural 'tricks' and chewing gum. Prompted by a recent study by Ou et al. [85], we conducted a meta-analysis demonstrating that there is currently no evidence to back the use of chewing gum in CE [86].

The issue of improving CR in small-bowel CE is contentious. Although some evidence exists, current guidelines indicate that there is no strict recommendation on the use, type and/or mode of administration of prokinetics in small-bowel CE [83,87,88]. However, in a recent meta-analysis we showed that the use of prokinetics for capsule ingestion improves CR in small-bowel CE [89]. This effect appears to be particularly evident with metoclopramide, when used concurrently with purging and/or use of real-time monitoring. Furthermore, in a small number of studies, erythromycin showed - through its gastrokinetic effect - marginal benefit. However, perhaps the most important message of our meta-analysis was that none of the prokinetic in current use has a beneficial effect on smallbowel CE DY. Although it is anticipated that in the foreseeable future the use of newer capsule endoscopes (with extended battery life) will improve both CR and potentially DY, there is a constant interest to standardize the CE procedure and lead to the development and content validation of reporting competence, reflective of practice across institutions [89,90]. To this end, the 'smart', selective and judicious use (before as well as during small-bowel capsule endoscopy) of prokinetics in combination with other modalities, such as real time and/or purge, in improving the CR of small-bowel CE [90].

FICE & blue mode

In recent years, virtual chromo-endoscopy techniques have been proposed to enhance microvascular contrast and facilitate minute resolution of superficial patterns and color differences. In 2005, Fujinon Corp (Saitama, Japan) developed FICE as a new type of image-enhanced endoscopy with the potential to improve detection of lesions in the upper GI tract and enhance differentiation between neoplastic and non-neoplastic tissue [91]. FICE is a digital imaging technology based on arithmetical processing of ordinary images; this is executed by external software and allows processing of ordinary images that were captured by the standard video CE devices [92]. The spectrum of wavelength used for creation of optical images is influenced by several factors such as the light spectrum of the light source, the optical device and the spectral sensitivity of the sensing elements. The wavelengths are associated with laminar structures and blood flow in the GI mucosa that has been altered by inflammation or neoplasm, which acts as a scattering element and interferes with the reflectance spectrum [93].

The FICE software was successfully implemented within the RAPID® Reader reporting software (Given Imaging Ltd). The CE reviewer can select flexibly between standard imaging and three different FICE-enhanced settings with different wavelength patterns by a simple push on the relevant toggle button [93]. Essentially, FICE can provide high-contrast images by selecting the wavelength suitable for a specific structure of mucosal structures or vessels. In CE, three FICE settings with different spectral specifications (wavelengths) have been introduced. Data available thus far show that application of FICE in small-bowel CE videos leads to improved image quality and definition of the surface texture of small-bowel lesions [1,92,93]. Although this seems to facilitate the visualization of smallbowel findings, its beneficial effect on lesion detectability, and overall its clinical impact, is still debatable [1,94]. A similar function from Olympus Inc. showed promising results [95].

An additional filter named the RAPID interface offers is the blue mode (BM) filter. BM filter is a color coefficient shift of light in the short wavelength range (490-430 nm) superimposed onto a white (red, blue, green; RGB) light image. There is a growing pool of experts' opinions that BM improves lesion visualization in the majority of cases. However, our results have

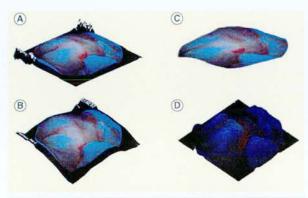


Figure 1. 3D reconstruction of a capsule endoscopy images with four different shape-from-shading (SfS) algorithms. (A) Tsai's, (B) Ciuti's, (C) Barron's, (D) Torreao's.

failed to prove a benefit of applying BM in few clinical scenarios [96-98]. Further multicenter studies are required to guide a more standardize approach in CE review and application of relevant software.

QV & capsule endoscopy

As aforementioned, one of the limitations of small-bowel CE is the reading time required for the interpretation of lengthy video streams. QV is a computational tool, which scans all images and scores them according to the possible level of significance. Eventually, its output is CE images of potential interest to the CE reader, providing a fast pre-viewing option [99]. The number of images to be considered 'frames of interest' can be set as a percentage (e.g., 5, 10, 20, 80%, etc.) of the full video. Then, according to the percentage level set by the user, QV displays a shortened video as compared with normal mode view. Recently published data give evidence that this target seems to be accomplished in small-bowel CE video reading with a high sensitivity in the per-patient per-lesion analysis (1,98,100,101).

Recently, we showed that QV pre-read in urgent cases, but fails to show any benefit in other clinical scenarios. Although the benefits of QV are outweighed to some extent by a decrease in the overall DY, this mode can be used confidently in overt OGIB in an urgent inpatient setting and in outpatients with occult OGIB or suspected CD. As the usefulness of QV may vary, depending on the number of small-bowel lesions, standard review settings are still recommended in all other cases. Furthermore, we confirm that BM does not confer any additional advantage in the QV setting [1,98]. However, Halling et al. [100] suggest that, despite a significant number of missed lesions, QV-CE is a safe and time reducing method for diagnosing small-bowel CD. To avoid false-negative cases, they recommend viewing the terminal ileum in standard view. Furthermore, a recent study from Germany [101] shows that the reliability of QV in detecting colorectal polyps in colon capsule endoscopy as compared with regular review reading is notable. However, if no significant polyp is presented by QV, normal type reading must be performed afterward.

3D reconstruction in capsule endoscopy

To date, limited research has been carried out in developing methods and materials that are required to make 3D representation of the digestive tract [102]. Since the capsule needs 6-8 h to traverse through the small bowel [103,104], cameras within the currently marketed capsule endoscopes work at a capture rate of 0.5-3 fps in order to comply with power requirements [1.7.8]. However, this has an adverse effect on the smoothness of motion between consecutive frames and creates a visually unpleasant effect to the human eye [13,62,105]. Furthermore, shape is an important element in human perception; yet, unlike other diagnostic modalities, that is, computed tomography, MRI, CE suffers from lack of 3D information [105]. 3D technology is currently in use, for example, a magnetometer can provide not only acceleration values on the three axes, but also the 3D orientation of the device. Commercial time-offlight range cameras (i.e., Microsoft's Kinect Project), already exist in the market and in the near future this may be further improved and miniaturized for use inside a capsule endoscope [106]. These cameras offer information on depth and color. Furthermore, we should not forget that 3D guidance systems are already used for endoscopic surgeries offering 3D position information of the sensor. Therefore, using the acquired information (orientation, acceleration, depth values, position, etc.) from these miniature sensors in conjunction with sophisticated registration software algorithms, an accurate 3D representation of the digestive tract could be created successfully [105].

For conventional endoscopy systems, stereo technology has been introduced to capture stereo images and to create depth information and therefore 3D reconstruction of digestive structures. However, due to issues with size, such systems have not been widely accepted [8,107]. Likewise, in CE there has been a hardware approach that provides in real time both 3D information and texture using an infrared projector and a CMOS camera. The major drawbacks of this system are its size, power consumption and packaging issues [8].

Therefore, in order to tackle the problem of the current hardware limitations, a software approach based on monocular images - shape-from-shading (SfS) - has been proposed to approximate a 3D representation of digestive tract surface utilizing current CE technology. The SfS technique, firstly proposed by Horn [108], is a member of a family of shape recovery algorithms called shape-from-X techniques [106], which has the capability to recover the shape of objects presenting a single image using the gradual variation of shading. The SfS problem is to compute a 3D shape from a grayscale image [108]. However, this problem has no single solution (105,108). There are four publicly available SfS algorithms. In a recent study, we used three CE experienced reviewers and asked to evaluate 54 2D images (categories: protrusion/inflammation/vascular), which were transformed to 3D by the aforementioned SfS algorithms (Figure 1) [109]. The best algorithm was selected and inter-rater agreement was calculated. Tsai's algorithm unanimously outperformed other 3D representation software [109].

Study (year)	Title	Aim	Methods	Ref.
Kolar <i>et al.</i> (2010)	A system for an accurate 3D reconstruction in video endoscopy capsule	An embedded active vision hardware system that is able to give in real time both 3D information and texture	An integrated wireless 3D vision system based on active stereovision technique. It uses CMOS technology for the camera and RF transmitter	[106]
Karargyris et al. (2010)	3D representation of the digestive tract surface in CE videos	Retrieve 3D shape approximation from individual CE frames	Use shape-from-shading technique (Tsai's linear method) on CE frames to estimate shape from 'flat' CE frames	[61]
Ciuti <i>et al.</i> (2012)	Intra-operative monocular 3D reconstruction for image-guided navigation in active locomotion capsule endoscopy	Accurate trajectory planning and ultimately automatic CE active capsule navigation	Calibrate a shape-from-shading system to recover the unknown scale factor immediately prior to a CE procedure	[155]
Prasath <i>et al.</i> (2012)	Mucosal region detection and 3D reconstruction in CE videos using active contours	Obtain a 3D reconstruction of the mucosal tissues	Use a near-light perspective shape-from-shading technique for 3D reconstruction of CE frames	[116]
Sun <i>et al</i> . (2010)	3D reconstruction based on capsule endoscopy image sequences	Build up 3D model of the patient's tract, which can supply exact locating information and support navigation during the intervention	Camera calibration, features detecting and matching, fundamental matrix computation, extrinsic matrix obtained and 3D reconstruction	[117]
Fan <i>et al.</i> (2010)	3D reconstruction of CE images	Create a realistic friendly three dimension view to help the physicians to get a better perception of the GI tract	Apply SIFT algorithm to extract the feature points for two consecutive CE frames. Then apply the epipolar geometry to calculate the extrinsic parameters to find the 3D spatial point location	[118]

However, light reflections on the surface of the digestive tract are still a significant problem. Therefore, we constructed a phantom model/simulator in an attempt to check the validity of a highlight suppression algorithm. Our results confirmed that 3D representation software performs better with simultaneous application of a highlight reduction algorithm. Furthermore, 3D representation follows a good approximation of the real distance to the lumen surface [109.110].

Tsai's algorithm was also tested in a phantom simulator, prepared from readily available materials such as cardboard boxes [111.112]. To represent the different colors and shapes seen inside the small intestine, flat or protruding objects in red, yellow and white were used in the phantom models. Our experiments showed that the accuracy of the 3D representation was 90, 70 and 45% for red, yellow and white phantom models, respectively. Subsequently, 192 CE images were reviewed: 50 vascular, 73 inflammatory and 69 protruding lesions. Visualization was more enhanced for vascular pathology than it was for inflammatory or protruding lesions (56 vs 23 vs <10%, respectively) [111.112].

Of course, improved visualization - or even detection - does not automatically lead to more accurate diagnosis. The latter is perhaps more evident when CE reviewers are facing the 'mass or bulge' diagnostic dilemma [10,113]. The results of a recent study confirm that the distinction between masses and mucosal bulges in small-bowel CE is still a challenging task even for experienced readers. In this situation, review experience seems to have a primary role [71.114]. However, the adjunct of 3D reconstruction to standard 2D video reading software significantly improves the performance of novice CE readers in distinguishing masses from bulges, thus potentially shortening their learning and lead to a reduced rate of false-negative diagnosis in expert hands. Similar results have been obtained by the application of the same software in esophageal capsule endoscopy [Koulaouzidis A, Bartzis L, Plevris JN. ABSTRACT IN UEGW 2014, OCT 2014, UNPUBLISHED DATA]. Further studies are needed to test the feasibility of 3D reconstruction in clinical practice and to evaluate the impact on the reviewing process in terms of both time and DY. In TABLE 3, the current research in 3D is tabulated [107,115-119].

Construction of panoramic visual summaries

Recently, a revolutionary approach to the visualization of CE videos has been proposed as a means to artificially broaden the field of view of capsule endoscopes [119-121]. It is based on an

Study (year)	Abnormalities	Largest dataset	Features	Best result	S	Ref.
		Images/Patients		Accuracy	Sens/Spec	
Sainju et al. (2014)	Blood	1500/3	C	81.0-98.0	71.0-99.4/72.1-99.3	[129]
Figueiredo et al. (2013)	Blood	4000/10	C	84.9-92.7	62.1-92.9/>90.0	[130]
Pan et al. (2012)	Blood	40	C		90.0/97.0	[131]
Charisis et al. (2012)	Ulcers	174/6	C, T	95.4	90.9/89.4	[132]
Kumar et al. (2012)	CD lesions	533/47	C, T	92.0		[133]
Li & Meng (2012)	Tumors	1200	C, T	92.4		[134]
Li & Meng (2012)	Tumors	1200	C, T	83.5 ± 1.3	84.7 ± 1.5/82.3 ± 1.9	[135]
Li & Meng. (2011)	Tumors	1200	C, T	90.5	92.3/88.7	[136]
Mamonov et al. (2014)	Polyps	18,900/5	C, S		81.0/90.0	[137]
Li & Meng (2012)	Polyps	1200/10	C, T	91.6		[138]
Karargyris & Bourbakis (2011)	Polyps, ulcers	100	C, T, S		Polyps: 96.2/70.2 Ulcers: 75.0/73.3	[139]
Szczypinski et al. (2011)	Blood ulcers Petechiae	800/20	С, Т		Blood: 100.0/97.0 Ulcers: 98.0/88.0 Petechiae: 90.0/94.0	[140]
Szczypinski et al. (2014)	Blood ulcers	613/50	C, T		Blood: 100.0/99.0 Ulcers: 83.0/94.0	[141]
Chen et al. (2013)	Hookworm	1700/10	C, T	88.7 ± 2.0	84.5 ± 6.4/93.0 ± 2.0	[142]
Segui et al. (2012)	Intestinal content	50,000-100,000/50	C, T	91.6	80.1 ± 16.7/93.1 ± 7.9	[143]
HajiMaghsoudi et al. (2012)	Informative frames	400/52	C	93.7	95.1/92.7	[144]

image processing and analysis methodology, according to which consecutive CE video frames are automatically transformed, for example, rotated and scaled, so as to find matches between them, and stitched together in a way that they seamlessly form a panoramic image [121]. By repeating this process for consecutive clusters of video frames over the original CE video, a new video composed of panoramic video frames is formed. The new video is composed of fewer frames than the original video since the frames of the new video are composed of multiple transformed frames of the original video. Therefore, the new video can be considered as a summary of the original one, and it requires shorter reading times by the reviewers. The experimental evaluation of this methodology on publicly available CE videos showed that it possible to reduce the number of images down to less than 15% of the original videos.

A similar approach has been proposed for next-generation capsule endoscopes equipped with special optics capable of capturing 360° panoramic images [122]. That study suggests the application of image stitching as a general approach to form a dissected view of the whole GI tract. Current approaches are still early; however, the perspectives of automatic image stitching in CE imaging are promising. Advances in other domains, such as the endoscopy of the bladder [123], indicate that it could be extended for the visualization of a whole organ as a surface mosaic.

Detection software; the present & the future

In order to improve the DY of CE, a variety of computer-based medical systems have been proposed. Such systems are capable of analyzing CE image sequences using algorithms that quantify the image features discriminating the abnormalities, and classifying them based on these features, for example, into normal and abnormal. The image features considered by these systems mainly include color (C) and texture (T), since these features have been documented as most discriminative by the endoscopists [124,125]. The shape (S) of the findings has also been considered as a feature for the discrimination of abnormalities; however, considering the diversity of the lesions and the deformability of the intestine, they may be suitable for the description of only a limited set of abnormalities, for example, small adenomatous polyps, which usually have an elliptic (2D) or hemispherical (3D) shape. Image classification is usually based on supervised machine-learning algorithms, such as neural networks, and support vector machines [126]. These algorithms are called supervised because they are trainable with annotated images considered as 'gold standard'. These images should include information about the presence, the location and the pathology of their contents, as assessed, usually, by a group of experts.

Automatic lesion detection methods have first appeared for polyp detection in flexible endoscopy [127]. One of the most

Study (year)	Project	Capsule device	Status	Active actuation	Magnetic propulsion	Therapeutic capabilities	Ref.
Tang et al. (2002)	IDEAS: a miniature lab-in-a-pill multisensory microsystem	Type I (rpe 2	Prototype	No	Yes	Yes	[166]
Karagozler et al. (2006)	Miniature endoscopy capsule robot using biomimetic micro- patterned adhesives	诗	Prototype	Yes 1 •	No	No	[148]
Quirini et al. (2007)	An approach to capsular endoscopy with active motion	20	Prototype	Yes	No	No	[149]
Valdastri et al. (2008)	Wireless therapeutic endoscopic capsule in vivo experiment	The same of the sa	Prototype	No	Yes	Yes	[150]
Glass et al. (2008)	A legged anchoring mechanism for capsule endoscopes using micro- patterned adhesives		Prototype	Yes	No	No	[151]
Valdastri et al. (2009)	An endoscopic capsule robotL a meso-scale engineering case study	Gears Leg-holder Screw Nut Cap Leg Motor	Concept	Yes	No	No	[152]

Study (year)	Project	Capsule device	Status	Active actuation	Magnetic propulsion	Therapeutic capabilities	Ref
Fortora <i>et al.</i> 2009)	Propeller-based wireless device for active capsular endoscopy in the gastric district		Prototype	Yes	No	No	[153
Valdastri <i>et al.</i> (2010)	A magnetic internal mechanism for precise orientation of the camera in wireless endoluminal applications	Andrew seed	Prototype	No	Yes	No	(154
Ciuti et al. (2009)	Robotic magnetic steering and locomotion of capsule endoscope for diagnostic and surgical endoluminal procedures	ROLL a	Prototype	No	Yes	Yes	[185
Bourbakis <i>et al.</i> (2010)	Design of new- generation robotic capsules for therapeutic and diagnostic endoscopy		Concept	Yes	No	Yes	156
Gao et al. (2010)	Design and fabrication of a magnetic propulsion system for self-propelled capsule endoscope	Magnet RF transmitter LEDs Anter Batteries Image sensor	Concept	No.	Yes	No	[157
Simi <i>et al.</i> (2010)	Design, fabrication and testing of a capsule with hybrid locomotion for gastrointestinal tract exploration	Abdominal wall	Concept	No	Yes	No	[15

Study (year)	Project	Capsule device	Status	Active actuation	Magnetic propulsion	Therapeutic capabilities	Ref.
Morita <i>et al.</i> (2010)	A further step beyond wireless capsule endoscopy	Propelling direction Rotation magnet Permanent Spring Capsule Capsule		No	Yes	No.	[159]
Vena et al		(A)		e voc	Ne	Na	1100
Yang et al. (2011)	Autonomous locomotion of capsule endoscope in gastrointestinal		Concept	Yes	No	No	[160]
Filip <i>et al.</i> (2011)	Electronic stool (e- stool): a novel self- stabilizing video capsule endoscope for reliable non- invasive colonic imaging	Stabilizing component MiroCam	Prototype	Yes	No	No	[161]
Yim & Sitti (2012)	Design and rolling locomotion of a magnetically actuated soft capsule endoscope		Prototype	Yes	No	No	[162]
Kong <i>et al</i> . (2012)	A robotic biopsy device for capsule endoscopy		Prototype	Yes	No	Yes	[163]
Woods & Constandinou (2013)	Wireless capsule endoscope for targeted drug delivery: mechanics and design considerations		Prototype	Yes	No	Yes	[13]

thorough review studies in this field [128] indicates that the technological revolution of CE led to a consequent increase of scientific contributions focused mainly on CE. Since then, over 30 different studies have been published on automatic detection of abnormalities in CE video sequences. A selection of the most representative ones is presented in Table 4 [129-145]. For each study, this table indicates the type of abnormalities being detected, the largest dataset used in the study (because some studies evaluate their methods in more than a single dataset), the features used and the best results reported. The results are presented in terms of average accuracy (number of correctly detected abnormal samples divided by the total number of samples) and/or average sensitivity and specificity.

Most studies investigate methods for the detection of blood [130-132], ulcers [133,140,142], polyps [138-140] or tumors in general [136,137]. Fewer studies investigate the detection of CD lesions [134], petechiae [141] and hookworms [143], whereas others aim to discriminate intestinal content, such as bubbles and turbid [144], or as it is more generally expressed, uninformative frames, including also dark parts of the images [145]. Hence, Table 4 shows that most studies focus on the detection of one class of abnormalities, and only a few studies address two or maximum three classes of abnormalities [140-143]. However, this is far from the real clinical problem posed by CE, where the detection of tens or even hundreds of abnormalities is necessary.

A relevant method aims to the detection of suspicious CE video frames, regardless of the pathology [146]. Instead of aiming to the detection of specific lesions, this method is capable of detecting any video frame with content that deviates from the content of the majority of video frames in a video segment. By repeating this process along the whole CE video, a number of representative video frames is bookmarked as possibly suspicious. Another advantage of this method is that it is unsupervised, that is, it does not require training, since it is based solely on the relations between the video frames. A drawback of this method is that it may return many false positives; however, its sensitivity has been evaluated high [147].

The results presented by the recent (and older) studies are generally high. However, a major problem is that they can be misleading for the actual performance of the investigated methodologies. Main reasons for that include: the datasets and the gold standards are usually unavailable; the evaluation may include bias; the studies rarely clarify if the training and the test include different images obtained from the same lesion, or other studies use very small datasets without the application of re-sampling methods, for example, cross validation; the accuracy, the sensitivity and the specificity are improper indicators.

of the system's performance, especially if the datasets are imbalanced [148].

Therefore, another important challenge, beyond the necessity of systems coping with multiple lesion detection, is the constituction of open access data repositories, which will provide QE images and videos along with gold standard information for reproducible experimentation by all researchers.

New capsules

Several research groups are working to design new models able to either actively move or remotely maneuvered through their journey in the small bowel [1.9]. These new capsules would allow not only recognizing a small-bowel lesion, but also, in a near future, collection of tissue samples and/or targeted delivery of drugs (Table 5) [13,149-164].

Expert commentary & five-year view

It is envisaged that longer battery times will lead to a marked reduction of incomplete small-bowel examinations; at the same time, cameras with different angle of view should permit assessment of depth and hence accurate, real 3D luminal views. The latter should be combined with higher quality imagers, allowing potentially the ability to zoom and get closer to the requirement of optical biopsying. The technological frenzy of our days will eventually lead to the production of remarkable small parts and this might allow the production of dissolvable capsules, including the use of nontoxic batteries. Furthermore, software developments should facilitate more efficient reporting and minimize false negatives. A computer-aided lesion detection has the potential to reduce reporting time and allow a more accurate use of capsule technology. However, research for automatic lesion detection can become more essential by providing solid public access to endoscopic data libraries.

The issue of improving the DY in CE has no epilogue. As with every technological achievement, realizing current limits is just a step to a subsequent exciting development. However, it is our opinion that the issue of automatic lesion detection and interpretation is one of the niche developmental areas in CE.

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Key issues

- · Automatic lesion detection and reporting and development of an accurate lesion localization system are the main software challenges
- · The 'smart', selective and judicious use (before as well as during small-bowel capsule endoscopy) of prokinetics, in combination with other modalities, such as real-time and/or purge, is crucial in improving the completion rate of small bowel capsule endoscopy. Caution is advised in unnecessary use of domperidone or metoclopramide for the elderly and those on multiple medications to avoid drug interactions, although such risk is most likely to be present with chronic rather than acute use.
- · Further studies are needed to test the feasibility of 3D reconstruction in clinical practice and to evaluate the impact on the reviewing process in terms of both time and diagnostic yield.
- The construction of open-access data repositories will provide capsule endoscopy images and videos along with gold standard information for reproducible experimentation by all researchers.

References

- Koulaouzidis A, Rondonotti E, Karargyris A. Small-bowel capsule endoscopy: a ten-point contemporary review. World J Gastroenterol 2013;19:3726-46
- Iddan G, Meron G, Glukhovsky A, et al. Wireless capsule endoscopy. Nature 2000:405:417
- Eliakim R. Video capsule endoscopy of the small bowel. Curr Opin Gastroenterol 2013:29:133-9
- ASGE Technology Committee. Wang A, Banerjee S, Barth BA, et al. Wireless capsule endoscopy. Gastrointest Endosc 2013;78:
- Ladas SD, Triantafyllou K, Spada C, et al. ESGE Clinical Guidelines Committee. European Society of Gastrointestinal Endoscopy (ESGE): recommendations (2009) on clinical use of video capsule endoscopy to investigate small-bowel, esophageal and colonic diseases. Endoscopy 2010;42:220-7
- Sidhu R, Sanders DS, Morris AJ, et al. Guidelines on small bowel enteroscopy and capsule endoscopy in adults. Gut 2008;57: 125-36
- Eliakim R, Carter D. Endoscopic assessment of the small bowel. Dig Dis 2013;31:194-8
- Fisher LR, Hasler WL. New vision in video capsule endoscopy; current status and future directions. Nat Rev Gastroenterol Hepatol 2012;9:392-405
- Swain P. At a watershed? Technical developments in wireless capsule endoscopy J Dig Dis 2010;11:259-65
- Girelli CM, Porta P, Colombo E, et al. Development of a novel index to discriminate bulge from mass on small-bowel capsule endoscopy. Gastrointest Endosc 2011;74:1067-74; quiz 1115.e1-5
- 11. Lewis BS. How to read wireless capsule endoscopic images: tips of the trade.

- Gastrointest Endosc Clin N Am 2004;14: 11-16
- 12. Adler SN, Metzger YC, Roesch T. The flat polyp: does too much flattening occur with full air insufflation on colonoscopy? Endoscopy 2010;42(Suppl 2)):E167-8
- 13. Woods SP, Constandinou TG. Wireless capsule endoscope for targeted drug delivery: mechanics and design considerations. IEEE Trans Biomed Eng 2013;60:945-53
- 14. Karargyris A, Koulaouzidis A. OdoCapsule: next generation wireless capsule endoscopy with accurate localization and video stabilization. IEEE Trans Biomed Eng 2014:Under review
- 15. Filip D. Self-stabilising capsule endoscope for early detection and biopsy of colonic polyps. Thesis for PhD, Dept of Electrical and Computer Engineering Calgary. Alberta, Canada 2013. Available from: http://theses.ucalgary.ca/handle/11023/495
- 16. Kopylov U, Papageorgiou NP, Nadler M, et al. Head or tail: the orientation of the small bowel capsule endoscope movement in the small bowel. Dig Dis Sci 2012;57:694-8
- Koulaouzidis A, Douglas S, Plevris JN. Heads or tail orientation in small-bowel capsule endoscopy: 2 capsule models with 2 reviewers. Dig Dis Sci 2012;57:1102-3
- Adler SN, Metzger YC. Heads or tails, does it make a difference? Capsule endoscope direction in small bowel studies is important. Endoscopy 2007;39:910-12
- 19. Metzger YC, Adler SN, Bar-Gil Shitrit A, et al. Comparison of a new PillCam^{TS} SB2 video capsule versus the standard PillCam™ SB for detection of small bowel disease. Reports in Medical Imaging 2009;2:
- Koulaouzidis A. Upper esophageal images and Z-line detection with 2 different

- small-bowel capsule systems. World J Gastroenterol 2012;18:6003-4
- 21. Chung JW, Hwang HJ, Chung MJ, et al. Safety of capsule endoscopy using human body communication in patients with cardiac devices. Dig Dis Sci 2012;57: 1719-23
- Bandorski D, Höltgen R, Stunder D, et al. Capsule endoscopy in patients with cardiac pacemakers, implantable cardioverter defibrillators and left heart assist devices. Ann Gastroenterol 2014;27:3-8
- Choi EH, Mergener K, Semrad C, et al. A multicenter, prospective, randomized comparison of a novel signal transmission capsule endoscope to an existing capsule endoscope. Gastrointest Endosc 2013;78:
- 24. Drew K, McAlindon ME, Sanders DS, et al. The nurse endoscopist: moving ahead with time. Gastroenterol Nurs 2013;36: 209-13
- 25. Koulaouzidis A, Pendlebury J, Douglas S, et al. Aspiration of video capsule: rare but potentially life-threatening complication to include in your consent form. Am J Gastroenterol 2009;104:1602-3
- Rajan E, Iyer PG, Oxentenko AS, et al. Training in small-bowel capsule endoscopy: assessing and defining competency. Gastrointest Endosc 2013;78:617-22
- Krupinski EA. Graham AR, Weinstein RS. Characterizing the development of visual search expertise in pathology residents viewing whole slide images. Hum Pathol 2013;44:357-64
- Cave DR. Reading wireless video capsule endoscopy. Gastrointest Endosc Clin N Am 2004;14:17-13
- Krupinski EA, Tillack AA, Richter L. et al. Eye-movement study and human performance using telepathology virtual slides: implications for medical education

- and differences with experience. Hum Pathol 2006;37(12):1543-56
- Helle L, Nivala M, Kronqvist P, et al. Do prior knowledge, personality and visual perceptual ability predict student performance in microscopic pathology? Med Educ 2010;44:621-9
- Zheng Y, Hawkins L, Wolff J, et al. Detection of lesions during capsule endoscopy: physician performance is disappointing. Am J Gastroenterol 2012;107:554-60
- Lo SK. How should we do capsule reading?
 Tech Gastrointest Endosc 2006;8:146-8
- Rondonotti E, Soncini M, Girelli CM. et al. AIGO, SIED and SIGE Lombardia. Can we improve the detection rate and interobserver agreement in capsule endoscopy? Dig Liver Dis 2012;44:1006-26
- Mishkin DS, Chuttani R, Croffie J, et al. Technology Assessment Committee, American Society for Gastrointestinal Endoscopy. ASGE Technology Status Evaluation Report: wireless capsule endoscopy. Gastrointest Endosc 2006;63: 539-45
- Fleischer DE. Capsule endoscopy: the voyage is fantastic-will it change what we do? Gastrointest Endosc 2002;56:452-6
- Galinsky T. Rosa R. Warm J. et al. Psychophysical determinants in sustained attention. Hum Factors 1993;35:603-14
- Butterly L, Robinson CM, Anderson JC, et al. Serrated and adenomatous polyp detection increases with longer withdrawal time: results from the New Hampshire colonoscopy registry. Am J Gastroenterol 2014;109:417-26
- Lee TJ, Rees CJ, Blanks RG, et al. Colonoscopic factors associated with adenoma detection in a national colorectal cancer screening program. Endoscopy 2014;46:203-11
- Spyrou E, lakovidis DK. Video-based measurements for wireless capsule endoscope IOP publishing: tracking. Meas Sci Technol 2014;25:015002; 14pp
- Korean Gut Image Study Group. Lim YJ, Joo YS, Jung DY, et al. Learning curve of capsule endoscopy. Clin Endosc 2013;46: 633-6
- Jensen MD, Nathan T, Kjeldsen J. Inter-observer agreement for detection of small bowel Crohn's disease with capsule endoscopy. Scand J Gastroenterol 2010;45: 878-84
- 42. Postgate A, Haycock A, Thomas-Gibson S, et al. Computer-aided learning in capsule

- endoscopy leads to improvement in lesion recognition ability. Gastrointest Endosc 2009;70:310-16
- Shiotani A, Honda K, Kawakami M, et al. Evaluation of RAPID(®) 5 Access software for examination of capsule endoscopies and reading of the capsule by an endoscopy nurse. J Gastroenterol 2011;46:138-42
- Brock AS, Freeman J, Roberts J, et al. A resource-efficient tool for training novices in wireless capsule endoscopy. Gastroenterol Nurs 2012;35:317-21
- Dokoutsidou H, Karagiannis S, Giannakoulopoulou E, et al. A study comparing an endoscopy nurse and an endoscopy physician in capsule endoscopy interpretation. Eur J Gastroenterol Hepatol 2011;23:166-70
- Shiotani A, Honda K. Kawakami M, et al. Analysis of small-bowel capsule endoscopy reading by using quickview mode: training assistants for reading may produce a high diagnostic yield and save time for physicians. J Clin Gastroenterol 2012;46: e92-5
- Riphaus A, Richter S, Vonderach M, et al. Capsule endoscopy interpretation by an endoscopy nurse - a comparative trial. Z Gastroenterol 2009;47:273-6
- 48. Postgate A. Haycock A, Fitzpatrick A, et al. How should we train capsule endoscopy? A pilot study of performance changes during a structured capsule endoscopy training program. Dig Dis Sci 2009;54: 1672-9
- Levinthal GN, Burke CA, Santisi JM. The accuracy of an endoscopy nurse in interpreting capsule endoscopy. Am J Gastroenterol 2003;98:2669-71
- Fernández-Urién I, Espinet E, Pérez N, et al. [Capsule endoscopy interpretation: rhe role of physician extenders]. Rev Esp Enferm Dig 2008;100:219-24
- Sidhu R, Sanders DS, Kapur K, et al. Capsule endoscopy: is there a role for nurses as physician extenders? Gastroenterol Nurs 2007;30:45.8
- Bossa F, Cocomazzi G, Valvano MR, et al. Detection of abnormal lesions recorded by capsule endoscopy. A prospective study comparing endoscopise's and nurse's accuracy. Dig Liver Dis 2006;38:599-602
- Niv Y, Niv G. Capsule endoscopy examination-preliminary review by a nurse. Dig Dis Sci 2005;50:2121-4
- Jang BI, Lee SH, Moon JS, et al. Inter-observer agreement on the interpretation of capsule endoscopy findings based on capsule endoscopy structured

- terminology: a multicenter study by Korean Gut Image Study Group. Scand J Gastroenterol 2010;45:370-4
- Buscaglia JM. "Drivers ed" with a road test for the capsule endoscopist. Gastrointest Endosc 2013;78:623-4
- Faigel DO, Baron TH, Adler DG, et al. ASGE. ASGE guideline: guidelines for credentialing and granting privileges for capsule endoscopy. Gastrointest Endosc 2005;61:503-5
- 57. Than TD, Alici G, Zhou H, et al. A review of localization systems for robotic endoscopic capsules. IEEE Trans Biomed Eng 2012;59:2387-99
- Fischer D, Schreiber R, Levi D, et al. Capsule endoscopy: the localization system. Gastrointest Endosc Clin N Am 2004;14: 25-31
- Marya N, Karellas A, Foley A, et al. Computerized 3-dimensional localization of a video capsule in the abdominal cavity: validation by digital radiography. Gastrointest Endosc 2014;79:669-74
- Karargyris A, Koulaouzidis A. Capsulcodometer: a concept to improve accurate lesion localization. World J Gastroenterol 2013;19:5943-6
- Karargyris A, Bourbakis N. Wireless capsule endoscopy and endoscopic imaging: a survey on various methodologies presented. IEEE. Eng Med Biol Mag 2010;29:72-83
- Iakovidis DK, Spyrou E, Diamantis D, et al. Capsule endoscope localization based on visual features. In Proceedings of IEEE International Conference on Bioinformatics and Bioengineering (BIBE), Chania, Greece, 2012
- Scaramuzza D, Fraundorfer F. Visual odometry, Part I: the first 30 years and fundamentals. IEEE Robot Autom Mag 2011:80-92
- Koulaouzidis A, Rondonotri E, Giannakou A, et al. Diagnostic yield of small-bowel capsule endoscopy in patients with iron-deficiency anemia: a systematic review. Gastrointest Endosc 2012;76:983-92
- Liao Z, Gao R, Xu C, et al. Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. Gastrointest Endosc 2010;71:280-6
- 66. Rondonotti E, Marmo R, Petracchini M, et al. The American Society for Gastrointestinal Endoscopy (ASGE) diagnostic algorithm for obscure gastrointestinal bleeding: eight burning questions from everyday clinical practice. Dig Liver Dis 2013;45:179-85

- Appleyard M, Fireman Z, Glukhovsky A, et al. A randomized trial comparing wireless capsule endoscopy with push enteroscopy for the detection of small-bowel lesions. Gastroenterology 2000;119:1431-8
- Cass OW. Is half-knowledge worse than ignorance? Gastrointest Endosc 2006;64: 542-3
- Koulaouzidis A, Plevris JN. Detection of the ampulla of Vater in small bowel capsule endoscopy: experience with two different systems. J Dig Dis 2012;13:621-7
- Rondonorti E, Koulaouzidis A, Karargyris A, et al. Utility of three-dimensional image reconstruction in the diagnosis of small-bowel masses in capsule endoscopy. Gastrointest Endosc 2014. [Epub ahead of print]
- Friedrich K, Gehrke S, Stremmel W, et al. First clinical trial of a newly developed, capsule endoscope with panoramic side view for small bowel: a pilot study. J Gastroenterol Hepatol 2013;28:1496-501
- Koulaouzidis A, Dabos KJ. Looking forwards: not necessarily the best in capsule endoscopy? Ann Gastroenterol 2013;26: 365-7
- Hale MF, Drew K, Baldacchino T, et al. Gastroscopy without a Gastroscope! feasibility in a porcine model using a magnetic capsule. Gut 2013;62:A156
- Swain P. The future of wireless capsule endoscopy. World J Gastroenterol 2008;14: 4142-5
- Rokkas T, Papaxoinis K, Triantafyllou K, et al. Does purgative preparation influence the diagnostic yield of small bowel video capsule endoscopy?: a meta-analysis. Am J Gastroenterol 2009;104:219-27
- Mergener K, Ponchon T, Gralnek I, et al. Literature review and recommendations for clinical application of small-bowel capsule endoscopy, based on a panel discussion by international experts. Consensus statements for small-bowel capsule endoscopy. 2006/ 2007. Endoscopy 2007;39:895-909; Erratum in: Endoscopy 2007;39:1105
- Yazici C, Losurdo J, Brown MD, et al. Inpatient capsule endoscopy leads to frequent incomplete small bowel examinations. World J Gastroenterol 2012;18:5051-7
- Triantafyllou K, Papadopoulos AA, Kalantzis N, et al. Diabetes mellitus is a risk factor for incomplete small-bowel capsule endoscopy. Gastrointest Endosc 2009;69: 1408-9
- Westerhof J, Weersma RK, Koornstra JJ. Risk factors for incomplete small-bowel

- capsule endoscopy. Gastrointest Endosc 2009;69:74-80
- Shibuya T, Mori H, Takeda T, et al. The relationship between physical activity level and completion rate of small bowel examination in patients undergoing capsule endoscopy. Intern Med 2012;51:997-1001
- Fatima H, Rex DK, Rothstein R, et al. Cecal insertion and withdrawal times with wide-angle versus standard colonoscopes: a randomized controlled trial. Clin Gastroenterol Hepatol 2008;6:109-14
- Villa F, Signorelli C, Rondonotti E, et al. Preparations and prokinetics. Gastrointest Endosc Clin N Am 2006;16:211-20
- 83. Koulaouzidis A, Dimitriadis S, Douglas S, et al. The use of Domperidone increases the completion rate of small bowel capsule endoscopy but does this come at the expense of diagnostic yield? J Clin Gastroenterol 2014. [Epub ahead of print]
- Champion MC, Hartnett M, Yen M. Domperidone, a new dopamine antagonist CMAJ 1986;135:457-61
- Ou G, Svarta S, Chan C, et al. The effect of chewing gum on small-bowel transit time in capsule endoscopy: a prospective, randomized trial. Gastrointest Endosc 2014;79:630-6
- Dabos KJ, Giannakou A, Koulaouzidis A. Chewing gum and completion rate in small-bowel capsule endoscopy: meta-analyzing the data. Gastrointest Endosc 2014;79(6):1032-4
- de Franchis R, Avgerinos A, Barkin J, et al. ICCE. ICCE consensus for bowel preparation and prokinetics. Endoscopy 2005;37:1040-5
- Koulaouzidis A, Giannakou A, Yung DE, et al. Do prokinetics influence the completion rate in small-bowel capsule endoscopy? A systematic review and meta-analysis. Curr Med Res Opin 2013;29:1171-85
- Koulaouzidis A, Giannakou A, Plevris JN. Prokinetics in small-bowel capsule endoscopy: smart use is the key. Eur J Gastroenterol Hepatol 2014;26;492-3
- Pohl J, Nguyen-Tat M, Pech O, et al. Computed virtual chromoendoscopy for classification of small colorectal lesions: a prospective comparative study. Am J Gastroenterol 2008;103:562-9
- Pohl J. Aschmoneir I. Schuhmann S, et al. Computed image modification for enhancement of small-bowel surface structures at video capsule endoscopy. Endoscopy 2010;42:490-2

- Imagawa H, Oka S, Tanaka S, et al. Improved visibility of lesions of the small intestine via capsule endoscopy with computed virtual chromoendoscopy. Gastrointest Endosc 2011;73:299-306
- Spada C, Hassan C, Costamagna G. Virtual chromoendoscopy: will it play a role in capsule endoscopy? Dig Liver Dis 2011;43: 927-8
- Aihara H, Ikeda K, Tajiri H.
 Image-enhanced capsule endoscopy based on the diagnosis of vascularity when using a new type of capsule. Gastrointest Endosc 2011;73:1274-9
- Krystallis C, Koulaouzidis A, Douglas S, et al. Chromoendoscopy in small bowel capsule endoscopy: blue mode or Fuji intelligent colour enhancement? Dig Liver Dis 2011;43(12):953-7
- Koulaouzidis A, Douglas S, Plevris JN. Blue mode does not offer any benefit over white light when calculating Lewis score in small-bowel capsule endoscopy. World J Gastrointest Endosc 2012;4:33
- Koulaouzidis A, Smirnidis A, Douglas S, et al. QuickView in small-bowel capsule endoscopy is useful in certain clinical settings, but QuickView with Blue Mode is of no additional benefit. Eur J Gastroenterol Hepatol 2012;24:1099-104
- Westerhof J, Koornstra JJ, Weersma RK. Can we reduce capsule endoscopy reading times? Gastrointest Endosc 2009;69: 497-502
- 99. Saurin JC, Lapalus MG, Cholet F, et al. French Society of Digestive Endoscopy (SFED). Can we shorten the small-bowel capsule reading time with the "Quick-view" image detection system? Dig Liver Dis 2012;44:477-81
- 100. Halling ML, Nathan T, Kjeldsen J, et al. High sensitivity of quick view capsule endoscopy for detection of small bowel Crohn's disease. J Gastroenterol Hepatol 2014;29(5):992-6
- 101. Farnbacher MJ, Krause HH, Hagel AF, et al. QuickView video preview software of colon capsule endoscopy: reliability in presenting colorectal polyps as compared to normal mode reading. Scand J Gastroenterol 2014;49:339-46
- 102. Koulaouzidis A, Douglas S. Capsule endoscopy in clinical practice: concise up-to-date overview. Clin Exp Gastroenterol 2009;2:111-16
- Buscaglia JM, Kapoor S, Clarke JO, et al. Enhanced diagnostic yield with prolonged small bowel transit time during capsule endoscopy. Int J Med Sci 2008;5:303-8

- 104. Koulaouzidis A, Karargyris A. Three-dimensional image reconstruction in capsule endoscopy. World J Gastroenterol 2012;18:4086-90
- 105. Karargyris A, Bourbakis N. Three-dimensional reconstruction of the digestive wall in capsule endoscopy videos using elastic video interpolation. IEEE Trans Med Imaging 2011;30:957-71
- 106. Kolar A, Romain O, Ayoub J, et al. Prototype of video endoscopic capsule with 3-d imaging capabilities. IEEE Trans Biomed Circuits Syst 2010;4:239-49
- 107. Horn BKP. Shape from shading: a method for obtaining the shape of a smooth opaque object from one view. PhD thesis, MIT, 1970. Available from: http://dspace.mit.edu/ handle/1721.1/6885
- 108. Karargyris A, Rondonotti E, Mandelli G, et al. Evaluation of 4 three-dimensional representation algorithms in capsule endoscopy images. World J Gastroenterol 2013;19:8028-33
- 109. Koulaouzidis A, Karargyris A. Use of enhancement algorithm to suppress reflections in 3-D reconstructed capsule endoscopy images. World J Gastrointest Endosc 2013;5:465-7
- 110. Koulaouzidis A, Karargyris A, Rondonotti E , et al. Three-dimensional representation software as image enhancement tool in small-bowel capsule endoscopy: a feasibility study. Dig Liver Dis 2013;45:909-14
- Ghoshal UC. Small bowel endoscopy in 2013: the reality and the potential. Nat Rev Gastroenterol Hepatol 2014;11:86-7
- 112. Girelli CM, Porta P. Bulge or mass? A diagnostic dilemma of capsule endoscopy. Endoscopy 2008;40:703-4
- 113. Postgate A, Tekkis P, Fitzpatrick A, et al. The impact of experience on polyp detection and sizing accuracy at capsule endoscopy: implications for training from an animal model study. Endoscopy 2008:40:496-501
- 114. Karargyris A, Karargyris O, Bourbakis N. 3D Representation of the Digestive Tract Surface in Wireless Capsule Endoscopy Videos. BioInformatics and BioEngineering (BIBE), 2010 IEEE International Conference; 31 May 2010–3 June 2010. p. 279-80
- 115. Ciuti G, Visentini-Scarzanella M, Dore A, et al. Intra-operative monocular 3D reconstruction for image-guided navigation in active locomotion capsule endoscopy. Biomedical Robotics and Biomechatronics (BioRob), 2012 4th IEEE RAS & EMBS

- International Conference: 24-27 June 2012. p. 768-774
- 116. Prasath VBS, Figueiredo IN, Figueiredo PN, et al. Mucosal region detection and 3D reconstruction in wireless capsule endoscopy videos using active contours. Engineering in Medicine and Biology Society (EMBC), 2012 Annual International Conference of the IEEE; 28 August 2012–1 September 2012. p. 4014-4017
- 117. Sun B, Liu L, Hu C, et al. 3D reconstruction based on Capsule Endoscopy image sequences. Audio Language and Image Processing (ICALIP), 2010 International Conference; 23-25 November 2010. p. 607-612
- 118. Fan Y, Meng MQH, Li B. 3D reconstruction of wireless capsule endoscopy images, Engineering in Medicine and Biology Society (EMBC). 2010 Annual International Conference of the IEEE. 31 August 2010—4 September 2010. p. 5149-52
- 119. Iakovidis DK. Spyrou E, Diamantis D. Efficient Homography-Based Video Visualization for Wireless Capsule Endoscopy, In Proceedings of, IEEE International Conference on Bioinformatics and Bioengineering (BIBE), Chania, Greece, 2013
- 120. Spyrou E, Diamantis D, Iakovidis DK. Panoramic Visual Summaries for Efficient Reading of Capsule Endoscopy Videos. In Proceedings of, IEEE International Workshop on Semantic and Social Media Adaptation and Personalization (SMAP), Bayonne, France, 2013. p. 41-6
- 121. Szeliski R, Image alignment and stitching: a tutorial. Foundations and trends in computer graphics and vision. 2006. p. 1-104
- 122. Yi S, Xie J, Mui P, Leighton JA. "Achieving real-time capsule endoscopy (CE) video visualization through panoramic imaging," IS&T/SPIE Electronic Imaging. 2013. p. 865601
- 123. Soper TD, Porter MP, Seibel EJ. Surface mosaics of the bladder reconstructed from endoscopic video for automated surveillance. IEEE Trans Biomed Eng 2012;59(6): 1670-80
- 124. Tanaka M, Kidoh Y, Kamei M, et al. A new instrument for measurement of gastrointestinal mucosal color. Dig Endosc 1996;8(2):139-46
- 125. Kudo S, Kashida H, Tamura T, et al. Colonoscopic diagnosis and management of nonpolypoid early colorectal cancer. World J Surg 2000;24(9):1081-90

- Theodoridis S, Koutroumbas K. Pattern Recognition. 4th edition. Elsevier; 2008
- 127. Karkanis SA, Iakovidis DK, Maroulis DE, et al. Computer aided tumor detection in endoscopic video using color wavelet features. IEEE Trans Inf Technol Biomed 2003;7:141-52
- Liedlgruber M, Uhl A. Computer-aided decision support systems for endoscopy in the gastrointestinal tract: A review. IEEE Rev Biomed Eng 2011;4:73-88
- Sainju S, Bui FM, Wahid KA. Automated bleeding detection in capsule endoscopy videos using statistical features and region growing. J Med Syst 2014;38(4):1-11
- Figueiredo IN, Kumar S, Leal C,
 Figueiredo PN. Computer-assisted bleeding detection in wireless capsule endoscopy images. Comput Methods Biomech Biomed Engin 2013;1(4):198-210
- Pan GB, Xu F, Chen JL. Bleeding detection in wireless capsule endoscopy using color similarity coefficient. Appl Mech Mater 2012;195:307-12
- 132. Charisis VS, Hadjileontiadis LJ, Liatsos CN, et al. Capsule endoscopy image analysis using texture information from various color models. Comput Methods Programs Biomed 2012;107(1):61-74
- 133. Kumar R, Zhao Q, Seshamani S, et al. Assessment of Crohn's disease lesions in wireless capsule endoscopy images. IEEE Trans Biomed Eng 2012;59(2):355-62
- 134. Li B, Meng MH. Tumor recognition in wireless capsule endoscopy images using textural features and SVM-based feature selection. IEEE Trans Inf Technol Biomed 2012;16(3):323-9
- Li BP, Meng MQH. Comparison of several texture features for tumor detection in CE images. J Med Syst 2012;36(4):2463-9
- 136. Li B, Meng MQH, Lau JY. Computer-aided small bowel tumor detection for capsule endoscopy. Artif Intell Med 2011;52(1):11-16
- 137. Mamonov AV, Figueiredo IN, Figueiredo PN, Tsai YHR. Automated polyp detection in colon capsule endoscopy. IEEE Trans Med Imaging 2014;33(7): 1488-502
- Li B, Meng MQH. Automatic polyp detection for wireless capsule endoscopy images. Expert Syst Appl 2012;39(12): 10952-8
- 139. Karargyris A, Bourbakis N. Detection of small bowel polyps and ulcers in wireless capsule endoscopy videos. IEEE Trans Biomed Eng 2011;58(10):2777-86

- 140. Szczypinski P, Klepaczko A, Strzelecki M. Án intelligent automated recognition system of abnormal structures in WCE images. In: Hybrid artificial intelligent systems. Springer; 2011. p. 140-7
- 141. Szczypinski P, Klepaczko A, Pazurek M, Daniel P. Texture and color based image segmentation and pathology detection in capsule endoscopy videos. Comput Methods Programs Biomed 2014;113(1):396-411
- 142. Chen H, Chen J, Peng Q, et al. Automatic hookworm image detection for wireless capsule endoscopy using hybrid color gradient and contourlet transform. In: Biomedical Engineering and Informatics (BMEI), 2013 6th International Conference on. IEEE; 2013. p. 116-20
- 143. Segui S, Drozdzal M, Vilarino F, et al. Categorization and segmentation of intestinal content frames for wireless capsule endoscopy. IEEE Trans Inf Technol Biomed 2012;16(6):1341-52
- 144. HajiMaghsoudi O, Talebpour A, Soltanian-Zadeh H, Soleimani HA. Automatic informative tissue's discriminators in WCE. In: Imaging Systems and Techniques (IST), 2012 IEEE International Conference on. IEEE; 16-17 July 2012. p. 18-23
- Iakovidis DK, Tsevas S, Polydorou A. Reduction of capsule endoscopy reading times by unsupervised image mining. Comput Med Imaging Graph 2010;34(6): 471-8
- 146. Koulaouzidis A, Tsevas S, Iakovidis DK. Automatic Detection of 'Suspicious' Capsule Endoscopy Video Segments. In Proceedings of, British Society of Gastroenterology (BSG), Annual Meeting, Manchester, 2014
- 147. Fawcett T. An introduction to roc analysis. Pattern Recogn Lett 2006;27(8):861-74
- 148. Karagozler ME, Cheung E, Kwon J, Sitti M. Miniature endoscopic capsule robot using biomimetic micro-patterned adhesives. First IEEE/RAS-EMBS International Conference

- on Biomedical Robotics and Biomechatronics. New York, USA. 2006, p. 105-11
- 149. Quirini M, Scapellato S, Valdastri P, et al. An approach to capsular endoscopy with active motion. Conf Proc IEEE Eng Med Biol Soc 2007;2007:2827-30
- Valdastri P, Quaglia C, Susilo E, et al. Wireless therapeutric endoscopic capsule: in vivo experiment. Endoscopy 2008;40: 979-82
- 151. Glass P, Cheung E, Sitti M. A legged anchoring mechanism for capsule endoscopes using micropatterned adhesives. IEEE Trans Biomed Eng 2008;55:2759-67
- Valdastri P, Webster RJ 3rd, Quaglia C, et al. A new mechanism for meso-scale legged locomotion in compliant tubular environments. IEEE T Robot 2009;25: 1047-57
- 153. Tortora G, Valdastri P, Susilo E. et al. Propeller-based wireless device for active capsular endoscopy in the gastric district. Minim Invasive Ther Allied Technol 2009;18:280-90
- 154. Valdastri P, Quaglia C, Buselli E, et al. A magnetic internal mechanism for precise orientation of the camera in wireless endoluminal applications. Endoscopy 2010;42:481-6
- Ciuti G, Valdastri P, Menciassi A, Dario P. Robotic magnetic steering and locomotion of capsule endoscope for diagnostic and surgical endoluminal procedures. Robotica 2010;28:199-207
- 156. Bourbakis N, Giakos G, Karargyris A. Design of new-generation robotic capsules for therapeutic and diagnostic endoscopy. IEEE International Conference on Imaging Systems and Techniques. New York.2010. p. 1-6
- 157. Gao M, Hu C, Chen Z, et al. Design and fabrication of a magnetic propulsion system for self-propelled capsule endoscope. IEEE Trans Biomed Eng 2010;57:2891-902

- 158. Simi M, Valdastri P, Quaglia C, et al. Design, fabrication, and testing of a capsule with hybrid locomotion for gastrointestinal tract exploration. IEEE-ASME T Mech 2010;15:170-80
- 159. Morita E, Ohtsuka N, Shindo Y, et al. In vivo trial of a driving system for a self-propelling capsule endoscope using a magnetic field (with video). Gastrointest Endosc 2010;72:836-40
- 160. Yang S, Park K, Kim J, et al. Autonomous locomotion of capsule endoscope in gastrointestinal tract. Conf Proc IEEE Eng Med Biol Soc 2011;2011:6659-63
- 161. Filip D, Eggermont M, Nagel J, Andrews CN. Electronic Stool (e-Stool): a novel self-stabilizing video capsule endoscope for reliable non-invasive colonic imaging. International Mechanical Engineering Congress and Exposition, Volume 2, Biomedical and Biotechnology Engineering; Nanoengineering for Medicine and Biology In: Proceedings of the ASME; New York, ASME, 2011. 711-22
- 162. Yim S, Sitti M. Design and rolling locomotion of a magnetically actuated soft capsule endoscope. IEEE T Robot 2012;28: 183-94
- 163. Kong K, Yim S, Choi S, Jeon D. A Robotic biopsy device for capsule endoscopy. J Med Devices 2012;6(3):031004
- 164. http://www.research.philips.com/initiatives/ intellicap/
- Laursen EL, Ersbøll AK, Rasmussen AM, et al. [Intra- and interobserver variation in capsule endoscopy reviews]. Ugeskr Laeger 2009:171:1929-34
- 166. Tang TB, Johannessen EA, Wang L, et al. IDEAS: A minatrue lab-in-a-chip pill multisensor microsystem. In: Proceeding IEEE NORCHIP Conference 2002, Copenhagen. Denmark

Original article

Detection of the ampulla of Vater in small bowel capsule endoscopy: Experience with two different systems

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OBJECTIVE: The aim of this study was to determine the detection rate of the ampulla of Vater (AoV) during small bowel capsule endoscopy (SBCE) examinations and compare the two SBCE systems used in our center.

METHODS: SBCE procedures performed in our center from March 2005 to June 2011 were reviewed retrospectively. A single reviewer, following a detailed protocol, analyzed 30 min of each recording to identify the AoV.

RESULTS: A total of 619 SBCE procedures were enrolled in the study, including 262 with a PillCam SB1, 148 with a PillCam SB2 and 209 with a MiroCam. AoV was identified in 59 SBCE examinations (9.5%), consisting of 28 with a PillCam SB1 (28/262, 10.7%), 13 with a PillCam SB2 (13/148, 8.8%) and 18 with a MiroCam (18/209, 8.6%)

(P = 0.665). The AoV was visualized in 53.2 frames (median 12 frames, range 1–1056 frames); and the detection rate was low regardless of indication, patients' characteristics, SBCE system used or capsule transit parameters. Bile spout was associated with a higher AoV detection (P = 0.003).

CONCLUSIONS: The persistently low AoV detection rate using two different SBCE systems underlines the weakness of non-steerable capsule endoscopy. Furthermore, if AoV detection is taken as a surrogate marker of small polyp detection, it becomes obvious both that non-steerable SBCE cannot replace a side-viewing endoscope in the evaluation of periampullary polyps in familial adenomatous polyposis and that it is an infallible method in other small bowel polyposis states.

KEY WORDS: ampulla, capsule endoscopy, marker, small intestine.

INTRODUCTION

Over the last decade, capsule endoscopy (CE) has been established as a very useful tool in the investiga-

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© 2012 The Authors Journal of Digestive Diseases © 2012 Chinese Medical Association Shanghai Branch, Chinese Society of Gastroenterology, Renji Hospital Affiliated to Shanghai Jiaotong University School of Medicine and Wiley Publishing Asia Pty Ltd. tion of small bowel diseases. A recent pooled analysis has demonstrated that small bowel capsule endoscopy (SBCE) has a minimal miss rate of <1% for small bowel ulcer. Although SBCE provides a high information yield on mucosal lesions, it does not permit the assessment of small bowel wall thickness or extraluminal findings. Furthermore, concerns have arisen that SBCE may underestimate the number of small bowel polyps in patients with a known high polyp burden, that is, patients with hereditary or familial polyposis syndromes or other sinister pathological findings. Therefore, SBCE is currently far from perfect due to its technical limitations such as its rigid structure, inability to insufflate, lack of

directionality or steer control and a set field of view.⁹ Over the last 5 years clinical researchers have highlighted the use of markers (some in positions where they are difficult to spot) which are present in intestine as quality assurance indicators in SBCE.¹⁰ The major duodenal papilla, or ampulla of Vater (AoV), which is present in all individuals who have not undergone duodenal resection and is located on the posteromedial aspect of the duodenal sweep,¹⁰ 8–10 cm distal to the pylorus, is a reasonable candidate marker. It is difficult to see, as the translucent dome of the propelled CE tends to point towards the outer aspect of sharply angulated bowel loops.¹⁰

On the other hand, choosing the AoV as the marker and extrapolating the results of the detection to polyp lesions may not be completely reliable. The factors that make the AoV difficult to observe, such as the location, size/lumen protrusion and capsule transit speed, are at least part of the reason why small bowel lesions such as polyps may be missed in the SBCE examination.

This study aimed to evaluate the detection rate of the AoV by two different SBCE systems in our cohort and to compare the results from our center with published reports.

PATIENTS AND METHODS

Data of all the SBCE procedures that were carried out in our center from March 2005 to June 2011 were reviewed retrospectively. Duplicate examinations, performed for the purpose of clinical need, were included. SBCE was performed with a PillCam SB1/SB2 (Given Imaging, Yokneam, Israel) and/or a MiroCam (IntroMedic, Seoul, Korea) CE, using pre-procedural and procedural protocols (small bowel cleansing with polyethylene glycol, simethicone with or without prokinetic for CE ingestion). Patients were allowed to drink clear liquid 2 h after capsule ingestion and to eat a light meal 4 h after capsule ingestion. This study was conducted in accordance with the Research Ethics Guidelines of the UK. After being reviewed by the local ethics committee, further specific ethical reviews and approval were not required, as the study was considered to be an audit using data obtained as part of regular patient care.

All SBCE sequences were reviewed using a detailed protocol for the identification of the AoV outlined

below with the RAPID v7 (Given Imaging) and the MiroView v2.0 (IntroMedic). SBCE video sequences were not de-identified, but any previously captured thumbnails were deleted. The automatic viewing mode at a speed of 6 frames per second (fps) was used on the single frame mode with the reviewer seated at arm's length from the screen in a room with dimmed light for maximal pick-up yield. Only a desktop spotlight was employed, when illumination was required, for data input in the datacollecting Excel 2007 spreadsheet (Microsoft, Redmond, WA, USA). A 'roll-through' mode was utilized, where needed, to aid the delineation of mucosal/surface details.12 Fujinon intelligent color enhancement or blue mode (in RAPID software), ALICE or color mode (in MiroView) were not used in the study.

The predefined settings for the white light CE video sequence review with RAPID software in our center are sharpness 1, brightness 1 and color 2. Equivalent settings for the MiroView software are 2, 0 and 0, respectively. The duration of review, following the CE entry to the duodenal bulb, was prolonged from 15 min in a previous study¹³ to 30 min to minimize the possibility of missing the AoV. Furthermore, the reviewing time was accordingly adjusted to start from the point of permanent duodenal entry.¹⁴

Age, gender, AoV detection, the number of frames at which the papilla was visible, the presence of bile spout, indication and date of the SBCE, the type of CE used, the type and dose of prokinetics used as well as transit parameters including the time of duodenal entry (gastric transit time [GTT]), small bowel transit time (SBTT) and the transit time from pylorus to first duodenal papilla frame, the completion to cecum or not and the quality of small bowel cleansing (and, where available, the quantity of laxatives used) were recorded.

To date, there is no standardized bowel cleansing score for an SBCE, hence we adopted a modified 4-point grading scale from the study by Park *et al.*¹⁵ depending on the proportion of visualized mucosa and the extent of obscuration by intraluminal food debris, turbid fluids, bubbles or bile: score 3 (very good visibility), >75% mucosa visible; score 2 (good visibility), 50–75% mucosa visible; score 1 (average visibility), 25–50% mucosa visible; and score 0 (poor visibility), <25% mucosa visible. Cleansing scores referred to the first 30 min of the small bowel recording.

Statistical analysis

Statistical analyses were carried out with StatsDirect 2.7.8 (StatsDirect, Altrincham, UK). Continuous data were presented as mean \pm standard deviation (SD) and range. Student's t-test was used to compare parametric variables. A one-way ANOVA for independent samples was used to compare the papilla detection rate based on indication and diagnosis. A two-tailed P value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the patients

A total of 839 SBCE procedures in 758 patients were performed in our institution between March 2005 and June 2011. Due to the technical issues (i.e., only initial written reports available, corrupt SBCE video sequences stored in compact disks and/or failure to re-download), 189 SBCE videos were unavailable for review. Another 22 examinations with gastric or proximal duodenal capsule retention and nine of endoscopic capsule delivery in the duodenum were also excluded. Therefore, a total of 619 SBCE procedures on 533 patients were included in this study for further analysis.

Of these, 208 (39.0%) were men and 325 (61.0%) were women, with a mean age of 52.8 years (range 14–90 years). Of the SBCE procedures, 262 examinations were performed with PillCam SB1, 148 with PillCam SB2 and the remaining 209 with MiroCam.

Table 1. Indications for small bowel capsule endoscopy (SBCE) in our cohort

Indications for SBCE	SBCE procedures, n (%)
Obscure GI bleeding	138 (22.3)
Iron deficiency anemia	206 (33.3)
Clinical suspicion of CD	101 (16.3)
Reassessment of known CD	30 (4.8)
Polyposis syndrome	11(1.8)
Celiac disease	12(1.9)
Others	121 (19.6)

CD, Crohn's disease; Gl, gastrointestinal.

The indications for SBCE are presented in Table 1. More than half of the examinations were performed for overt and/or occult gastrointestinal bleeding.

In 591 procedures (95.5%), pre-procedure bowel preparation was used. A total of 273 procedures (44.1%) were performed without the use of prokinetics. Of the remainder, 267 (43.1%) were done with the administration of domperidone (mean dose 5.6 mg) and 79 (12.8%) with metoclopramide (mean dose 5.3 mg).

The mean small bowel cleansing score for the first 30 min was 2.14. Out of the 619 SBCE, 540 CE (87.2%) were realized at the cecum by the end of the recording. The positive diagnostic yield for all indications was 34.6%.

Detection of AoV

The AoV was detected in 59 SBCE procedures (9.5%; Table 2, Fig. 1). No difference was observed in the detection rate between either of the two generations of PillCam SB (P = 0.609) or the two technically different SBCE systems (PillCam vs MiroCam, P = 0.665). Furthermore, the mean number of frames of the duodenal papilla visualized was 53.2 (range 1-1056), with no significant difference between either of the two generations of PillCam (P = 0.800) or the two different SBCE systems (P = 0.247). Bile spout was detected in 62.2% of SBCE (385/619) and in 81.4% of the procedures (48/59) in which the AoV was seen (P = 0.003). The mean time of AoV detection after the first duodenal image capture was 3.56 min (range 0.05-29.60 min for the whole cohort), and there was no statistical difference between the two SBCE systems $(3.53 \pm 5.65 \text{ min for the PillCam } vs 3.63 \pm 5.40 \text{ min})$ for the MiroCam; P = 0.95). The detection rate of papilla was independent of the indication for SBCE, type of CE used, diagnostic yield, patients' characteristics, and use of prokinetics or gut transit parameters. Furthermore, there was no significant difference in the detection rates of the AoV among the SBCE in regard to either cecal completion or small bowel cleansing (P < 0.05; Table 3).

Table 2. Number of small bowel examinations per capsule endoscopy

	PillCam SB1	PillCam SB2	MiroCam
SBCE (N)	262	148	209
Detection of AoV, n(%)	28(10.7)	13 (8.8)	18 (8.6)
Frames AoV visible, n (mean \pm SD)	36.35 ± 73.24	42.46 ± 69.30	87.20 ± 248.40

AoV, ampulla of Vater; SBCE, small bowel capsule endoscopy; SD, standard deviation.

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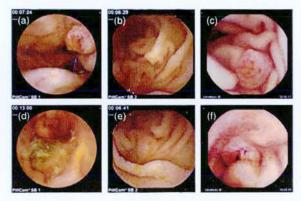


Figure 1. The ampulla of Vater as detected by different small bowel capsule endoscopy models. First row without bile spout and second row with bile spout: (a,d) PillCam SB1, (b,e) PillCam SB2 and (c,f) MiroCam.

Interestingly, the detection rate of duodenal papilla in SBCE performed after bowel preparation was lower than that in patients who received no bowel preparation (SBCE [43/509, 8.4%] vs SBCE [6/28, 21.4%]; P = 0.033), probably demonstrating that patients who received bowel preparation had a more rapid movement of CE.

Finally, in the group of patients who, for the purpose of clinical work-up/care (n = 17), had a repeat SBCE with a different CE system (from that initially employed), the AoV detection rate was identical (1:17) for both SBCE systems (PillCam: Miro-Cam = 1:17). Eight patients had repeat examinations with the same type of CE, including four with PillCam SB1, one with PillCam SB2 and three with MiroCam. The AoV was not identified in any of the first examinations and in only one of the repeat studies with PillCam SB1. Interestingly, four patients underwent CE examinations with all the three SBCE types, and in one patient, the AoV was visible with both types of PillCam but not with the MiroCam.

DISCUSSION

The use of the AoV as a surrogate marker of the detection power of SBCE has been suggested after various reports of polyps or tumors missed by SBCE were published. 5,6,16 Since then, evidence of pathology unidentified by SBCE (detected by device-assisted enteroscopy, computed tomography enteroclysis or magnetic resonance imaging) have increased. 6 16-18 Although the advent of CE has revolutionized the diagnostic work-up of small bowel diseases, the amount of information we get (or in fact, do not get)10

ndication	OCIB	IDA	Clinical suspected CD CD reassessment	CD reassessment	Polyposis	Celiac disease	Other
SBCE (n)	138	206	101	30	==	1.2	121
AoV visible (n)	16	13	11	NO.	0	0	14
No bile spout (n)	76	136	99	1.5	4	00	7.1
GTT (min, mean ± SD)	42.78 ± 53.46	43.28 ± 42.56	37.12 ± 32.84	41.58 ± 36.24	33.9 ± 116.5	47.96 ± 50.86	45.3 ±
SBTT (min, mean ± SD)	267.9 ± 108.77	226.82 ± 94.18	229.35 ± 92.2	319.36 ± 116.68	329.4 ± 140.13	212.5 ± 104.2	312.5 ±
MiroCam (n)	47	80	29	10	8	10	35
PillCam SB1 (n)	64	84	45	6	10	2	53
PillCam SB2 (n)	2.7	42	27	П	3	5	33
(+) Diagnostic vield (n)	54	62	41	21	7	m	26
(-) Diagnostic yield (n)	84	144	09	6	4	6	95
No prokinetic (n)	72	85	46	10	4	2	99
Domperidone (n)	49	98	38	1.7	4	100	40
Metoclopramide (n)	1.7	23	16	60	23	2	25
Completed to cecum (n)	119	186	93	18	10	11	92
Mean cleansing score	2.14	2.13	50	1.73	2	2.6	CH

is a combination of various factors such as capsule technical characteristics, SBTT, the amount and transparency of intraluminal liquids and, finally, the degree of small bowel wall contraction.

In the current study, to date the biggest single center study on the detection rate of the AoV, we included SBCE with technically different systems and confirmed results from the existing literature. First, AoV detection in unselected patients is a difficult task in CE; second, visualization of the AoV is not related to CE, the indications, diagnostic yield, cecal completion, administration of prokinetics of CE or patients' characteristics such as age and gender. Interestingly, the diagnostic yield in our study, which included more than 300 SBCE procedures performed for overt/occult gastrointestinal bleeding, was lower than that of a previous report. This probably represents not only accumulated experience in CE reporting but also more widespread use of CE with easier access to the service and implementation of CE sooner in the diagnostic work-up.

Bile spout, as described earlier, 11.19 is a major herald of the AoV and the main factor that helps in the identification of the AoV, although it is believed to be an accidental phenomenon in endoscopy. A simple explanation is that the spurting of bile physiologically occurs when the duodenal wall, together with the smooth muscle of the sphincter of Oddi, is relaxing. Therefore, bile spout should be seen as surrogate marker of reduced mucosal folding, slower capsule propulsion and hence greater detection ability from a non-steerable device. Furthermore, it is likely that patients with slower capsule propulsion who have not taken a purgative preparation may explain the higher AoV detection in this group, compared with those who had been given laxatives for small bowel cleansing.

Although two different SBCE systems were used, their performances, as reflected by the detection rate of the AoV, were similar. Despite the similar size and weight (PillCam SB: size 11 mm × 26 mm, weight 3.45 g; MiroCam: size 11 mm × 24 mm, weight 3.4 g), the two systems have a different transmission technology, image capture rate and pixel resolution (PillCam SB: 2 fps and 256 × 256 pixels vs MiroCam: 3 fps and 320 × 320 pixels). At a working distance of 2.2 mm from the tip of the translucent CE dome, PillCam SB1 and SB2 and MiroCam offer a field of view of 140°, 165° and 150°, respectively. Their mucosal coverage area at 4.5 mm working distance is 500 mm², 1100 mm² and 202 mm², respectively.

Some researchers propose that the results of the AoV detection should be extrapolated to the detection rate of angioectasias (especially when not actively bleeding) and/or other small bowel pathology (similar in size to the duodenal papilla such as Brunner gland adenomas, lipomas or other submucosal tumors, which are presumed to be randomly distributed),¹⁰ thus establishing the AoV as the worse case of possible misses.

In other words, they recommend the AoV detection rate as a quality assurance measurement for CE. Kong et al.11 performed a retrospective study on the detection rate of the AoV in 110 consecutive SBCE patients. Inclusion criterion was a normal (in shape and position) duodenal papilla, as confirmed by conventional esophagogastroduodenoscopy (EGD), thus, those with an abnormally positioned papilla or whose papilla was not readily identified by EGD were excluded. It is, therefore, not surprising that although they used a high video sequence reviewing speed (15 fps) and only the first generation M2A Given Imaging model, they detected the AoV in 43.6% of the patients (48/110). As visualization of the AoV by conventional front-viewing endoscopes is not always an easy task, it is likely that this study suffered from significant selection bias, as only the more prominent and hence easy to detect AoV were included for CE.

Clarke et al.9 repeated the study with a similar number (n = 125) of consecutive SBCE patients (again with M2A; Given Imaging) and a more realistic setting. Two reviewers, blinded to each other, used the lowest possible automated viewing speed (5 fps) and found that the AoV was detected in 10.4% of the patients (13/125). Wijeratne and Condon21 have demonstrated that the AoV is identified only in 6% of SBCE examinations (9/138). Lee et al.22 reviewed 30 SBCE performed with PillCam SB and the same number of examinations with PillCam SB2 and concluded that the AoV detection rate was 46.6% (28/60), equivalent for both PillCam types (Table 4). However, other investigators presented less favourable results.23,24 One would think that results should improve with advanced CE technical characteristics, but the experience from the studies using double-headed CE with improved optics and frame acquisition rate are only partially concordant. 19,23,25 Furthermore, although different generations of small bowel PillCam models and types have been scrutinized (with regard to the AoV detection rate), other CE systems have not been put under the test.20,22,23,26

Table 4. Studies on the ampulla of Vater (AoV) detection rate

Study	CE (n)	Type of CE	AoV seen (n, %)	Reviewers (n)	Reviewing speed (fps)	Frames AoV visible (n), mean ± SD	Comments
Clarke et al." (2008)	125	M2A	13 (10.4)	2	5	n/s	
Kong et al.11 (2006)	110	M2A	48 (43.6)	. ' 2	15	3.5 ± 2.5	
Katsinelos et al.13 (2009)	14	n/s	0(0)	1	n/s	n/s	FAP patients
Nakamura et al.14 (2009)	96	PillCam SB1	18(18)	. 2	10	n/s	
Koulaouzidis et al.19 (2011)	11	PillCam ESO1	4 (36.4)	1	7 .	n/s	
	7	PillCam ESO2	1 (14.3)		9		
Metzger et al.20 (2009)	20	PillCam SB1 PillCam SB2	1 (5) 5 (25)	n/s	n/s	n/s	Repeat exams
Wijeratne and Condon ²¹ (2006)†	138	n/s	9 (6)	1	n/s	n/s	
Lee et al.22 (2010)†	30	PillCam SB	13 (43.3)	n/s	n/s	n/s	
25	30	PillCam SB2	15 (50.0)	10			
Selby and Prakoso ²³ (2011)	50	PillCam SB1	0(0)	2	n/s	n/a	
	50	PillCam SB2	9(18)		7/	n/s	
	8	PillCam ESO1	0(0)			n/a	
	12	PillCam ESO2	1(8)			n/s	
Iaquinto et al.24 (2008)	23	PillCam SB	0(0)	2	n/s	n/a	FAP patients
Karagiannis et al.25 (2010)	10	PillCam Colon	6 (60)	n/s	n/s	n/s	2000 00 BURELON 1000
Park et al.26 (2012)	30	PillCam SB	13 (43.3)	n/s	n/s	n/s	
ertain anna erro meantain ann ann ann ann ann ann ann ann ann	30	PillCam SB2	15 (50.0)	5. 19. 10. 14. 15. 15. 15. 15. 15. 15. 15. 15. 15. 15		.	

†Published only as abstract

In conclusion, this study raises awareness regarding the limitations of CE. More specifically, it raises important issues on the usefulness of CE in the detection of periampullary lesions. In such cases, standard practice remains to use a side-viewing duodenoscope for inspection of these areas if a standard forward-viewing endoscope cannot provide satisfactory views. This study also highlights the technical limitations of CE in the identification of small lesions with a non-steerable device. The limitations of our study are its retrospective nature and the use of a single reviewer, although the SBCE evaluation was performed using a strict protocol and blinded review to any archived thumbnail images. Furthermore, a large number of studies were not available for review due to either corrupt compact disks or loss of sequences during their transfer from one large capacity storage device to another. Moreover, the fact that the comparison was not done on the same patients (other than a subgroup of 17 patients) and the same day, together with the unavailability of systematic endoscopic confirmation of visibility of the papilla by a conventional sideviewing duodenoscope, might be seen by some as a further limiting factor.

REFERENCES

- 1 de Franchis R, Rondonotti E, Villa F. Capsule endoscopy state of the art. Dig Dis 2007; 25: 249–51.
- Lewis BS, Eisen GM, Friedman S. A pooled analysis to evaluate results of capsule endoscopy trials. *Endoscopy* 2005; 37: 960-5.
- 3 Leighton JA, Triester SL, Sharma VK. Capsule endoscopy: a meta-analysis for use with obscure gastrointestinal bleeding and Crohn's disease. Gastrointest Endosc Clin N Am 2006; 16: 229-50.
- 4 Hara AK, Leighton IA, Heigh RI et al. Crohn disease of the small bowel: preliminary comparison among CT enterography, capsule endoscopy, small-bowel follow-through, and ileoscopy. Radiology 2006; 238: 128–34
- 5 Wong RF, Tuteja AK, Haslem DS et al. Video capsule endoscopy compared with standard endoscopy for the evaluation of small-bowel polyps in persons with familial adenomatous polyposis (with video). Gastrointest Endosc 2006; 64: 530-7.
- 6 Chong AK, Chin BW, Meredith CG. Clinically significant small-bowel pathology identified by double-balloon enteroscopy but missed by capsule endoscopy. *Gastrointest Endosc* 2006; 64: 445–9.
- 7 Ross A, Mehdizadeh S, Tokar J et al. Double balloon enteroscopy detects small bowel mass lesions missed by capsule endoscopy. Dig Dis Sci 2008; 53: 2140-3.
- 8 Hakim FA, Alexander JA, Huprich JE, Grover M, Enders FT. CT-enterography may identify small bowel tumors not detected by capsule endoscopy: eight years

CE, capsule endoscopy; FAP, familial adenomatous polyposis; fps, frames per second; n/a, not applicable; n/s, not stated.

- experience at Mayo Clinic Rochester. Dig Dis Sci 2011; 56: 2914-9.
- 9 Clarke JO, Giday SA, Magno P et al. How good is capsule endoscopy for detection of periampullary lesions? Results of a tertiary-referral center. Gastrointest Endosc 2008; 68: 267–72.
- 10 Cass OW. Is half-knowledge worse than ignorance? Gastrointest Endosc 2006; 64: 542-3.
- 11 Kong H, Kim YS, Hyun JJ et al. Limited ability of capsule endoscopy to detect normally positioned duodenal papilla. Gastrointest Endosc 2006; 64: 538–41.
- 12 Selby WS, Prakoso E. Reply to: identification of the ampulla of Vater during oesophageal capsule endoscopy: two heads and viewing speed make a difference. Eur J Gastroenterol Hepatol 2011; 23: 362.
- 13 Katsinelos P, Kountouras J, Chatzimavroudis G et al. Wireless capsule endoscopy in detecting small-intestinal polyps in familial adenomatous polyposis. World J Gastroenterol 2009; 15: 6075–9.
- 14 Nakamura M, Ohmiya N, Shirai O et al. Advance of video capsule endoscopy and the detection of anatomic landmarks. Hepatogastroenterology 2009; 56: 1600-5.
- 15 Park SC, Keum B, Hyun JJ et al. A novel cleansing score system for capsule endoscopy. World J Gastroenterol 2010; 16: 875–80.
- 16 Gupta A, Postgate AJ, Burling D et al. A prospective study of MR enterography versus capsule endoscopy for the surveillance of adult patients with Peutz-Jeghers syndrome. AJR Am J Roentgenol 2010; 195: 108–16.
- 17 Mavrogenis G, Coumaros D, Renard C et al. lejunal gastrointestinal stromal tumor missed by three capsule endoscopies. Endoscopy 2011; 43: 735–6; author reply 737.
- 18 Crook DW, Knuesel PR, Froehlich IM et al. Comparison of magnetic resonance enterography and video capsule endoscopy in evaluating small bowel disease. Eur I Gastroenterol Hepatol 2009; 21: 54–65.
- 19 Koulaouzidis A, Douglas S, Plevris IN. Identification of the ampulla of Vater during oesophageal capsule endoscopy:

- two heads and viewing speed make a difference. Eur J Gastroenterol Hepatol 2011; 23: 361.
- 20 Metzger YC, Adler SN, Shitrit AB, Koslowsky B, Bjarnason I. Comparison of a new PillCam™ SB2 video capsule versus the standard PillCam™ SB for detection of small bowel disease. Rep Med Imaging 2009; 2: 7-11.
- Wijeratne R, Condon D. Ampulla of Vater is infrequently visualised by capsule endoscopy. Gastrointest Endosc 2006; 63: AB172.
- 22 Lee IIS, Lee KG, Kim J et al. Comparison of PillCam SB and SB2 – Study of normally positioned ampulla of Vater detection. Gastrointest Endosc 2010; 71: AB370–1.
- 23 Selby WS, Prakoso E. The inability to visualize the ampulla of Vater is an inherent limitation of capsule endoscopy. Eur J Gastroenterol Hepatol 2011; 23: 101–3.
- 24 laquinto G, Fornasarig M, Quaia M et al. Capsule endoscopy is useful and safe for small-bowel surveillance in familial adenomatous polyposis. Gastrointest Endosc 2008; 67: 61–7.
- 25 Karagiannis S, Dücker C, Dautel P, Strubenhoff J, Faiss S. Identification of the duodenal papilla by colon capsule endoscope. Z Gastroenterol 2010; 48: 753–5.
- 26 Park S, Chun HJ, Keum B et al. Capsule endoscopy to detect normally positioned duodenal papilla: Performance comparison of SB and SB2. Gastroenterol Res Pract 2012; 2012: 202935.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Video \$1. A rare sighting, the major duodenal papilla (ampulla of Vater) and the minor duodenal papilla (accessory pancreatic duct of Santorini) seen in the same small bowel capsule endoscopy.

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Review

Do prokinetics influence the completion rate in small-bowel capsule endoscopy? A systematic review and meta-analysis

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Keywords

Capsule endoscopy - Completion rate - Daikenchuto - Erythromycin - Lubiprostone - Metoclopramide Mosapride - Motility - Prokinetics - Real-time viewer

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Abstract

Background:

The use of purging for bowel cleansing prior to small-bowel capsule endoscopy (SBCE) has now been established in clinical practice. Despite that, the number of incomplete SBCEs is still around 15-20%. To date, the use of prokinetics in SBCE - aiming to improve completion rate (CR) - remains a contentious issue resulting in lack of consensus among capsule experts.

Extensive medical literature searches were conducted (to November 2012), using suitable MeSH terms and keywords, in search of studies that compared capsule ingestion with prokinetic agents vs. controls or placebo. We examined the effects of prokinetic administration on SBCE CR (primary end point), as well as on the following secondary end points: diagnostic yield (DY), gastric transit time (GTT) and small-bowel transit time (SBTT) by meta-analysis of all relevant studies.

A total of 17 eligible studies (14 prospective, 3 retrospective) were identified, including 1028 individuals who ingested the capsule with no prokinetic vs. 876 who received a prokinetic. Overall, there was a higher CR in patients who ingested the capsule with prokinetics vs. controls (OR [95% CI]: 1.96 [1.38-2.78]). Of the two most readily available prokinetics, metoclopramide was associated with superior SBCE CR vs. control (OR [95% CI]: 2.8 [1.35-3.21]), while erythromycin showed no benefit (OR [95% CI]: 1.36 [0.61-3.03]). Where prokinetics were used alone, neither metoclopramide nor erythromycin showed any benefit on CR. There was no benefit of prokinetics (over controls) on DY. However, metoclopramide had a significant effect on GTT and SBTT.

Limitations:

The majority of the included studies were heterogeneous, and the effect of prokinetics on image quality and mucosal visualization was not examined.

Conclusion:

Our pooled data shows that the use of prokinetics for capsule ingestion improves CR in SBCE. This effect appears to be particularly evident with metoclopramide, when used concurrently with purging and/or use of real-time monitoring. In a small number of studies, erythromycin showed - through its gastrokinetic effect - marginal benefit. No prokinetic has a beneficial effect on SBCE DY.

Introduction

Optimal diagnostic yield (DY) in small-bowel capsule endoscopy (SBCE) requires not only optimal visualization of the small-bowel mucosal surface and lumen 1,2 but also complete capsule transit through the entire small bowel i.e. total enteroscopy3. If results are negative and/or inconclusive and complete enteroscopy is not achieved, concerns remain over missed smallbowel pathology. Recent systematic reviews showed that SBCE completion rate (CR) varies between 81.3-83.5% (for retrospective and prospective studies, respectively)4,5. Besides small-bowel structural integrity, hospitalization, advancing age and diabetes are considered high risk factors for incomplete enteroscopy with SBCE⁶⁻⁸. Therefore, it is expected that decreasing gastric transit time (GTT) and small-bowel transit times (SBTT) will allow a capsule to successfully reach the caecum by the end of its battery life³. Hence prokinetics, e.g. metoclopramide and erythromycin, as well as postural 'tricks', i.e. change of patient position following capsule ingestion, have been applied to improve SBCE CR9.

Recent meta-analyses on the use of bowel preparation in SBCE showed – in subgroup analysis – that there is no difference in the use of erythromycin 10–12. Although some evidence exists, current guidelines indicate that there is no strict recommendation on the use, type and/or mode of administration of prokinetics in SBCE⁸. Moreover, no previous systematic review and/or meta-analysis has been carried out to address whether adding prokinetics prior to capsule ingestion can increase the CR of the SBCE and/or the DY. This study was performed to assess the current evidence base on the use of prokinetics for CR and explore their effect on GTT and SBTT by meta-analysing all relevant studies.

Methods

Literature search strategy

A recursive search of PubMed/Medline, Embase and Scopus databases for studies published up to the end of November 2012 was performed. The last computerized search was carried out on 30th November 2012. No language, start date or age search limits were applied. In order to capture as many articles as possible, a broad search strategy was employed, using the MeSH term 'capsule endoscopy' (with 'automatic explosion' and 'all fields' search) linked in simple search strings by 'AND' with the following text terms: 'antiemetic', 'completion', 'domperidone', 'erythromycin', 'gastric emptying', 'ingestion', 'intramuscular', 'metoclopramide', 'ondensetron', 'oral/liquid', 'preparation', 'prokinetic', 'promotility', 'retention', 'tegaserod', and 'transit'. Furthermore, a combined recursive/manual search of all pertinent review articles and recently published editorials was performed.

Publications selection

After retrieving the full text of selected papers, data were extracted by the first author (A.K.) using a predefined form and were (at parts) verified by another author (K.J.D.). A full manual search for potentially suitable references was also performed in the reference list of all retrieved original studies. As no language restriction was applied, publications were translated into English as required by one of the authors (D.E.Y.). In the event of uncertainty, any discrepancies were resolved by discussion with the senior co-author and consensus.

Selection criteria

Inclusion and exclusion criteria were drafted before commencing the literature search. Therefore, studies eligible for inclusion in this meta-analysis were those meeting all of the following criteria:

- (1) published as full articles, reporting (prospective or retrospective) comparative data
- (2) used prokinetics in (at least) one of the reported patient subgroups
- contained information on the type of the SBCE system/model used
- specified the type, mode of administration and dose of prokinetics used, and
- contained data on one or more of the following SBCE parameters: completion rate (to caecum) (CR), DY, GTT, SBTT.

DY was defined as the total number of positive (diagnostic and suspicious) findings. GTT was defined as the time interval between the first gastric image and the first duodenal image. SBTT was defined as the time interval between the first duodenal images and the first caecal image.

Studies not meeting the aforementioned inclusion criteria, those examining the effect of postural 'tricks', and/or duplicate publications were excluded. We also excluded cohort studies with no control arm, review articles, and/or case reports or case series. It was decided that when two papers reported the same study, the most recent and/or the more informative publication would be selected.

Statistical analysis

Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated and outcomes of individual studies were compared by using the fixed-effects model (Mantel-Haenszel method)¹³ unless significant statistical heterogeneity was detected, where the random-effects model was applied (DerSimonian-Laird method)¹⁴. Heterogeneity was assessed using the inconsistency index (I^2) and the chi-square (χ^2) test for heterogeneity; evidence of heterogeneity was considered to be present if

 $P < 0.10^{15}$. In case of significant heterogeneity in study design, results were pooled using the DerSimonian-Laird random-effects model. This is preferable to a fixed-effects model (Mantel-Haenszel method), as it takes into account differences between studies and treatments when estimating 95% CI and P values. Apart from adjusting for heterogeneity by applying the random-effects model, reasons for heterogeneity were explored. This lead to the stratification of the studies into more homogeneous groups, therefore more reliable estimates16. The candidate factors for stratification were: the randomization quality (Jadad score)¹⁷; the study design (prospective vs. retrospective); the use of bowel purging (bowel purging and prokinetic vs. prokinetic alone); and the most readily available (therefore more frequently used) prokinetics (metoclopramide and erythromycin vs. the rest).

A sensitivity analysis was performed in order to evaluate the consistency of our results. First, to evaluate any possible excessive influence of a single study, we examined whether the exclusion of this study substantially altered the magnitude or heterogeneity of the summary estimate. This was achieved by repeating the meta-analysis with exclusion of each individual study one at a time, to assess the overall effect of the exclusion on the pooled ORs¹⁸. Forest plots were constructed for the visual display of ORs across selected studies. Statistical analysis was performed by using the Metan package of Stata version 12.1 (StataCorp, College Station, TX, USA)¹⁹.

Publication bias assessment

The likelihood of publication bias was assessed by constructing funnel plots, which were obtained by plotting the log ORs vs. SE (log [OR]) of individual studies²⁰.

Methodological quality assessment

The methodological quality of randomization of the studies was assessed and graded according to criteria described in the Jadad scale which has already been extensively described elsewhere¹⁷. Therefore, the following items were independently scored for each study:

- Was the study described as randomized (this includes words such as randomly, random, and randomization)? (0/1)
- (2) Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)? (0/1)
- (3) Was the study described as double blind? (0/1)
- (4) Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc.)? (0/1), and
- (5) Was there a description of withdrawals and dropouts? (0/1).

- (6) Furthermore, one (1) point was deducted for each of the following two:
- (7) if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.); and
- (8) if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy) (Table 1).

Furthermore, it is known that evidence based on retrospective studies begins as low quality, with a potential to decrease further because of study limitations, inconsistency of results (heterogeneity), impression and other considerations (including publications bias)²¹; therefore, the overall quality (for each study) was a combination classified as high, moderate or low, according to a combination of Jadad score and type of study design.

Data extraction

For each included study, the following variables were extracted and entered into an Excel data sheet: author, year of publication, number of participants, type of SBCE system, use of prokinetic/promotility agent, dose, mode and time of administration (in regard to capsule ingestion), GTT, SBTT, CR or rate of total enteroscopy and DY. Furthermore, the rerention/obstruction rate (RR), where reported, was extracted. Relevant studies were analysed according to the type of prokinetic used with the following primary and secondary end-points: a) CR, b) GGT, c) SBTT, and d) DY.

Results

Descriptive assessment and study characteristics

A flow chart describing the process of data/study identification and selection is shown in Figure 1. A total of 703 titles were initially identified with the aforementioned search strategy. Of those, 402 were excluded after preliminary review of the titles and/or abstracts, leaving 301 articles for further/detailed evaluation. Of those, 278 were excluded following thorough review of the abstracts. Moreover, a further two articles were identified from reference review. Therefore, the full text of 26 articles (with potentially extractable data) was evaluated further. Consequently, 17 articles met the inclusion criteria and entered this meta-analysis^{22–38}. The main characteristics of the studies eligible for review, including their Jadad scores¹⁷, are shown in Table 2.

A total of 1899 individuals (1859 patients and 40 healthy participants; 1028 subjects ingested the capsule with no prokinetic [n=1008] or placebo [n=20] and

Table 1. Jadad scores¹⁷ of the studies included in this meta-analysis.

TOTAL score	-1	3	0	0	0	3	3	2	0	2	-1	3	3	-1	-1	0	5
Item 7	0	0	0	Θ	0		0	0	0	0	0	0	0	0	0	0	
Item 6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Item 5	0	0	•	0	•	•	•	0	•	0	0	•	•	0	0	0	
Item 4	0	0		0	0	0	0	0	0	0	0	0	0	0	0	0	
Item 3	0	0		0	0	0	0	0	0	0	0	0	0		0	0	
Item 2	0	•	0		0	•	•	•	0		0			0	0	0	
Item 1	0		0	•	0	•	•	•	0		0			0			
Authors, year	Selby ²²	Leung et al. ²³	Caddy et al.24	Wei et al.26	Apostolopoulos et al. ²⁵	Niv et al.	Hooks 3rd et al.29	Postgate et al.28	Almeida et al. ³³	lwamoto et al.29	Song et al.31	Hosono er al. 75	Nakaji et al. ³³	Zhang et al ³⁴	Shiotani et al. 36	Xiong er al. ³³	lda er al.'#

●+1; ■ 0 or not clear, not available; □ -1.

876 with a prokinetic; 982 males/917 females; mean age: 54.73 ± 21.1 years) were included in these studies. Fifteen studies^{22–30,32–36,38} (n = 1690 subjects) were published in English and two 31,37 (n = 209 patients) in the Chinese language. All, apart from one study²⁷, were single-centre papers; ten studies (58.8%) were conducted in the Far East (China: 5 studies^{23,26,31,34,37} Japan: 5 studies^{32,33,35,36,38}), two in Australia^{22,24} and one in each of the following countries: Greece, Israel, Portugal, UK and USA 25,27-30. Fourteen of them were prospective 22,24-30,32-36,38 and three were retrospective studies^{23,31,37}. Capsule endoscopy was performed with M2A and/or PillCam SB capsule endoscope models (Given Imaging Ltd, Yokneam, Israel) in all but two Chinese studies - including a total of 286 patients where the OMOM capsule endoscope (Jinshan Science & Technology Company, Chongqing, China) was used^{34,37}. Furthermore, in one study both EndoCapsule (Olympus Medical Systems, Tokyo, Japan) and PillCam were utilized³⁸. Nine studies evaluated the use of metoclo-pramide^{22,28,30–32,34–37}, three of erythromycin^{23,24,27}, two of mosapride26,38 and from one the effect of chewing gum25, lubiprostone²⁹, and the combined effect of daikenchuto + metoclopramide (post real-time check)33.

All subjects were prepared with overnight fast and in nine studies purgatives were used either prior to and/or during capsule endoscopy^{22,24,25,28,33–35,37,38}. Furthermore, in five studies simethicone was administered for capsule ingestion^{22,23,30,33,35}. Lastly, a real-time viewer (RTV) was utilized in the protocol of five studies^{33–37}, although external RTV should be considered instrumental only in the protocol of two metoclopramide studies^{36,37}.

Lastly, eight studies (four on metoclopramide, two on erythromycin, one on lubiprostone and one on mosapride)^{23,26–31} examined the usefulness of the aforementioned prokinetics, without potential external interference/bias effect by laxatives, RTV and/or complex study protocols, and are considered separately in the sensitivity analysis (subgroup 1). Overall, in the metanalysed studies, there were 17 sets of primary endpoint data (CR) and 24 sets of secondary endpoints data (GGT: 8, SBTT: 9, and DY: 7).

Primary endpoint: SBCE completion rate

SBCE CR was defined as the capsule reaching the caecum. All included studies presented such data (17 sets), examining the SBCE CR in 1028 subjects who ingested the



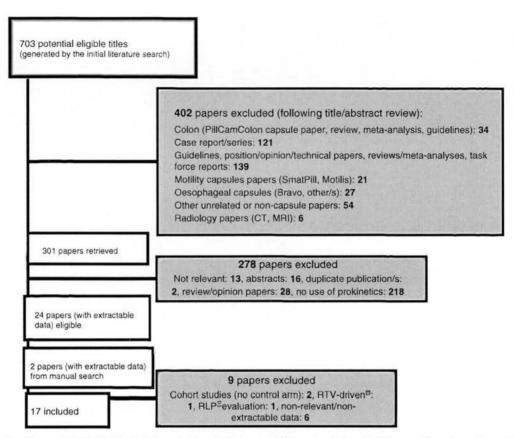


Figure 1. Flow diagram of the identification of studies and of the selection process of this meta-analysis, @RTV-driven; real-time viewer driven; ERLP; right lateral position.

capsule without prokinetic as opposed to 876 individuals who received a prokinetic. There was evidence of hererogeneity between study results ($1^2 = 37.9\%$, P = 0.058; Figure 2). Because of heterogeneity, the DerSimonian-Laird random-effects model was used for pooling of results: this model is recommended - as the method of choice - by the International Cochrane Collaboration 21,39 in order to avoid unrealistically low 95% CIs that may arise from a fixed-effects model analysis21. The results indicated that the odds of having a complete SBCE were superior for patients who ingested the capsule with a prokinetic than for those who did not receive a prokinetic agent; OR (95% CI) = 1.96 (1.38–2.78), Figure 2. Furthermore, studies of the same prokinetic were grouped together; for the erythromycin studies^{23,24,27}, no heterogeneity – in study design or results – was detected ($I^2 = 37.6\%$, P = 0.201; Figure 2) and the pooled OR (95% CI) was 1.36 (0.61-3.03). In the metoclopramide group^{22,28,30-37}, evidence of heterogeneity between the studies was weak but present $(I^2 = 38.3\%, P = 0.103;$ Figure 2); the pooled randomeffect estimate of the OR (95% CI) for SBCE CR was

2.08 (1.35-3.21). Lastly, for the remaining four studies, some evidence of heterogeneity was detected $(I^2 = 58.7\%, P = 0.064;$ Figure 2); the random-effect estimate of the OR (95% CI) was 1.89 (0.75-4.82).

Studies that used prokinetics with no bowel purge and a straightforward study protocol (subgroup 1)^{23,26-31} were chosen to investigate further the reasons for heterogeneity. In order to exclude any possible influence of a single study, we repeated the meta-analysis with exclusion of each individual study one at a time. This did not alter the pooled results. Moreover, we performed sensitivity analyses by stratifying studies by factors which could potentially influence the pooled results, i.e. study design (prospective vs. retrospective), use of bowel purge (bowel purge + prokinetic vs. prokinetic alone), the most frequently and readily available prokinetics used (metoclopramide vs. erythromycin vs. rest), and Jadad scores. The results of these subgroup analyses are shown in Figure 3. The number of included studies was not sufficient to draw a conclusion regarding other stratification factors.

Table 2. Study characteristics.

Authors, year	Country	Study type	Centre	Jadad	Exclusion criteria	RTV used	Purgative used Type/dose	Simethicone used	Prokinetic used	Dose/mode/time of administration	CE used	# Controls (M/F) # Prokinetic (M/F)	Outcome data CR, DY, GTT, SBTT
Selby 22	Australia	Prospective	Single centre	0	Unclear	No.	No (26)/Yes (113+11)	Yes	Metoclopramide	10 mg/P0/15' pro-ingestion	PillCam SB/M2A (29)	83 (45/38)	CR, DY, GTT, SBTT
Leung et al. 4^{23}	China	Retrospective	Single centre	0	Yes	No	NaPico (10 mg)/PEG (1 l) No	Yes	Erythromycin	250 mg/PO/ pro-ingestion	M2A	67 (30/37) 14 (8/6)	CR, n/a, GTT, SBTT
Caddy et al. ²⁴	Australia	Prospective	Single centre	2	Yes	No	Yes NaPico (250 ml)/	No	Erythromycin	250 mg/P0/60' pro-ingestion	PiliCam SB	24 (9/15) 23 (8/15) 22 (10/12)	СВ, п/а, GTT, SВТТ
Apostolopoulos et al.25	Greece	Prospective	Single centre	89	Yes	No.	PEG (500 ml) Yes	No	Chewing-gum	1 pc/P0/chewed for 30' alt. h.	PillCam SB	46 (24/22)	CR, n/a, GTT, SBTT
Wei et al.⇔²8	China	Prospective	Single centre	က	Yes	No No	No	No	Mosapride	10 mg/P0/60* pro-ingestion	M2A	30 (19/11)	CR, DY, GTT, SBTT
Niv et al.♦²७	Israel	Prospective	Two-centre	0	Unclear	No	No	No	Erythromycin	200 mg/P0/60' pro-ingestion	PillCam SB	50 (32/18)	СR, n/a, GTT, SBTT
Postgate et al. 428	¥	Prospective	Single centre	ю	Yes	Q	Yes/No Citramag	N _o	Metoclopramide	10 mg/P0/10' pro-ingestion	PillCam SB	37 (14/23) + 39 (17/22) 37 (10/27)	CR, DY, GTT, SBTT
Hooks 3rd et al.❖²9	USA	Prospective	Single centre	S	Yes	9 <u>V</u>	(2 I) + Senna (2 pk)	No	Lubirpostone	24 µg/P0/ pro-ingestion	PillCam SB1	+37 (19/18) 20 (5/15) (placebo) – healthy subjects 20 (8/12) –	СВ, n/a, GTT, SВТТ
Almeida et al. 430	Portugal	Prospective	Single centre	8	Yes	No	No	Yes	Metoclopramide	10 mg/P0/15' pro-ingestion	PillCam SB	nealmy subjects 48 (25/23)	CR, DY, GTT, SBTT
Song et al. 431	China	Retrospective	Single centre	7	Yes	No	No	No	Metoclopramide	10 mg/IM/15' pro-ingestion	M2A	47 (19/28) 74 (n/a)	CR, n/a (total), GTT, SBTT
Wamoto et al.♦32	Japan	Prospective	Single centre	0	Yes	S.	No	No	Metoclopramide	10 mg/IV/ pro-ingestion	PillCam SB	26 (n/a) 57 (36/21)	CR, DY, GTT, SBTT
Nakaji <i>et al.</i> ³³	Japan	Prospective	Single centre	0	Yes	Yes (16)	Yes Citramag (900 ml)	Yes	Daikenchuto Metoclopramide	7.5 grx2/P0/12 h pro-ingestion 10 ma/lV/60*	PillCam SB1/SB2	43 (25/18) 99 (59/40) 29 (18/11)	CR, n/a, n/a, n/a
Zhang et al.34	China	Prospective	Single centre	m	Yes	Yes (177)	pro-ingestion PEG (41)	No	(12 post-RTV) Metoclopramide	post-ingestion 10 mg/IM/15' pro-ingestion	омом	88 (47/41)	CR, n/a, GTT, SBTT
Hosono et al. 35	Japan	Prospective	Single centre	2	Yes	Yes (40)	PEG (500 ml post-RTV)	Yes	Metoclopramide (7 post-RTV)	10 mg/IM/60' post-ingestion	PillCam SB1/SB2	89 (44/45)	СЯ, DУ, GTT, SВТ
Shiotani <i>et al.</i> ³⁶	Japan	Prospective	Single centre	7	Yes	Yes (100)	No.	N _O	Metoclopramide (26 post-RTV)	10 mg/lV/90' post-ingestion (12) 10 mg/lV/7–8 h	PillCam SB	40 (2//13) 100 (54/46) 100 (29/51)	CR, DY, GTT, SBTT
Xiong et al.37	China	Retrospective	Single centre	7	Yes	Yes (109)	NaPhospho (45 ml)	No	Metoclopramide (post-RTV)	10 mg/IN/60' post-ingestion	ОМОМ	69 (38/31)	CR, n/a, n/a, n/a
lda et al. 38	Japan	Prospective	Single centre	7	Yes	o _N	PEG (1 or 21)	No	Mosapride	10 mg/P0/30–60° pro-ingestion	PiliCam SB1/SB2 EndoCapsule	106 (n/a)	CR, n/a, n/a, n/a

RTY: real-time viewer. PEG: polyethylene glycol, pk: packet, PO: per os: ': min, pc:piece, alt: alternate, h: hour, IM: intranuscularly, IV: intravenously, n/a: not available, CR: Completion rate, DY: diagnostic yield, GTT: gastric transit time, SBTT: small-bowel transit time. *Studies of subgroup 1 (studies with homogeneous protocol i.e. no real-time monitoring for intervention and no prioruse of prokinetics).

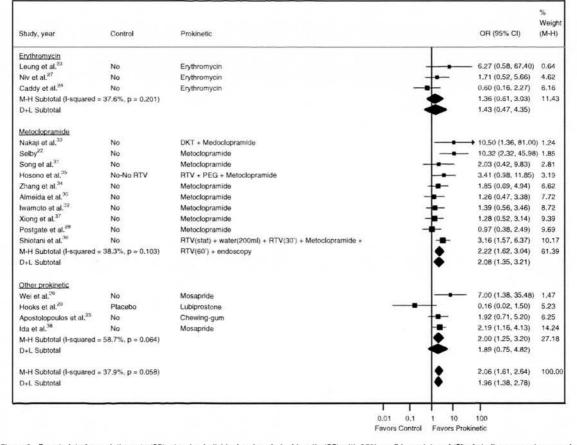


Figure 2. Forest plot of completion rate (CR), showing individual and pooled odds ratio (OR) with 95% confidence interval (CI) of studies comparing capsule ingestion with prokinetics vs. no prokinetics. Overall, prokinetics improve the CR. This is more obvious with those studies that used metoclopramide for capsule ingestion.

Secondary endpoints

Diagnostic yield (DY)

Seven studies^{22,26,28,30,32,35,36} examined SBCE DY in 401 patients who ingested the capsule with prokinetics (371 metoclopramide/30 mosapride) as opposed to 434 patients who did not use prokinetics for capsule ingestion. Six of the seven meta-analysed studies used metoclopramide as prokinetic. There was no evidence of heterogeneity between these studies ($I^2 = 0$, P = 0.914), therefore the fixed-effects model was used for synthesis and presentation of pooled results. There was a weak trend that the SBCE DY ratio (pooled DY in the group who receive prokinetic/ total number of cases in the prokinetic group)/(pooled DY in the control group/total number of control cases) was superior for the patients who received prokinetics for capsule ingestion as opposed to controls, pooled RR (95% C1) = 1.10 (0.96-1.27) (Figure 4). This may be due to the small number of studies and the heterogeneity due to the different prokinetic agents used and diverse study designs.

Gastric transit time (GTT)

Eight studies 22,23,25,27,29,32,35,36 measured the average SBCE GTT (min) in 391 subjects who ingested the capsule with prokinetics (250 metoclopramide/74 erythromycin/20 lubiprostone/47 chewing gum) as opposed to 410 subjects (20 placebo) who used no prokinetic for capsule ingestion. There was evidence of heterogeneity between studies ($I^2 = 64.5\%$, P = 0.006). More specifically, heterogeneity was detected in the erythromycin group 23,27 ($I^2 = 73.8\%$, P = 0.051) and lubiprostone/chewing gum studies 25,29 ($I^2 = 87.2\%$, P = 0.005). However, no difference between prokinetic and control in GTT was noted. In the metoclopramide studies group, there was no evidence of heterogeneity and the use of metoclopramide seem to affect GTT over controls; pooled difference in

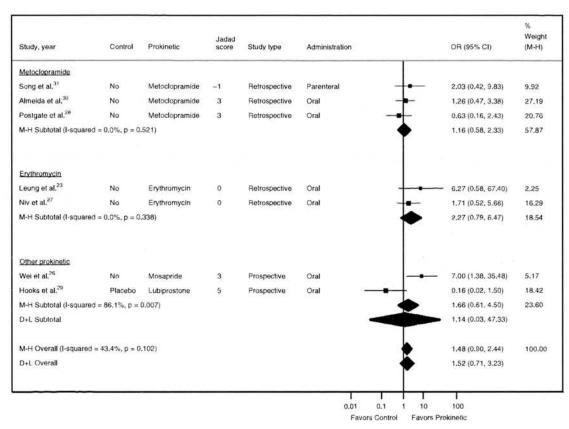


Figure 3. Forest plot of completion rate (CR), showing individual and pooled odd ratios (OR) with 95% confidence intervals (CI) of subgroup 1 studies (studies with more homogenous protocols in which purging and/or real-time monitoring were not used) comparing capsule ingestion with prokinetics vs. no prokinetics. In this subgroup of studies, there is no evidence of improved CR when the capsule was ingested with metoclopramide, erythromycin, mosapride or lubiprostone.

the means in this group (GTT of control - GTT of prokinetic group) was 16.83 (14.30-19.37) (Figure 5). It is noteworthy that although the latter group included the two studies that had RTV in their protocol 35,36, a clear effect of metoclopramide on GTT was also evident in the studies^{22,32} which did not utilize real-time monitoring.

Small-bowel transit time (SBTT)

Nine studies^{22,23,25,27,29,30,32,35,36} measured the average SBCE SBTT (min) in 438 subjects who ingested the capsule with prokinetics (297 metoclopramide/74 erythromycin/20 lubiprostone/47 chewing gum) and 458 controls (20 placebos) who did not receive prokinetics for capsule ingestion. There was no evidence of heterogeneity within the prokinetic groups. More specifically, the erythromycin studies^{23,24,27} showed $I^2 = 0\%$, P = 0.342(and lubiprostone/chewing gum $I^2 = 0\%$, P = 0.8616) in the heterogeneity test. In the erythromycin group, no difference between prokinetic and control in STT was noted (pooled difference in the means [95% CI]: -20.41 [-54.28, 13.45]). In the metoclopramide group, there was no evidence of heterogeneity ($I^2 = 37.3$, P = 0.173) and its use had an effect on SBTT over controls; pooled difference in the means (GTT of control - GTT of prokinetic group) [95% CI]) = 24.30 [20.90-27.70] (Figure 6).

Publication bias

Evidence of publication bias was also present (Figure 7) as, when looking at the metoclopramide group, small studies with small effect were not found in the literature review.

Safety

No fatal complications were reported in any of the studies included in this meta-analysis. More specifically, cases of capsule retention were reported², but no capsule aspiration was recorded and no bowel obstruction (Table 3).

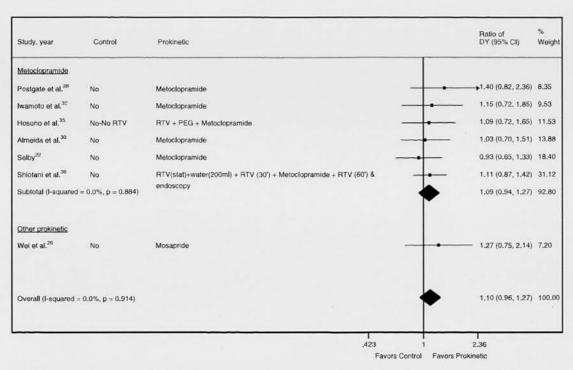


Figure 4. Forest plot of diagnostic yield (DY), showing individual and pooled relative ratio (RR) with 95% confidence intervals (CI) of studies comparing capsule ingestion with prokinetics vs. no prokinetics (data from studies reporting relevant data).

More importantly, no sinister adverse effects from the use of prokinetics were reported (Table 3).

Discussion

Since the image quality of SBCE is high⁴⁰, the DY of SBCE is only limited by two confounders which hamper SBCE performance in complete evaluation of small-bowel mucosal features: a) poor luminal visualization, and b) slow gastric and/or small-bowel transit time, which can prevent the capsule from reaching the IC valve/caecum within the capsule's battery life⁸. Although the latter may appear as less of a problem, because of new capsule technology with extended battery life, complete small-bowel transit theoretically offers enhanced DY. Conversely, there has been data to suggest that it is in fact the prolonged small-bowel passage that may be associated with increased DY41,42. Therefore, various techniques and interventions have been developed aiming to improve the clinical chances for total enteroscopy'

To date, there are three published meta-analyses 10-12 showing that purgative cleansing of the small bowel before SBCE significantly improves the quality of mucosal visualization, in comparison to clear fluid diet, although it does

not seem to affect the SBCE completion rate11. In fact, data suggest that up to 20-25% of patients undergoing SBCE have an incomplete examination⁴. As a direct comparison, if we were to measure colonoscopy caecal intubation rates ≤80%, this would undoubtedly be considered very low, and every effort would be made to improve it3. It is possible that hypertonic purge regimens may delay gastric emptying²⁸. With all that in mind, several prokinetics^{8,9} have been assessed, yet there is still no consensus on their use in SBCE. At the ICCE Consensus Meeting in Miami (2006), it was recognized that although there were several studies involving promotility preparations and manoeuvres, this remains to date a contentious issue^{8,9}. Although different in regards to weight/size (3.6 g vs. $6.2 \text{ g/}11 \times 26 \text{ mm}$ vs. $13 \times 27.9 \text{ mm}$, for PillCam/ EndoCapsule and OMOM, respectively), all these systems have comparable battery life (8h)43

Erythromycin, a macrolide antibiotic with appealing safety profile, acts on motilin receptors of the endocrine cells of the duodenum²⁴ and has well known prokinetic properties. It induces high amplitude gastric propulsive contractions. As a result, it accelerates gastric emptying for both liquids and solids including that of non-digestible particles²⁷. Its commonest side effect is nausea, which in the case of SBCE may limit its use²².

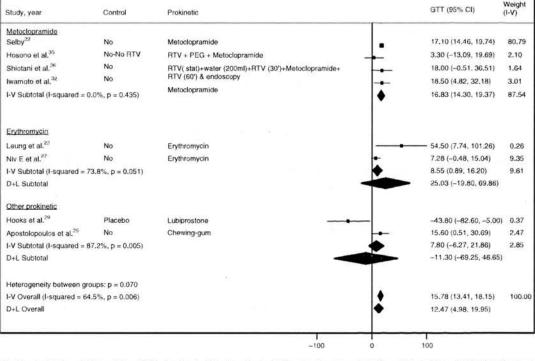


Figure 5. Forest plot of gastric transit time (GTT), showing individual and pooled difference of means with 95% confidence intervals (CI) of studies comparing capsule ingestion with prokinetics vs. no prokinetics (data from studies reporting relevant data). There was reduced GTT with metoclopramide, less clear effect seen with erythromycin.

Metoclopramide, a dopamine D2 receptor agonist, has a combination action of relaxing the pyloric sphincter and improving the antro-duodenal co-ordination⁴⁴. It has a good rapid oral absorption³⁰, with a peak plasma concentration at 56 min and half-life of 5 h. Tardive dyskinaesia and other extra-pyramidal/dystonic reactions have been – not infrequently – reported as idiosyncratic adverse effect of its use.

Mosapride citrate is a prokinetic agent that acts as a serotonin 5-hydroxytryptamine-4 (5-HT4) agonist that is mostly available in Asia and increases gastrointestinal motility. Tegaserod, another 5-HT4 agonist is available in Western countries³⁸. The latter was initially approved by the FDA in 2002, but it was subsequently removed from the market in 2007 due to FDA concerns about possible adverse cardiovascular effects⁴⁵. A few years earlier, cisapride – an effective gastrokinetic agent – was associated with fatal arrhythmias in susceptible individuals and was withdrawn by the FDA in 1999⁴⁶.

Lubiprostone (Amitiza, Takeda Pharmaceuticals North America, Deerfiled, IL, USA) activates selectively the type 2 chloride channels in the apical membrane of the GI epithelium, resulting in net fluid secretion²⁹. It has been approved by the FDA for the treatment of chronic idiopathic constipation and constipation-predominant IBS. Recent studies revealed that it accelerates small-bowel transit as well as colonic transit time⁴⁷.

Daikenchuto (DKT) is well known in Japan as an effective treatment for reduced GI motility, but the mechanism of action remains largely unknown. However, one of the ingredients in DKT, Sancho (Xanthoxylum piperitum) promotes acetylcholine release at the neuromuscular junction of the digestive tract. It also increases motilin release, hence gastrointestinal peristalsis³³.

Chewing gum, as a proxy for sham feeding, acts by a cephalic–vagal axis. It increases salivary flow leading to increased gastric emptying. It also increases the motility of the small bowel and the colon²⁵. Apostolopoulos *et al.* used commercially available sugarless chewing gum, containing xylitol as sweetener.

Our study demonstrates a lack of consensus in using prokinetics in SBCE as well as a variety in study designs which included different mode (oral or parenteral) and timing of administration of prokinetics⁹. We found that erythromycin studies^{23,24,27} were more homogeneous in terms of study design (no RTV used, no concurrently

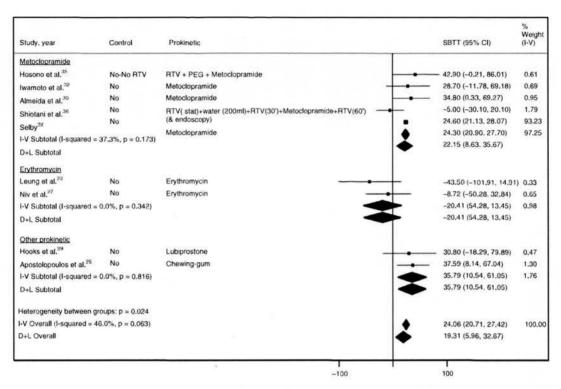


Figure 6. Forest plot of small-bowel transit time (SBTT), showing individual and pooled difference of means with 95% confidence intervals (CI) of studies comparing capsule ingestion with prokinetics vs. no prokinetics (data from studies reporting relevant data). There was improved SBTT with metoclopramide; erythromycin showed the opposite effect.

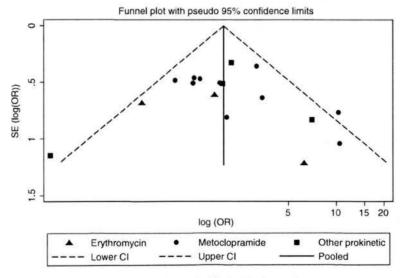


Figure 7. Funnel plot of studies included in this meta-analysis; evidence of publication bias is present.

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Table 3. Exclusion criteria, reported capsule retention episodes, bowel obstruction/capsule aspiration cases and adverse effects of the prokinetics used in the studies of this meta-analysis.

Authors, year	Exclusion criteria	Capsule retention [◆]	Bowel obstruction/ capsule aspiration	Prokinetic-related side effects (prokinetic used)
Selby ²²	n/a	None	None	None (metoclopramide)
Leung <i>et al.</i> ³❖	Swallowing difficulties; previous gastric/bowel surgery; prior use of prokinetic agents	None	None	None (erythromycin)
Caddy et al. ²⁴	Age<18 years; diabetes mellitus; unwillingness to participate	None	None	None (erythromycin)
Apostolopoulos et al. ²⁵	Diabetes mellitus; prior gastric/abdominal surgery; dys- thyroidism; unwillingness to participate	None	None	None (chewing gum)
Wei <i>et al.</i> ²6❖	Known bowel obstruction; stricturer/fistula; diabetes mel- litus; pregnancy; prior narcotic drug use; dysthyroid- ism; prior gastric or bowel surgery	None	None	None (mosapride)
Niv et al. ²⁷ ❖	n/a	None	None	None (erythromycin)
Postgate et al.28 🌣	n/a	None	None	None (metoclopramide)
Hooks 3rd <i>et al.</i> ²⁹ ❖	Age<19 years; previous bowel perforation and/or resection; known/suspected bowel obstruction; current ileus; severe IBD; faecal impaction/diarrhoea; current pregnancy or lactation	None	None	(lubiprostone): diarrhoea (n=4F), headache/nausea (n=1F), abdominal cramping (n=1M)
Almeida <i>et al.</i> ³⁰❖	Cardiac pacemaker/defibrillator; age <18 years; preg- nancy; swallowing difficulties; stricture or previous gastric/bowel surgery	None	None	None (metoclopramide)
Song et al.³¹❖	Known/suspected bowel obstruction; cardiac pacemaker/ defibrillator; severe/reported swallowing difficulties	None	None	None (metoclopramide)
Iwamoto et al.32.	Known/suspected bowel obstruction	None	None	None (metoclopramide)
Nakaji <i>et al.</i> ³³	Known or suspected bowel stenosis; cardiac pacemaker/ defibrillator; pregnancy	Cricopharyngeous $(n=1)$ Small-bowel retention $(n=1)$	None	None (DKT + metoclopramide)
Zhang et al.34	Known/suspected bowel obstruction; stricture/fistula or known Crohn's disease; age <18 years; pregnancy; diabetes mellitus	None	None	None (metoclopramide)
Hosono et al. ³⁵	Gastric/bowel surgery; gastric dysmotility; age <18 years; pregnancy; prior use of medications that affect GI motility	None	None	None (metoclopramide)
Shiotani et al.36	Known/suspected bowel obstruction; stricture/fistula; prior use of medications that affect GI motility	None	None	None (metoclopramide)
Xiong et al.37	Criteria of exclusion for SBCE by Chinese Society Of Digestive Endoscopy Guidelines	None	None	None (metoclopramide)
lda et al. 38	Participation in other clinical trial; total gastrectomy; inability to swallow capsule; recorder malfunction; missing medical records	None	None	None (mosapride)

n/a: not available.

*Defined as the presence of the capsule in the gut (confirmed by imaging) >14 days following ingestion. Capsule retention: refers only to study participants and not excluded cases (especially for retrospective studies).

*Studies of subgroup 1 (studies with homogeneous protocol, i.e. no real-time monitoring for intervention and no prior use of prokinetics).

|BD: inflammatory bowel disease; GI: gastrointestinal; SBCE: small-bowel capsule endoscopy; F: female; M: male; DKT: Daikenchuto

administered prokinetic or postural tricks), but there were only a few studies regarding number of participants. On the other hand, metoclopramide-based studies^{22,28,30–37} were higher in number and larger in terms of participants, yet they were more heterogeneous in design and mode/time of administration of the medication. Lastly, prokinetics used in a number of studies^{26,29,33,38} are not widely available^{26,33,38} and/or associated with mild or significant side effects²⁹ (another one, Tegaserod considered as the 'Western world counterpart' of mosapride, has been withdrawn due to cardiovascular side effects)⁴⁵.

Pooled results on CR show that ingesting the capsule with prokinetics leads to a higher rate of complete smallbowel examination than in controls (OR [95% CI]: 1.96 [1.38-2.78]). More specifically, metoclopramide is associated with higher CR (OR [95% CI]: 2.8 [1.35-3.20]); no such effect is seen with erythromycin (OR [95% CI]: 1.36 [0.61-3.03]). Furthermore, when a smaller group of 'clear' i.e. more homogeneous in design studies was examined (subgroup 1), where bowel purging and real time monitoring were not used^{23,26-31}, the effect of either prokinetic (metoclopramide and erythromycin) on completion rate was not significant (Figure 2); metoclopramide CR pooled OR (95% CI): 1.16 (0.58-2.33), erythromycin CR pooled OR (95% CI): 2.27 (0.79-6.47) and for the whole group pooled OR (95% CI) for CR of prokinetic vs. control was 1.52 (0.71-3.23).

With regards to capsule transit parameters (GTT and SBTT), the effect of prokinetics over control was clear for both parameters. Metoclopramide administration for capsule ingestion resulted in a shorter GTT and SBTT (pooled difference in the means [95% CI]: 12.47 [4.98–19.95] and 19.31 [5.96–32.67], respectively). When the RR of DY was calculated, there was no evidence that the use of prokinetics confers any benefit in increasing the DY.

The present study had certain limitations. As with every meta-analysis, conclusions are as reliable as the underlying evidence available. The majority of the included studies were heterogeneous and of low quality with regards to randomization and design for the purpose of meta-analysis. It is noteworthy that patient populations are heterogeneous as some studies have excluded participation of individuals with diabetes mellitus^{24,26,34}, one of the main patient groups to get benefit from the use of prokinetics. Furthermore, although we studied the pooled DY in our meta-analysis, we did not examine the effect of prokinetics on image quality and mucosal visualization for two reasons: a) prokinetics are unlikely to have any significant effect on the intraluminal content (quantity and/or consistency), and b) there is no standardized or validated scoring system for visualization/preparation quality of SBCE.

In order to avoid further bias, we have excluded abstracts and cohort studies that may have reported further useful results on the field⁴². Furthermore, we excluded

studies, published as full papers, that looked mainly at the effect of positional tricks i.e. right lateral position at capsule ingestion 48,49. There were only four studies using a more rational and flexible approach by means of external or integrated real-time monitoring (nowadays an indispensable accessory in SBCE practice) and only two used the combination approach of certain predefined non-invasive interventions prompted by RTV results. The latter method should be considered most applicable in selected inpatients with poor mobility, advanced age and/or diabetes. Moreover, some retrospective studies excluded the participants who developed gastric capsule retention and/ or prolonged gastric stasis of the capsule. Although it is unlikely that future research will refute the results of existing evidence, it is worth noting that as technology advances and batteries are getting smaller and more potent, incomplete SBCE (due to slow transit time) will probably be phased out. Furthermore, future studies should evaluate specifically the benefit of a complete SBCE in patient management.

In conclusion, the results of this meta-analysis show that the use of prokinetics – and specifically that of meto-clopramide with purgative and/or RTV – in SBCE improves completion rate. Although CR may appear as less of a problem, due to new capsule technology with extended battery life, as described in this manuscript, it is important to conclude the efficacy of prokinetics.

Therefore, our results complement similar and extensive recent work in the field and relevant guidelines 50-52.

Transparency

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This study was not funded by any grant and represents the authors' own work.

Specific author contributions: A.K. conceived and drafted this study, extracted the data and participated in the statistical analysis; A.G. and A.K. performed the literature searches. K.J.D. and D.E.Y. participated in data collection/extraction. A.G. performed the statistical analysis. The initial manuscript was prepared by A.K. and A.G. Significant editing and major revision was performed by J.N.P. Editing and final draft revisions were provided by all co-authors. A.K. is guarantor of the article.

Declaration of financial/other relationships

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References

- 1. Wu L, Cao Y, Liao C, et al. Systematic review and meta-analysis of randomized controlled trials of simethicone for pastrointestinal endoscopic visibility. Scand J Gastroenterol 2011:46:227-35
- Höög CM, Bark LÅ, Arkani J, et al. Capsule retentions and incomplete capsule endoscopy examinations: an analysis of 2300 examinations. Gastroenterol Res Pract 2012;2012:518718. doi: 10.1155/2012/518718
- 3. Kaffes AJ. Achieving total enteroscopy with capsule endoscopy in all patients: are we stretching the limits of technology? Gastrointest Endosc 2009-69-81-3
- 4. Liao Z, Gao R, Xu C, et al. Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. Gastrointest Endosc 2010:71:280-6
- Rondonotti E, Soncini M, Girelli C, et al.; AIGO, SIED and SIGE Lombardia. Small bowel capsule endoscopy in clinical practice: a multicenter 7-year survey. Eur J Gastroenterol Hepatol 2010;22:1380-6
- Westerhof J. Weersma RK, Koornstra JJ, Risk factors for incomplete smallbowel capsule endoscopy. Gastrointest Endosc 2009;69:74-80
- Triantafyllou K, Papadopoulos AA, Kalantzis N, et al. Diabetes mellitus is a risk factor for incomplete small-bowel capsule endoscopy. Gastrointest Endosc 2009:69:1408-9
- Enns R. Transit times in capsule endoscopy: are all patients the same? Dig Liver Dis 2007:39:581-3
- Villa F, Signorelli C, Rondonotti E, et al. Preparations and prokinetics. Gastrointest Endosc Clin N Am 2006;16:211-20
- Niv Y. Efficiency of bowel preparation for capsule endoscopy examination: a meta-analysis. World J Gastroenterol 2008;14:1313-17
- 11. Rokkas T. Papaxoinis K. Triantafyllou K. et al. Does purgative preparation influence the diagnostic yield of small bowel video capsule endoscopy?: A meta-analysis. Am J Gastroenterol 2009;104:219-27
- Belsey J, Crosta C, Epstein O, et al. Meta-analysis: efficacy of small bowel preparation for small bowel video capsule endoscopy. Curr Med Res Opin 2012:28:1883-90
- 13. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719-48
- 14. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986:7:177-88
- Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in metaanalyses. BMJ 2003;327:557-60
- Moayyedi P. Meta-analysis: can we mix apples and oranges? Am J 16. Gastroenterol 2004:99:2297-301
- 17. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996:17:1-12
- Sutton AJ, Abrams KR, Jones DR, et al. Methods for Meta-Analysis in Medical Research. New York: Wiley, 2000
- Harris R, Bradburn M, Deeks J, et al. METAN: Stata Module for Fixed and Random Effects Meta-analysis. Statistical Software Components. Boston: Boston College Department of Economics, 2010
- Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol 2001;54:1046-55
- Leontiadis GI, Molloy-Bland M, Moayyedi P, et al. Effect of comorbidity on mortality in patients with peptic ulcer bleeding: systematic review and metaanalysis. Am J Gastroenterol 2013;108:331-45

- 22. Selby W. Complete small-bowel transit in patients undergoing capsule endoscopy: determining factors and improvement with metoclopramide. Gastrointest Endosc 2005:61:80-5
- 23. Leung WK, Chan FK, Fung SS, et al. Effect of oral erythromycin on gastric and small bowel transit time of capsule endoscopy. World J Gastroenterol 2005:11:4865-8
- 24. Caddy GR, Moran L, Chong AK, et al. The effect of erythromycin on video capsule endoscopy intestinal-transit time. Gastrointest Endosc 2006;63:262-6
- Apostolopoulos P, Kalantzis C, Gralnek IM, et al. Clinical trial: effectiveness of chewing-gum in accelerating capsule endoscopy transit time - a prospective randomized, controlled pilot study. Aliment Pharmacol Ther 2008;28:405-11
- Wei W, Ge ZZ, Lu H, et al. Effect of mosapride on gastrointestinal transit time and diagnostic yield of capsule endoscopy. J Gastroenterol Hepatol 2007:22:1605-8
- 27. Niv E, Bonger I, Barkay O, et al. Effect of erythromycin on image quality and transit time of capsule endoscopy: a two-center study. World J Gastroenterol 2008:14:2561-5
- Postgate A, Tekkis P, Patterson N, et al. Are bowel purgatives and prokinetics useful for small-bowel capsule endoscopy? A prospective randomized controlled study. Gastrointest Endosc 2009;69:1120-8
- Hooks 3rd SB, Rutland TJ, Di Palma JA, Lubiprostone neither decreases gastric and small-bowel transit time nor improves visualization of small bowel for capsule endoscopy: a double-blind, placebo-controlled study. Gastrointest Endosc 2009;70:942-6
- Almeida N, Figueiredo P, Freire P, et al. The effect of metoclopramide in capsule enteroscopy. Dig Dis Sci 2010;55:153-7
- Song ZQ. Gu F. Yao W. et al. [Evaluation of capsule endoscopy on the diagnosis of gastrointestinal diseases]. [Article in Chinese]. Beijing Da Xue Xue Bao 2010:42:539-42
- Iwamoto J, Mizokami Y, Shimokobe K, et al. The effect of metoclopramide in capsule endoscopy. Hepatogastroenterology 2010;57:1356-9
- Nakaji K, Suzumura S, Fujita A et al. Effectiveness of Dalkenchuto, a Traditional Japanese Herbal Medicine, in Accelerating Capsule Endoscopy Transit Time - A Prospective Pilot Study (2011). New Techniques in Gastrointestinal Endoscopy, Prof. Oliviu Pascu (Ed.). Available at: http:// www.intechopen.com/books/new-techniques-in-gastrointestinal-endoscopy/ effectiveness-of-daikenchuto-a-traditional-japanese-herbal-medicine-inaccelerating-capsule-endoscop [last accessed 21 May 2013]
- Zhang JS. Ye LP. Zhang JL. et al. Intramuscular injection of metoclopramide decreases the gastric transit time and does not increase the complete examination rate of capsule endoscopy: a prospective randomized controlled trial. Hepatogastroenterology 2011;58:1618-21
- Hosono K, Endo H, Sakai E, et al. Optimal approach for small bowel capsule endoscopy using polyethylene glycol and metoclopramide with the assistance of a real-time viewer. Digestion 2011;84:119-25
- Shiotani A, Honda K, Kawakami M, et al. Use of an external real-time image viewer coupled with prespecified actions enhanced the complete examinations for capsule endoscopy. J Gastroenterol Hepatol 2011;26:1270-4
- 37. Xiong GY, Wang M, Yang LH, et al. Relationship between gastric transit time and complete examination rate of the capsule endoscopy examinations. Shijle Huaren Xiaohua Zazhi 2012;20:2318-21
- Ida Y, Hosoe N, Imaeda H, et al. Effects of the oral administration of mosapride citrate on capsule endoscopy completion rate. Gut Liver 2012;6:339-43
- Hayden JA, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 2006;144:427-37
- Eliakim R. Video capsule endoscopy of the small bowel. Curr Opin Gastroenterol 2013;29:133-9
- Buscaglia JM, Kapoor S, Clarke JO, et al. Enhanced diagnostic yield with prolonged small bowel transit time during capsule endoscopy. Int J Med Sci 2008;5:303-8
- Westerhof J, Koornstra JJ, Hoedemaker RA, et al. Diagnostic yield of small bowel capsule endoscopy depends on the small bowel transit time. World J Gastroenterol 2012;18:1502-7
- 43. Fisher LR, Hasler WL, New vision in video capsule endoscopy: current status and future directions. Nat Rev Gastroenterol Hepatol 2012;9:392-405

- Schwarzberg MN. Pro-kinetic medications as aids in imaging the small bowel by video-capsule. Med Hypotheses 2005;64:602-7
- FDA Announces Discontinued Marketing of GI Drug, Zelnorm, for Safety Reasons (2007, March 30). Available at: http://www.fda.gov/NewsEvents/ Newsroom/PressAnnouncements/2007/ucm108879.htm [last accessed 21
- 46. Wysowski DK, Corken A, Gallo-Torres H, et al. Postmarketing reports of QT prolongation and ventricular arrhythmia in association with cisapride and Food and Drug Administration regulatory actions. Am J Gastroenterol 2001;96:1698-703
- 47. Camilleri M. New treatment options for chronic constipation: mechanisms, efficacy and safety. Can J Gastroenterol 2011;25(Suppl B):29-35B
- 48. Aparicio JR, Martínez J, Casellas JA. Right lateral position does not affect gastric transit times of video capsule endoscopy: a prospective study. Gastrointest Endosc 2009;69:34-7
- 49. Liao Z, Li F, Li ZS. Right lateral position improves complete examination rate of capsule endoscope: a prospective randomized, controlled trial. Endoscopy 2008:40:483-7
- Song HJ, Moon JS, Do JH, et al.; Korean Gut Image Study Group. Guidelines for bowel preparation before video capsule endoscopy. Clin Endosc 2013;46:147-54
- 51. Mathus-Vliegen E, Pellisé M, Heresbach D, et al. Consensus guidelines for the use of bowel preparation prior to colonic diagnostic procedures: colonoscopy and small bowel video capsule endoscopy. Curr Med Res Opin 2013. DOI 10.1185/03007995,2013,803055 Posted online on June 4, 2013 [Epub ahead of print]
- 52. Ladas SD, Triantafyllou K, Spada C, et al.; ESGE Clinical Guidelines Committee. European Society of Gastrointestinal Endoscopy (ESGE): recommendations (2009) on clinical use of video capsule endoscopy to investigate small-bowel, esophageal and colonic diseases. Endoscopy 2010;42:220-7

We agree with Singh et al and with the comments of Wallace⁴ in the editorial that accompanied our article that recently developed classifications may prove useful to characterize SSAs⁵ and that a single schema that distinguishes hyperplastic polyps, adenomas, and SSAs would be ideal.

We cannot lose sight of the fact that the first requirement for the appropriate management of an SSA is to see it. These lesions can be subtle. As Wallace points out, there is an emerging consensus to remove all serrated lesions proximal to the sigmoid colon, and all serrated lesions in the rectosigmoid larger than 5 mm. Thus, even if these lesions are misclassified on the basis of optical biopsy, the current standard of care is to remove them. The bar will be much higher if we ever contemplate a "diagnose and decide" instead of a "resect and discard" strategy for these lesions—because the consequence of misclassification would be to leave an SSA in place. A current priority must be to ensure that these lesions are seen in the first place.

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REFERENCES

- Kumar S, Fioritto A, Mitani A, et al. Optical biopsy of sessile serrated adenomas: do these lesions resemble hyperplastic polyps under narrow-band imaging? Gastrointest Endosc 2013;78:902-9.
- Oba S, Tanaka S, Sano Y, et al. Current status of narrow-band imaging magnifying colonoscopy for colorectal neoplasia in Japan. Digestion 2011;83:167-72.
- Rogart JN, Jain D, Siddiqui UD, et al. Narrow-band imaging without high magnification to differentiate polyps during real-time colonoscopy; improvement with experience. Gastrointest Endosc 2008;68:1136-45.

- Wallace MB. Not so NICE to be serrated. Gastrointest Endosc 2013;78: 910-1; quiz 912-912.e7.
- Hazewinkel Y, Lopez-Ceron M, East JE, et al. Endoscopic features of sessile serrated adenomas: validation by international experts using high-resolution white-light endoscopy and narrow-band imaging. Gastrointest Endosc 2013;77:916-24.

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Chewing gum and completion rate in small-bowel capsule endoscopy: meta-analyzing the data

To the Editor:

We read with great interest the study by Ou et al on the use of sugarless chewing gum in video smallbowel capsule endoscopy (SBCE). Indeed, the authors showed that chewing gum neither speeds up the capsule transit nor increases the completion rate (CR) of SBCE in patients without the "usual" risk factors for incomplete studies. Recently, we conducted a detailed meta-analysis of the use of prokinetics in SBCE and found that their administration improves the CR of the examination. However, we demonstrated a current lack of consensus in the use of prokinetics in SBCE.2 Our pooled results indicated that the odds of a complete SBCE were superior in patients who ingested the capsule with a prokinetic agent than in those who did not receive a prokinetic agent (odds ratio [OR] = 1.96; 95% confidence interval [CI], 1.38-2.78). However, because of the use of predefined criteria, we included only 1 study with chewing gum.3

Therefore, prompted by the data presented,¹ we decided to undertake a meta-analysis of a few studies that examined the use of chewing gum in SBCE.^{1,3,4} The pooled odds ratios and 95% confidence intervals were calculated, and the outcomes of individual studies

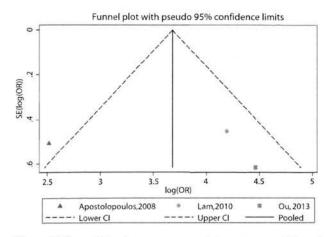
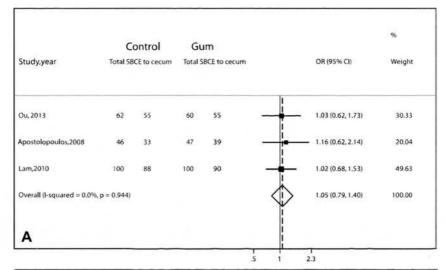


Figure 1. Effect of chewing gum on completion rate in small bowel capsule endoscopy (SBCE).



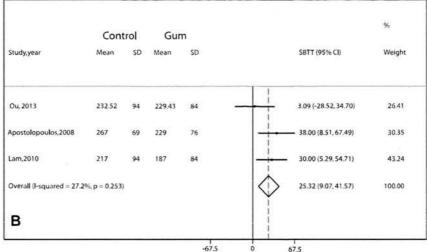


Figure 2. Effect of chewing gum on small bowel transit time (SBTT). CI, confidence interval; OR, odds ratio.

were compared by use of the fixed-effects model (Mantel-Haenszel method).⁵ Heterogeneity was assessed by use of the inconsistency index (I^2) and Cochran's Q test for heterogeneity; a low $I^2 \le 50\%$ would suggest that the differences in findings between studies could be due to chance alone.⁶ Evidence of heterogeneity was considered to be present if P < .10.

The included studies presented 3 sets of data, examining the SBCE CR in 208 individuals who acted as controls, as opposed to 207 individuals who ingested the capsule and chewed gum during the procedure. The 3 studies were homogeneous ($I^2=0$; P=.994) with a pooled OR = 1.05 (95% CI, 0.79-140), indicating that there was no evidence that chewing gum affects CR (Fig. 1). With regard to small-bowel transit time (SBTT), no evidence of heterogeneity could be detected

($I^2 = 27.2\%$; P = .253), although the latter may have been due to the small number of studies. Despite that, SBTT was estimated at a mean of 25.32 (95% CI, 9.07-41.57), indicating that there was a significant decrease in the SBTT of patients who chewed gum (Fig. 2). Overall, these data do not support the use of chewing gum in SBCE.

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REFERENCES

- Ou G, Svarta S, Chan C, et al. The effect of chewing gum on small-bowel transit time in capsule endoscopy: a prospective, randomized trial. Gastrointest Endosc 2014;79:630-6.
- Koulaouzidis A, Giannakou A, Yung DE, et al. Do prokinetics influence the completion rate in small-bowel capsule endoscopy? A systematic review and meta-analysis. Curr Med Res Opin 2013;29:1171-85.
- Apostolopoulos P, Kalantzis C, Gralnek IM, et al. Clinical trial: effectiveness of chewing-gum in accelerating capsule endoscopy transit timea prospective randomized, controlled pilot study. Aliment Pharmacol Ther 2008;28:405-11.
- Lam TT, Keegan AD. Chewing gum shortens small bowel but not gastric transit time during capsule endoscopy. Gastroenterology 2010;138(Suppl 1):S-669.

- Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22: 719-48.
- Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in metaanalyses. BMJ 2003;327:557-60.

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Radiofrequency ablation of Barrett's esophagus with the channel RFA endoscopic catheter

To the Editor:

Endoscopic radiofrequency ablation (RFA) is an effective and safe treatment for dysplastic Barrett's esophagus (BE). Current delivery methods in use include the circumferential balloon-based (Halo 360) and focal catheter-based devices (Halo 90, Halo 60). These devices can be easily advanced through nonobstructed esophagi. However, in a patient with a tortuous, deformed, partially stenotic esophagus or other anatomic abnormalities such as cricopharyngeal hypertrophy or cervical osteophytes, the passage of the RFA device can be impeded. Here we report the use of the novel channel RFA endoscopic catheter to perform RFA.

A 56-year-old man who had undergone radiation and chemotherapy for T3N0 HPVp16+ squamous cell carcinoma at the base of the tongue was found to have BE measuring C2 M3. He was planned for RFA treatment of dysplastic segment on the basis of histologic appearance. As a result of the previous radiation therapy, his

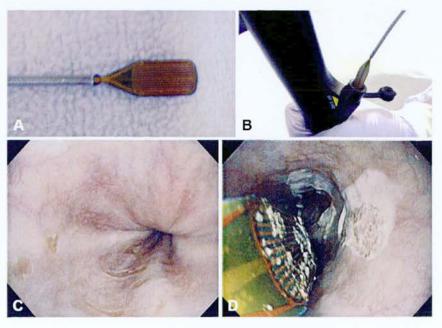


Figure 1. A, Electrode panel of the endoscopic ablation catheter. B, Through-the-scope insertion of the catheter through the working channel of the endoscope. C, Endoscopic view showing patchy areas of Barrett's esophagus. D, Postablation use of the endoscopic ablation cathether.

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Digestive Endoscopy

Chromoendoscopy in small bowel capsule endoscopy: Blue mode or Fuji Intelligent Colour Enhancement?

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ABSTRACT

Introduction: Virtual chromoendoscopy is used to enhance surface patterns and colour differences. One type of virtual chromoendoscopy is the Fuji Intelligent Colour Enhancement (FICE). Although widely applied in conventional endoscopy, data on FICE application in capsule endoscopy are limited. Furthermore, the validity of Blue filter (feature of RAPID® software) has not been examined.

Aim/s: We aimed to qualitatively evaluate the use of FICE and Blue filter enhancement, in images of lesions obtained during small bowel capsule endoscopy, comparing them with similar, conventional (white light) images.

Methods: A total of 167 images (6 different lesion categories) obtained from 200 capsule endoscopy examinations. Two gastroenterologists examined the images with white light, FICE and Blue filter in regards to the visibility of blood vessels, the contrast of the mucosal surface, and the demarcation of lesion borders. The agreed scores were: improved, similar, worse. Inter-observer agreement was calculated. Results: For all lesion categories, Blue filter provided image improvement (compared to white light) in 83%, (inter-observer agreement: 0.786). With FICE 1, improvement was observed in 34%, worse image in 55.9%, (inter-observer agreement: 0.646). With FICE 2, improvement was observed in 8.6%, worse in 77.5%, (inter-observer agreement: 0.617). With FICE 3, improvement was seen in 7.7%, worse in 79.9% (inter-observer agreement: 0.669).

Conclusion: Comparing with FICE, Blue filter offers better image enhancement in capsule endoscopy.

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1. Introduction

Virtual chromoendoscopy (VC) techniques are applied to enhance the microvascular contour and improve resolution of surface patterns and colour differences [1]. The two VC modalities in current clinical use are narrow-band imaging (NBI) [2] and computed VC with the Fuji Intelligent Colour Enhancement (FICE) system [1].

Computed VC (CVC) technology, developed at Chiba University by Miyake et al. [3], is based on the selection of spectral transmittance with a dedicated wavelength by narrowing the bandwidth of white light to narrowed blue and green light. In contrast to NBI though, where the bandwidth of the spectral transmittance is narrowed by optical filters [2], in CVC imaging is based on a new spectral estimation technique that replaces the need for optical filters.

In essence, the CVC software takes a conventional endoscopic image from the video processor and arithmetically processes the reflected photons to reconstitute virtual images for a choice of different wavelengths [1,3]. Over the past few years, several studies have examined the efficacy of VC in the detailed analysis of mucosal pit pattern, vascular intensity and enhancing detection and differentiation of neoplastic and non-neoplastic lesions of the upper and the lower GI tract [3–10]. Although discrepant to a degree, the majority of data point towards a positive effect in using VC.

Since its emergence, capsule endoscopy (CE) has had a major impact on small-bowel endoscopy practice. Its current indications include investigation of obscure gastrointestinal bleeding/iron deficiency anaemia, assessment of known or suspected small bowel Crohn's disease, coeliac disease, hereditary polyposis syndromes and small bowel tumours [11,12].

Although VC is widely applied in conventional bidirectional endoscopy and recently studied in double-balloon enteroscopy as

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well [13], its role in the detection of small bowel lesions has not yet been clearly established [14]. Furthermore, the application of NBI in CE – with its current level of technology – is limited. As NBI is a real-time imaging modality, developmental improvements are required in order for this technique to be useful in a clinical setting.

In contrast, FICE does not require re-engineering of the capsule device as such, but only integration of the FICE software in the reading platform [1]. The integration of the FICE digital processing system in the RAPID® v6.0 & 7.0 (Given® Imaging Ltd., Yokneam, Israel) enables an instant switchover between an unmodified image and a FICE image, at a click of a tab at the workstation. Blue Filter (BF), an additional setting incorporated into the RAPID® software, is a colour coefficient shift of light in the short wavelength range (490–430 nm) superimposed onto a white (red, blue, green; RGB) light image.

The spectrum of wavelength used for the creation of optical images differs between flexible endoscopy and CE, thus up to three mode settings have been selected as most suitable wavelengths required for the evaluation of the CE [14].

Both the validity of FICE in small bowel CE (SBCE) as well as the optimal settings for improved image recognition in various small bowel lesions has been studied only limited to present [14,15].

2. Aim

The aim of this retrospective study was to qualitatively evaluate the use of FICE and BF enhancement in images of lesions, obtained during SBCE, comparing them with similar images under white light (predefined settings-Quick Adjust) without any filters.

3. Materials and methods

We retrospectively evaluated all images of lesions captured (during SBCE) between December 2008 and January 2010. All images were selected from video sequences of consecutive patients who underwent SBCE as part of their regular diagnostic work-up. SBCE was performed with Pillcam® SB1/SB2 (Given Imaging Ltd, Yoqneam, Israel) capsule endoscopes, using the predefined for our unit small bowel preparation regimen and procedural protocol. One of the authors (SD), with extensive experience in CE, selected thumbnail frames depicting pathology images from 200 examinations and group them in 6 different lesion groups. Normal or low quality images were excluded from further review. This author did not participate in further evaluation of the images.

Two certified gastroenterologists, both familiar with SBCE [(CK) with SBCE reviewing experience >50 videos and (AK) with extensive SBCE reviewing experience >700 CE video sequences], evaluated the images using the RAPID® ver.7 software and blinded to each other. Both authors are familiar with FICE and use it regularly in conventional endoscopy.

The images were initially examined with white light and thereafter with the FICE mode.

The FICE settings used were as follows:

FICE 1 [RGB wavelength, nm (595, 540, 535)], FICE 2 [RBG wavelength, nm (420, 520, 530)], and FICE 3 [RBG wavelength, nm (595, 570, 415)].

In addition, BF (wavelength 490-430 nm) was also applied. Patient demographic, clinical characteristics and indications for SBCE were also recorded.

We had previously found that a specific combination of sharpness level (grade 3) and brightness level (grade 0) enhanced all images, even before the application of any filters and therefore

Table 1
Demographics and indications for small bowel capsule endoscopy (SBCE), type of lesions examined with white light, FICE and Blue filter. M/F; male/female, SD; standard deviation, GI; gastro-intestinal, PHE; portal hypertensive enteropathy.

No. of patients (M/F)	52 (21/31)
Age (years) mean ± SD, median	$56.13 \pm 19.13, 58$
Indications for SBCE Nine patients presented with more	than 1 indication
Iron deficiency anaemia	30
Obscure GI bleeding	9
Chronic abdominal pain	6
Diarrhoea	4
Weight loss	4 3 5
Raised faecal calprotectin	5
Definitive lesions	
Ulcers/aphthae	60
Villous oedema	17
Blood in lumen	15
Angioectasias/arterio-venous malformations	18
Mucosal cobblestoning	11
PHE	6
Lesions of indeterminate clinical significance	13
Lymphangiectasias	13
Polypoid lesion/structure	3
Denuded mucosal patches	3 2 4
Radiation enteritis	4
Fissure	1
Thickened fold	1
Pyloric erythema	1
Black stool	1
Stricture	1

we agreed to adopt those settings as our standard baseline for this study (Quick Adjust settings).

White light (with Quick Adjust toggle button on) SBCE images were compared with FICE and BF images applying the following criteria:

- (a) The visibility of blood vessels,
- (b) the contrast of the mucosal surface, and
- (c) the demarcation of lesion borders.

The side-by-side comparison between white light and FICE or BF images was qualitatively evaluated using three quality scores: Improved, Similar and Worse.

Improved was defined as: "improved visualisation, aiding lesion characterisation, and enhanced delineation of lesion surface or borders".

Similar was defined as: "no change in any of the aforementioned parameters".

Worse was defined as: "poor visualisation or inability to characterise a specific lesion".

The t-test for continuous variables and the chi-square (χ^2) test for categorical variables were used. A p value of <0.05 was considered statistically significant. Inter-observer agreement between two rates was calculated using Cohen's kappa coefficient. Kappa <0.4 was considered as poor agreement whereas between 0.41–0.6 as moderate, 0.61–0.80 substantial and 0.81–1.00 as excellent agreement.

4. Results

A total of 167 small bowel images/lesions, from 52 patients (21M/31F, mean age 56.13 ± 19.13 years; median age: 58 years) who underwent SBCE for a variety of indications, were included in our study (Fig. 1).

Patient demographics and clinical characteristics, as well as SBCE indications and types of lesions examined are summarised in Table 1.

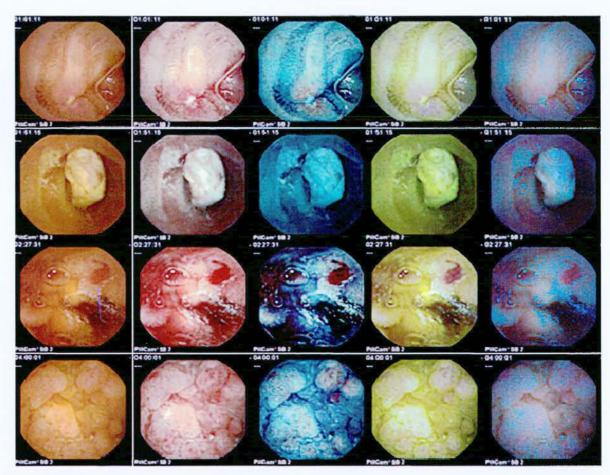


Fig. 1. Comprehensive table of images with white light, FICE 1. FICE 2, FICE 3 and Blue filter of ulcer row 1, polyp row 2, angiectasia row 3, cobblestone mucosa row 4.

Overall, with BF, as compared with white light, image improvement was observed in 83%, no change in 12% and worse in 3%. With FICE 1, improvement was observed in 34%, no change in 8.9% and worse in 55.9%. With FICE 2, improvement was observed in 8.6%, no change in 13% and worse in 77.5%. With FICE 3, improvement observed in 7.7%, no change in 12% and worse in 79.9%.

Inter-observer agreement was 0.786 for BM, 0.646, 0.617, 0.669 for FICE 1, FICE 2, FICE 3, respectively.

In the ulcer/aphthae images group: BF offered an image improvement in 93%, no change in 5.8% and made it worse in 3.3%. With FICE 1, improvement was observed in 36.6%, no change in 9% and worse in 54%. With FICE 2, an improvement was observed in 3%, no change in 13% and worse in 83%. With FICE 3, improvement was observed in 3%, no change in 6.6% and worse in 90%.

Inter-observer agreement was 0.476, 0.487, 0.710 and 0.642 for BF, FICE 1, FICE 2 and FICE 3, respectively.

In the villous oedema images group: with BF an improvement observed in 73.5%, no change in 26.4% and worse in 0%. With FICE 1, an improvement was observed in 14.7%, no change in 14.7% and worse in 70.6%. With FICE 2, an improvement observed in 5.8%, no change in 14.7% and worse in 79.5%. With FICE 3 an improvement observed in 14.7%, no change in 0% and worst in 85.3%.

Inter-observer agreement was 0.549, 0.625, 0.553 and 0.767 with BF, FICE 1, FICE 2 and FICE 3, respectively.

In intraluminal blood images group: with BF an improvement was observed in 73.3%, no change in 20% and worse in 6.7%. With

FICE 1, an improvement was observed in 56.6%, no change in 6.6% and worse in 30%. With FICE 2 an improvement was seen in 20%, no change in 6.6% and worse in 73.4%. For FICE 3, an improvement was observed in 13.3%, no change in 6.6% and worse in 80%.

Inter-observer agreement was 0.4, 0.528, 0.675 and 0.643 with BM, FICE 1, FICE 2 and FICE 3, respectively.

In lesions of indeterminate clinical significance (LICS) images group: with BF an improvement was observed in 92.3%, no change in 7.7% and worse in 0%. For FICE 1, an improvement was seen in 50%, no change in 7.6% and worse in 42.4%. For FICE 2 an improvement observed in 19.2%, no change in 19.2% and worse in 61.6%. For FICE 3, an improvement observed in 11.5%, no change in 3.8% and worse in 84.7%.

Inter-observer agreement was 1, 0.610, 0.604 and 0.536 for BF, FICE 1, FICE 2 and FICE 3, respectively.

In the angioectasias/arterio-venous malformations (AVM) images group: with BF an improvement observed in all patients (100%). For FICE 1 an improvement observed in 77.7%, no change in 8.3% and worse in 11.1%. For FICE 2 an improvement observed in 27.7%, no change in 13.8% and worst in 50%. For FICE 3 an improvement observed in 5.5%, no change in 38.8% and worse in 55.57%.

Inter-observer agreement was 1 in BF, 0.557 in FICE 1, 0.688 in FICE 2 and 0.583 in FICE 3.

In the mucosal cobblestoning images group: with BF an improvement observed in 86.36%, no change in 13.6% and worse in 0%. For FICE 1 no improvement observed, no change observed in

Table 2Results of the study of FICE 1, Z, 3 and Blue filter in image enhancement in SBCE: I/A: inter-observer agreement, LICS: lesions of indeterminate clinical significance, AVM: arterio-venous malformations. The presented numbers in the improved, similar and worse categories are percentages (%).

	Improved	Similar	Worse	I/A
FICE 1				
Ulcer/aphthae	36.6	9	54	.487
Villous oedema	14.7	14.7	70.6	.625
Blood in lumen	56.6	6.6	30	.528
LICS	50	7.6	42.4	.610
AVM	77.7	8.3	11.1	.557
Cobblestoning	0	13.6	86.36	.62
Overall	34	8.9	55.9	.646
FICE 2				
Ulcer/aphthae	3	13	83	.710
Villous oedema	5.8	14.7	79.5	.552
Blood in lumen	20	6.6	73.4	.675
LICS	19.2	19.2	61.6	.610
AVM	27.7	13.8	50	.688
Cobblestoning	9	0	91	.633
Overall	8.6	13	77.5	.617
FICE 3				
Ulcer/aphthae	3	6.6	90	.642
Villous oedema	14.7	0	85.3	.767
Blood in lumen	13.3	6.6	80	.643
LICS	11.5	3.8	84.7	.536
AVM	5.5	38.8	55.57	.55
Cobblestoning	0	0	100	1.0
Overall	7.7	12	79.9	.669
Blue filter				
Ulcer/aphthae	93	5.8	3.3	.470
Villous oedema	73.5	26.5	0	.549
Blood in lumen	73.3	20	6.7	.4
LICS	92.3	7.7	0	1.0
AVM	100	0	0	1.0
Cobblestoning	86.36	13.6	0	.62
Overall	83	12	3	.786

13.6% and worse in 86.36%. For FICE 2 an improvement observed in 9%, no change in 0% and worst in 91%. For FICE 3 worse images observed in all patients.

Inter-observer agreement was 0.621 in BF, 0.621 in FICE 1, 0.633 in FICE 2 and 1 in FICE 3. A summary of the results is presented in Table 2.

5. Discussion

CVC technique is based on narrowing the bandwidth of the conventional endoscopic image arithmetically, using spectral estimation technology [1]. FICE has been used both in upper and lower GI endoscopy and proved to be effective in improving diagnostic yield by enhancing contrast between background and surface abnormalities. Currently in the published literature, there is no agreement evaluating the accuracy of FICE, especially in regards to the optimal wavelength filters [15].

In one recent study, FICE-filter 4 [red, green, and blue (RGB) wavelengths of 520, 500, and 405 nm, respectively] with magnification has been shown to improve the image quality of the colonic vascular patterns obtained with white light endoscopy [8].

In another one, the combination of the following 3 FICE wavelengths (RBG): 420 nm, 490 nm, and 540 nm proved to be superior to conventional endoscopy for capillary-pattern diagnosis but not adding much to pit-pattern diagnosis, in regards to prediction of histology for small colorectal polyps [7].

The classification of colorectal tumours by FICE (RGB wavelengths of 540, 460, and 460 nm) with magnification correlated well with the histopathological diagnoses, whereas the findings were similar to NBI magnification [10].

In the upper GI tract, the wavelength that generated the optimal difference of the spectral reflectance between the normal

gastric mucosa and the early gastric cancers was 530 nm. The score of the FICE observation improved in 46% of cases [16]. In transnasal endoscopy, the FICE system wavelengths settings [RBG; 470 nm, 500 nm, 550 nm] enables greater colour difference between palisade vessels and provides better contrasting images of the demarcation between the BE mucosa and the gastric mucosa, and thus contributes to easier diagnosis of endoscopic BE comparing with white light endoscopy [6].

There are only limited data in literature evaluating the use of FICE system in small bowel capsule images [14,15]. Furthermore, there are no studies examining the validity of BM in image enhancement. We conducted a study of the newly developed CVC system (incorporated in RAPID® version 6 and 7) that enhances the contrast of the mucosal surface. BM improved most of the images (overall image enhancement 83%), with a range between 73.3 and 100%, in different lesions groups. Although we report an overall substantial inter-observer agreement of 0.786, the *k* coefficient varied between different groups. Ulcers, villous oedema, and blood in lumen presented a moderate inter-observer agreement, Crohn's mucosal cobblestoning substantial agreement, whereas angioectasias/AVMs and LICS excellent agreement.

Moreover, FICE 1 improved the definition in 34% of the images. FICE was effective in improving images in 56.6, 50 and 77.7% in blood in lumen, LICS and AVM, respectively. The inter-observer agreement was similar in these three subgroups. The results regarding AVM are comparable to the recent study by Oka et al. [15], reporting an improvement in 87% of cases.

FICE was only partially effective in ulcer/aphthae group with an image improvement in 36.6% of cases. In that respect, our results differ from those reported in study by Oka et al. [15], where a much higher image enhancement rate (55.3%) was perceived. There was no significant image improvement in other lesion subgroups.

FICE 2 and FICE 3 was ineffective to improve images (overall 8.6 and 7.7% improvement in FICE 2 and 3, respectively) with a significant agreement between the two readers. These results differs completely from the study by Oka et al. [15], reporting image quality improvement of FICE 2 settings in 87% and 25.5% of AVM and ulcerations, respectively. Thus, our opinion is that the use of FICE in the small bowel capsule is limited. On the contrary, BF showed promising results and its use as the main viewing mode, especially in cases of obscure GI bleeding, should be further examined in regards to feasibility and in connection with the diagnostic yield.

Conflict of interest

None declared.

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References

- Pohl J, May A, Rabenstein T, et al. Computed virtual chromoendoscopy: a new tool for enhancing tissue surface structures. Endoscopy 2007;39:80–3.
- [2] Gono K, Obi T, Yamaguchi M, et al. Appearance of enhanced tissue features in narrow-band endoscopic imaging. Biomed Opt 2004;9:568–77.
- [3] Haneishi H, Hasegawa T, Hosoi A, et al. System design for accurately estimating the spectral reflectance of art paintings. Appl Opt 2000;39:6621–32.
- [4] Pohl J, Nguyen-Tat M, Pech O, et al. Computed virtual chromoendoscopy for classification of small colorectal lesions: a prospective comparative study. Am J Gastroenterol 2008;103:562–9.
- [5] Pohl J, Lotterer E, Balzer C, et al. Computed virtual chromoendoscopy versus standard colonoscopy with targeted indigocarmine chromoscopy: a randomised multicentre trial. Gut 2009;58:73–8.
- [6] Osawa H, Yamamoto H, Yamada N, et al. Diagnosis of endoscopic Barrett's esophagus by transnasal flexible spectral imaging color enhancement. J Gastroenterol 2009;44:1125–32.
- [7] Togashi K, Osawa H, Koinuma K, et al. A comparison of conventional endoscopy, chromoendoscopy, and the optimal-band imaging system for the differen-

- tiation of neoplastic and non-neoplastic colonic polyps. Gastrointest Endosc 2009;69:734-41.
- [8] Parra-Blanco A, Jiménez A, Rembacken B, et al. Validation of Fuji non intelligent chromoendoscopy with high definition endoscopes in colonoscopy. World J Gastroenterol 2009;15:5266–73.
 [9] East JE, Tan EK, Bergman JJ, et al. Meta-analysis: narrow band imaging for lesion
- [9] East JE, Tan EK, Bergman JJ, et al. Meta-analysis: narrow band imaging for lesion characterization in the colon, oesophagus, duodenal ampulla and lung. Aliment Pharmacol Ther 2008;28:854–67.
 [10] Yoshida N, Naito Y, Kugai M, et al. Efficacy of magnifying endoscopy with flex-
- [10] Yoshida N, Naito Y, Kugai M, et al. Efficacy of magnifying endoscopy with flexible spectral imaging color enhancement in the diagnosis of colorectal tumors. J Gastroenterol 2010 Nov 9.
- [11] Ladas SD, Triantafyllou K, Spada C, et al. European Society of Gastrointestinal Endoscopy (ESGE): recommendations (2009) on clinical use of video capsule endoscopy to investigate small-bowel, esophageal and colonic diseases. Endoscopy 2010;42:220–7.
- [12] Liao Z, Gao R, Xu C, et al. Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. Gastrointest Endosc 2010;71:280-6.
- [13] Neumann H, Fry LC, Bellutti M, et al. Double-balloon enteroscopy-assisted virtual chromoendoscopy for small-bowel disorders: a case series. Endoscopy 2009;41:468–71.
- [14] Pohl J, Aschmoneit S, Schuhmann S, et al. Computed images modification for enhancement of small-bowel surface structures at video capsule endoscopy. Endoscopy 2010;42:490–2.
- [15] Oka S, Tanaka S, Imagawa H, et al. Improved visibility of lesions of the small intestine via capsule endoscopy with computed virtual chromoendoscopy. Gastrointest Endosc 2011;73:299–306.
 [16] Mouri R, Yoshida S, Tanaka S, et al. Evaluation and validation of com-
- [16] Mouri R, Yoshida S, Tanaka S, et al. Evaluation and validation of computed virtual chromoendoscopy in early gastric cancer. Gastrointest Endosc 2009;69:1052–8.

QuickView in small-bowel capsule endoscopy is useful in certain clinical settings, but QuickView with Blue Mode is of no additional benefit

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Background Analysis of small-bowel capsule endoscopy (SBCE) is time-consuming. QuickView (QV) has been added to the RAPID software to reduce the reading times. However, its validity is still under intense review. Recently, we have shown that Blue Mode (BM) provides improvements in images for most lesion categories.

Aim To assess the validity of QuickView with white light (QVWL) and QuickView with Blue Mode (QVBM) reading, in a group of patients who underwent SBCE in our centre, by comparing it with the standard video sequence review (used as reference) by experienced SBCE readers.

Methods This was a retrospective study; all SBCE (August 2008-November 2011), performed with PillCam SB, with complete small-bowel visualization were included. A clinician with previous SBCE experience, unaware of the SBCE reports, reviewed prospectively the video streams on RAPID platform using QVWL and QVBM. All SBCE had been reported previously using the standard mode; these reports were considered as the reference. There were 106 cases of obscure gastrointestinal bleeding (OGIB), 81 cases of known or suspected Crohn's disease (CD) and 10 cases of polyposis syndromes.

Results The mean small-bowel evaluation was 475 (±270) s and 450 (±156) s for QVWL and QVBM, respectively. In the OGIB (n=106; 21 overt/85 occult), with QVWL, 54 [P0 (28), P1 (18), P2 (8)] lesions were detected, 63 [P0 (48), P1 (13), P2 (2)] with QVBM, as compared with 98 [P0 (67), P1 (23), P2 (8)] by standard (reference)

Introduction

Small-bowel capsule endoscopy (SBCE) has revolutionized the investigation of the small bowel. Recent meta-analyses have shown that SBCE has a higher diagnostic yield in obscure gastrointestinal bleeding (OGIB), known or suspected Crohn's disease (CD) and small-bowel polyposis, compared with most radiological imaging modalities [1-3]. Furthermore, in most centres, it remains the first-line option over more invasive tools that is, deep (or deviceassisted) enteroscopy [4]. Nevertheless, one of the limitations of SBCE is the reading time required for the interpretation of lengthy video streams. It is generally accepted that the average time for video sequence analysis is between 40 and 120 min, depending on the overall recording time and the reviewer's experience [5].

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reporting. For P1 + P2 lesions, the sensitivity, specificity, positive predictive value and negative predictive value for QVWL (as compared with reference reporting) were 92.3, 96.3, 96 and 92.8%, respectively. For QVBM, the above values were 91, 96, 96.2 and 90.6%, respectively. Eightyone (n=81) patients underwent SBCE for small-bowel evaluation on the basis of a clinical history of suspected or known CD. With QVWL, 71 mucosal ulcers were detected, 68 with QVBM, as compared with 155 mucosal ulcers with reference reading. Finally, in the polyposis category with QVWL and QVBM, four polypoid lesions were detected compared with seven with standard (reference) review.

Conclusion QV can be used confidently in OGIB in an urgent inpatient setting and in outpatients with occult OGIB or suspected CD. Furthermore, BM does not confer any additional advantage in the QV setting. Standard review settings should be used in all other cases. Eur J Gastroenterol Hepatol 24:1099-1104 @ 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Keywords: capsule endoscopy, Crohn's disease, obscure gastrointestinal bleeding, PillCam, polyposis, QuickView, reading, small-bowel, software

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Because of high workloads, attempts have been made to reduce physician involvement through the use of assistants/ extenders for the preliminary review of the video sequence or through the use of software that aids interpretation [5,6]. The main question with the latter approach is whether a rapid review, where a percentage of images are discarded, would miss clinically relevant pathology. The current version of RAPID capsule review software incorporates the QuickView (QV) mode, allowing a speedy video review. However, the QV mode is still under clinical validation and there are only four studies that have examined the utility of this informatic algorithm [5,7-10]. Recently, we have shown that SBCE evaluation with Blue Mode (BM) yields promising results and have recommended further study of this, as the main viewing mode, especially in cases of

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OGIB [11]. BM or a blue filter is a colour coefficient shift of light in the short wavelength range (490–430 nm) superimposed onto a white light (WL) [red, blue, green (RGB)] image. It can be applied easily through the quick adjust toggle button menu.

Aim

To assess the validity of QuickView under white light (QVWL) and QuickView under Blue Mode (QVBM) reading mode, in a group of patients who had undergone SBCE in our centre, by comparing it with the standard (reference) video sequence review by experienced SBCE readers.

Materials and methods

Patients and small-bowel capsule endoscopy procedure

Between August 2008 and November 2011, 248 patients underwent SBCE with PillCam SB in our centre (132 performed with PillCam SB1 and 116 with PillCam SB2; Given Imaging Ltd, Yokneam, Israel). The demographics and clinical characteristics of this group are presented in Table 1. Our standard procedure protocol involves a strict liquid diet 12 h before the test and 2 litres of a polyethylene glycol-based purgative for small-bowel cleansing, with an overnight fast (Moviprep; Norgine, Harefield, Uxbridge, UK). The capsule is ingested with 40–100 mg of antifoam (simethicone) and 5 mg of liquid prokinetic (domperidone), except under exceptional circumstances. The patients are allowed to drink clear fluids after 2 h and consume a light meal/snack after 4 h.

For the purpose of this study, only SBCE videos with complete small-bowel transit were included for further QV analysis. The videos had already been reviewed – for the purpose of regular clinical care – by at least one of two experienced in SBCE readers (A.K. and S.D. >800 reviews each). Our standard viewing mode is SingleView or DualView on automatic speed at 12–20 frames per second (fps), respectively.

A research fellow (with experience in both conventional and capsule endoscopy; > 200 SBCE reviews), who had not been involved in either patient care or the initial SBCE review, analysed the video sequences with QV (under both WL and BM). The reviewer was blinded to any previously captured landmark or thumbnailed findings and to patients' clinical history and indications for the test.

QV mode reading SBCE analysis was performed using the RAPID 7 workstation (Given Imaging Ltd). One of the authors (A.S.) used only QV, selecting landmarks and thumbnailing abnormal images. All pathological images and times were entered in a spreadsheet. The reviewer used QVWL first (for the entire cohort) and QVBM second, reviewing sequences in a random order to minimize observer bias. He used QV with an image sampling rate (sensitivity) of 35% in the DualView display mode at 18 fps, sitting arms-length from a

Table 1 Demographics and indications for small-bowel capsule endoscopy in the study cohort

	N (%)					
Participants	Complete SBCE 200 (included)	Incomplete SBCE 48 (excluded)				
Male	85 (42.5)	22 (45.8)				
Age (±SD)	57.5 (±14.2)	63.1 (±13)				
SBCE with PillCam SB1	125 (62.5)	30 (62.5)				
Indications for SBCE						
OGIB	106 (53)	21 (43.7)				
CD (suspected or known)	81 (40.5)	26 (54.2)				
Polyposis syndromes	4 (2)	0				
Coeliac disease	3 (1.5)	0				
Possible SB lesion or mass	6 (3)	1 (3.4)				

CD, Crohn's disease; OGIB, obscure gastrointestinal bleeding; SBCE, small-bowel capsule endoscopy.

19-inch monitor in a quiet room with dimmed lights. The small-bowel evaluation time (time from entry to exit from the small bowel) was recorded for each patient. This included both the reading time and the thumbnail capture time for each of the two QV modes. To minimize reviewer tiredness, reviewing sessions were restricted to 10 video sequences per day. The results of QVWL and QVBM reviews were compared with the results of the conventional (reference) reviews, by checking each thumbnail against all previously captured thumbnails, by two reviewers (A.K. and A.S.).

Classification of lesions

Findings in the OGIB group were classified as P0 (nonpathological), P1 (low/intermediate) or P2 (high bleeding potential) lesions [12]. To avoid reporting bias, in the suspected or the known CD group, only the most objective capsule endoscopy parameters and descriptors of mucosal inflammation were used, that is ulcer (defined as any pale or yellow-based mucosal break surrounded by a red or a pink collar) less than 1/4 of the intestinal lumen circumference, ulcer 1/4–1/2 of the lumen circumference, ulcer more than 1/2 of the lumen circumference ± luminal stenosis, as defined by the Lewis score [13]. The performance of QV was defined as concordance between frames thumbnailed by the QV reader and frames selected during the standard/conventional review.

The sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) for QVWL and QVBM – compared with the reference review – for clinically relevant (i.e. P1/P2) vascular lesions and for mucosal ulcers of any size were calculated in the OGIB and suspected/known CD referral groups, respectively.

Ethics consideration

This study was carried out in accordance with UK research ethics guidelines. After review by the local ethics committee, further specific ethical review and approval were not required, as the study was considered a retrospective clinical audit work using data already obtained as part of regular patient care.

Statistical analysis

Values are expressed as mean \pm SD. A two-sided P value less than 0.05 was considered statistically significant. Statistical analysis was performed using the GraphPad InStat software (GraphPad Software, La Jolla, California, USA) for Windows.

Results General

A total of 200 SBCE examinations were complete to caecum and included in this study. The mean evaluation time (including reading and time to mark thumbnails) in this cohort was 475 (\pm 270) s and 450 (\pm 156) s for QVWL and QVBM, respectively (P = 0.363). If all findings (i.e. any P category lesion, any size ulcer and any size polyp) were counted, QVWL detected 129 lesions (49.6%), QVBM detected 135 lesions (51.9%) and the conventional (reference) review detected 260 lesions (P < 0.0001) (Table 2).

Obscure gastrointestinal bleeding

One hundred and six (53%) SBCE were performed for OGIB, 21 (10.5% included videos) for overt OGIB and 85 (42.5% of included videos) for occult OGIB. With QVWL, 54 (55.1%) lesions [P0 (28), P1 (18), P2 (8)] were detected, whereas with QVBM, 63 (64.3%) lesions were detected [P0 (48), P1 (13), P2 (2)]. Standard (reference) SBCE reading detected 98 lesions [P0 (67), P1 (23), P2 (8)] (P = 0.0506).

Concordant results (normal SBCE i.e. no findings and/or P0 lesions only) between QVWL and reference reading were observed in 101/106 (95.3%) cases and discordant results in five (4.71%), 4/5 false negative with QVWL. With QVBM reading, concordant results (for no findings and/or only P0 lesions) between QVBM and reference reading were observed in 89/106 (84%) cases and discordant results in 17 (16%), 14/17 false negative with QVBM.

For QVWL, the sensitivity, specificity, PPV and NPV for P1 + P2 lesions (as compared with reference reporting) were 92.3, 96.3, 96 and 92.8%, respectively. For QVBM, the above values were 91, 96, 96.2 and 90.6%, respectively.

Suspected/known Crohn's disease

Eighty-one (40.5%) patients underwent SBCE for smallbowel evaluation on the basis of a clinical history of suspected or known CD. With QVWL, 71 (45.8%) [< 1/4 (62), 1/4-1/2 (3), >1/2 (6)] mucosal ulcers were detected, 68 (43.9%) [< 1/4 (51), 1/4-1/2 (9), >1/2 (8)] with QVBM, as compared with 155 [< 1/4 (137), 1/4-1/2 (10), >1/2 (8)] ulcers with reference reading, P = 0.0003.

Concordant negative results (i.e. no findings/nonspecific findings and/or <3 small ulcers) between QVWL and reference reading were observed in 73 (90%) and discordant results in eight (9.9%), 8/8 false negative with QVWL. Concordant negative results between QVBM and reference

reading were observed in 73 (90%) and discordant results in eight (9.9%), 7/8 false negative with QVBM.

In the suspected CD category (15 patients; 12 mucosal ulcers with reference review of which ulcers <1/4: 10, ulcers > 1/4: 2), the overlooked lesions (ulcers < 1/4: 6) would have potentially changed the diagnosis in one case. When analysing QVWL and ulcer size (i.e. <1/2, 1/4-1/2 and >1/2 luminal circumference), the sensitivity was 42%, PPV 97% (as compared with reference reporting), increasing to 100% for large ulcers (1/4-1/2 and > 1/2). For QVBM, the sensitivity and PPV were 52 and 91%, respectively, again increasing to 100% for large ulcers (1/4-1/2 and > 1/2).

Polyposis syndromes

Ten (5%) patients underwent SBCE for the evaluation of polyposis syndromes or because of a strong clinical suspicion of a primary or a secondary small-bowel mass/ tumour lesion. With QVWL and QVBM, four polypoid lesions were detected (the same individual lesions for both modes) compared with seven with standard (reference) review.

Discussion

Reading SBCE has certain limitations. First, the diagnostic yield is usually dependent on the experience of the reader. Second, the uncontrolled capsule movement does not allow visualization of the entire small-bowel mucosa. However, the main limitation is that an accurate complete review of the generated videos is time-consuming, especially in a busy specialist GI department setting. Various strategies have been suggested to deal with the latter. The use of endoscopy nurses and physician assistants/extenders has been advocated [6,14,15] as, for many, SBCE represents a straightforward extension of existing endoscopic skills [16]. Although there is no strict guidance for the best standard/conventional SBCE reading technique and speed, the unique features of SBCE require the reader to be intensely focused and alert [16]. Nevertheless, lapses in concentration or distractions cannot be prevented in lengthy reading sessions.

In most tertiary, high case-volume centres, SBCE are usually reviewed by examiners who may not be further involved in the patient's management. This requires a quick turnaround time from capsule-to-report (for the nonurgent cases) and reviewer availability/flexibility [16]. Furthermore, there are clinical settings where a timely report is crucial for further clinical management that is, inpatients with OGIB and patients with severe CD. Therefore, there is immense interest in techniques and methods that reduce the evaluation time in capsule endoscope without jeopardizing diagnostic accuracy.

Software approaches have been developed to fulfil this requirement. One example is the QV reading mode. QV

Table 2 Angioectasias, ulcers and polyps detected with each of the study's viewing modes

	A		V)	Mucosal	ulcers (circumference-lum	ninal size)		
Type of lesions	PO	P1	P2	< 1/4	1/4-1/2	>1/2	Polyps	Total
Viewing mode								
Standard view	67	23	8	137	10	8	7	260
QVWL	28	18	8	62	3	6	4	129
QVBM	48	13	2	51	9	8	4	135

QVBM, QuickView with Blue Mode; QVWL, QuickView with white light.

creates a preview of the entire video sequence, thus allowing a fast-forward-type review of interesting sites. It highlights sample images, using different sampling rates, within each region of the video by analysing colours and patterns. RAPID current version allows the reviewer to set the QV sampling rate from 5 to 80% of video images at 5% increments. To date, studies have shown conflicting results in the clinical use of QV [5,7–10,17–19] (Table 3).

Recently, virtual chromoendoscopy (VC) has been reported to improve the performance of SBCE. We have shown that BM, a form of VC that is incorporated into the RAPID software, improves the definition of mucosal lesions and possibly increases the detection rate [11,20]. The two features, that is, QV and BM should be considered as 'quantitative' and 'qualitative' as they aim to decrease the reviewing time and enhance the detection of small-bowel lesions, respectively. The combination of QV and VC (BM) has not been studied to date.

Consequently, we aimed to evaluate the utility of combining the QV mode with BM and WL. Notably, this is the first study to check the QV reading on version 7 of the RAPID software. Moreover, a detailed and strict protocol was followed (single reviewer, not more than 10 video reviews/session, low reading speed of 18 fps on the viewing speed slider and DualView frame mode for all reviews), we included a large number of SBCE and did not restrict the study to a single indication to have a realistic representation of everyday clinical scenarios.

In our OGIB group, all P2 lesions were detected with QVWL; therefore, when urgent SBCE analysis is necessary – for further immediate management planning – the QV mode can provide an accurate diagnosis within a few minutes in the majority of cases. Furthermore, in this clinical setting, our study shows that BM does not confer any additional advantage over WL. QV has a high PPV (all P2 lesions and large ulcers were detected); however, the NPV was just above 90% (for small angioectasias), although this should be interpreted with caution as the clinical relevance of missing such lesions is not necessarily significant on clinical grounds [21–23].

Conversely, QV showed only 50% sensitivity for small ulcers and aphthae in the known/suspected CD group. In the suspected CD category, lesions that were detected with the reference review and missed by QVWL or QVBM review would have resulted in a different

diagnosis in only one case. These results are in agreement with those of Westerhof et al. [9], who advocate the use of QV solely in the suspected CD group, when multiple and widespread lesions of mucosal inflammation are present. Moreover, we found that BM, despite excellent results in lesion characterization [11], does not confer any additional benefit (over WL) in lesion detection in a QV setting. This is not dissimilar to a recently published study from our centre, where BM did not confer any added benefit over WL in Lewis score calculation [24]. Furthermore, this is not in agreement with recently reported data of Abdelaal et al. [25], although admittedly, the video-reviewing setting was different.

An inherent limitation of this study, similar to previous studies, is that QV has been compared against 'conventional/standard' viewing. Although the initial review was performed by experienced capsule endoscopists and at a low speed for the purpose of regular clinical care, it is not possible to determine whether strict reviewing conditions (similar to those applied by AS in the QVWL/QVBM review) were implemented constantly. Another intrinsic limitation of the present study is the use of a single, less experienced reviewer, for both QV modes (QVWL and QVBM, albeit not in a consecutive manner for each video stream), which increases the risk of interpretation bias. Moreover, although the review was performed in a random order, this has not offset the potential for observer bias. However, it is noteworthy that recent studies have shown that the SBCE detection rate is not necessarily linked to medical background or reviewer experience [14,15,26]. We should also acknowledge that by including only SBCE with complete small-bowel transit, we have introduced potential applicability limitations. Furthermore, two generations of PillCam SB have been used in this study and one should keep in mind the improvement in the field of view from SB1 to SB2 (although this does not alter our results). Finally, this paper is based on the number of lesions detected; as it is common to find several 'repetitive' lesions in the same patient, an overestimation of the concordance between the two reading modes may occur. In an attempt to overcome this, we reported the change in the diagnosis of patients with suspected CD.

Conclusion

Our study confirms the safety of QV preread in urgent cases, but fails to show any benefit in other clinical

Table 3 Studies evaluating QuickView to date

References	QV sampling rate (%)	QV reading frame mode speed		Comparison read frame mode speed	RAPID ver	No reviewers	Cases total	OGIB cases	CD cases	Polyposis cases	Other	QV sensitivity (%)	QV specificity (%)	Missed lesion (no cases)
Schmelkin [17] ^a	N/S	N/S	N/S	N/S	4.0	1	47	47	N/S	N/A	N/A	100	100	N/A
Diaz et al. [18]ª	N/S	N/S 25, 15, 5 fps		N/S	N/S	2	57	37	12	N/S	10	N/S	N/S	N/S
Appalaneni et al. [19] ^a	N/S	Single 25 fps	3	N/S		2	50	N/S	N/S	N/S	N/S	N/S	N/S	2
Westerhof et al. [9]	High (17)	N/S	4.4 (median)	Conventional DualView 18 fps	4.0	2	100	56	30	2	12	N/S	N/S	13
Hosoe et al. [8]	Normal	N/S	N/S	N/S	5.0	3	45	N/S	N/S	N/S	14	N/S	N/S	N/A
Shiotani et al. [5]	High (17)	Single 6 fps	17.9	N/S	5.0	3 3	44	N/S	N/S	N/S	14	N/S	N/S	10
Saurin et al. [7] ^b	N/S	N/S	11.6	Conventional N/S	5.0	12	106	106	N/A	N/A	N/A	89.2	84.7	8
Shiotani et al. [10]	(5, 15, 25, 35)	Single N/S	N/S	N/S	6.5	4	87	N/S	N/S	N/S	N/S	N/S	N/S	N/S

CD, Crohn's disease; fps, frames per second; N/A, not applicable; N/S, not stated; OGIB, obscure gastrointestinal bleeding (overt + occult); QV, QuickView. Studies presented only as abstracts.

scenarios. Although the benefits of QV are outweighed to some extent by a decrease in the overall diagnostic yield, this mode can be used confidently in overt OGIB in an urgent inpatient setting and in outpatients with occult OGIB or suspected CD. As the usefulness of QV may vary, depending on the number of small-bowel lesions, standard review settings are still recommended in all other cases. Furthermore, the present study confirms that BM does not confer any additional advantage in the QV setting.

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Conflicts of interest

There are no conflicts of interest.

References

- Dionisio PM, Gurudu SR, Leighton JA, Leontiadis GI, Fleischer DE, Hara AK, et al. Capsule endoscopy has a significantly higher diagnostic yield in patients with suspected and established small-bowel Crohn's disease: a meta-analysis. Am J Gastroenterol 2010; 105:1240-1248.
- 2 Triester SL, Leighton JA, Leontiadis GI, Fleischer DE, Hara AK, Heigh RI, et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with obscure gastrointestinal bleeding. Am J Gastroenterol 2005: 100:2407-2418.
- 3 Marmo R. Rotondano G. Piscopo R. Bianco MA, Cipolletta L. Meta-analysis: capsule enteroscopy vs. conventional modalities in diagnosis of small bowel diseases. Aliment Pharmacol Ther 2005; 22:595-604.
- Sidhu R, McAlindon ME, Drew K, Hardcastle S, Cameron IC, Sanders DS. Evaluating the role of small-bowel endoscopy in clinical practice: the largest single-centre experience. Eur J Gastroenterol Hepatol 2012; 24:513-519.
- Shiotani A. Honda K. Kawakami M. Murao T. Matsumoto H. Tarumi K. et al. Evaluation of RAPID(R) 5 Access software for examination of capsule endoscopies and reading of the capsule by an endoscopy nurse. J Gastroenterol 2011; 46:138-142.

- 6 Davison C. Reader extender of capsule endoscopy. Tech Gastrointest Endosc 2006: 8:188-193.
- Saurin JC, Lapalus MG, Cholet F, D'Halluin PN, Filoche B, Gaudric M, et al. The French Society of Digestive Endoscopy (SFED). Can we shorten the small-bowel capsule reading time with the 'Quick-view' image detection system? Dig Liver Dis 2012; 44:477-481.
- Hosoe N, Rey JF, Imaeda H, Bessho R, Ichikawa R, Ida Y, et al. Evaluations of capsule endoscopy software in reducing the reading time and the rate of false negatives by inexperienced endoscopists. Clin Res Hepatol Gastroenterol 2012: 36:66-71.
- Westerhof J, Koornstra JJ, Weersma RK. Can we reduce capsule endoscopy reading times? Gastrointest Endosc 2009; 69:497-502.
- Shiotani A, Honda K, Kawakami M, Kimura Y, Yamanaka Y, Fujita M, et al. Analysis of small-bowel capsule endoscopy reading by using Quickview mode: training assistants for reading may produce a high diagnostic yield and save time for physicians. J Clin Gastroenterol 2012 [Epub ahead of print].
- Krystallis C, Koulaouzidis A, Douglas S, Plevris JN. Chromoendoscopy in small bowel capsule endoscopy: Blue mode or Fuji Intelligent Colour Enhancement? Dig Liver Dis 2011; 43:953-957.
- Saurin JC, Delvaux M, Gaudin JL, Fassler I, Villarejo J, Vahedi K, et al. Diagnostic value of endoscopic capsule in patients with obscure digestive bleeding: blinded comparison with video push-enteroscopy. Endoscopy 2003: 35:576-584.
- Gralnek IM, Defranchis R, Seidman E, Leighton JA, Legnani P, Lewis BS. Development of a capsule endoscopy scoring index for small bowel mucosal inflammatory change. Aliment Pharmacol Ther 2008 27:146-154.
- Sidhu R, Sanders DS, Kapur K, Marshall L, Hurlstone DP, McAlindon ME. Capsule endoscopy: is there a role for nurses as physician extenders? Gastroenterol Nurs 2007: 30:45-48.
- Dokoutsidou H, Karagiannis S, Giannakoulopoulou E, Galanis P, Kyriakos N, Liatsos C, et al. A study comparing an endoscopy nurse and an endoscopy physician in capsule endoscopy interpretation. Eur J Gastroenterol Hepatol 2011; 23:166-170.
- Simon K.Lo. How should we do capsule reading? Tech Gastrointest Endosc 2006: 8:145-147.
- Schmelkin I, Rapid4 Quickview V4 has 100% negative and positive predictive values [abstract]. The 5th international conference of capsule endoscopy, Florida; 2006.
- Diaz AP, Viso LM, Asanza CG, Arregui EC, Fernandez-Pacheco PM. Evaluation of Quickview® System and Suspected Blood Indicator Test from of Given M2A Plus® Capsule Endoscopy Software in the Clinical Setting [abstract]. Gastrointest Endosc 2006; 63:AB227.
- 19 Appalaneni V. Glenn T, Hoffman BJ. Video capsule endoscopy: accuracy of QuickView [abstract]. Gastrointest Endosc 2007; 65:AB313.
- Spada C, Hassan C, Costamagna G. Virtual chromoendoscopy: will it play a role in capsule endoscopy? Dig Liver Dis 2011; 43:927-928.

^bMulticentre study.

- 21 Frieling T. The clinical impact of capsule endoscopy: to believe or not to believe. Eur J Gastroenterol Hepatol 2006; 18:873–874.
- 22 Hindryckx P, Botelberge T, De Vos M, De Looze D. Clinical impact of capsule endoscopy on further strategy and long-term clinical outcome in patients with obscure bleeding. Gastrointest Endosc 2008; 68:98-104.
- 23 Maeda M, Kanke K, Terano A, Hiraishi H. Management of obscure gastrointestinal bleeding based on the classification of capsule endoscopic bleeding findings. *Dig Endosc* 2010; 22:174–179.
- 24 Koulaouzidis A, Douglas S, Plevris JN. Blue mode does not offer any benefit over white light when calculating Lewis score in small-bowel capsule endoscopy. World J Gastrointest Endosc 2012; 4:33–37.
- 25 Abdelaal UM, Morita E, Nouda S, Kuramoto T, Miyaji K, Fukui H, et al. W1594: new method for better detection and visualization of vascular and non-vascular lesions of small bowel by using blue mode viewing: capsule endoscopy study [abstract]. Gastrointest Endosc 2010: 71:AB367.
- endoscopy study [abstract]. Gastrointest Endosc 2010; 71:AB367.
 Zheng Y, Hawkins L, Wolff J, Goloubeva O, Goldberg E. Detection of lesions during capsule endoscopy: physician performance is disappointing. Am J Gastroenterol 2012; 107:554-560.

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BRIEF ARTICLE

Evaluation of 4 three-dimensional representation algorithms in capsule endoscopy images

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Abstract

AIM: To evaluate the three-dimensional (3-D) representation performance of 4 publicly available Shape-from-Shading (SfS) algorithms in small-bowel capsule endoscopy (SBCE).

METHODS: SfS techniques recover the shape of objects using the gradual variation of shading. There are 4 publicly available SfS algorithms. To the best of our knowledge, no comparative study with images obtained during clinical SBCE has been performed to date. Three experienced reviewers were asked to evaluate 54 two-dimensional (2-D) images (categories: protrusion/inflammation/vascular) transformed to 3-D by the aforementioned SfS 3-D algorithms. The best algorithm was selected and inter-rater agreement was calculated.

RESULTS: Four publicly available SfS algorithms were compared. Tsai's SfS algorithm outperformed the rest (selected as best performing in 45/54 SBCE images), followed by Ciuti's algorithm (best performing in 7/54 images) and Torreão's (in 1/54 images). In 26/54 images; Tsai's algorithm was unanimously selected as the best performing 3-D representation SfS software. Tsai's 3-D algorithm superiority was independent of lesion category (protrusion/inflammatory/vascular; P = 0.678) and/or CE system used to obtain the 2-D images (MiroCam*/PillCam*; P = 0.558). Lastly, the interobserver agreement was good (kappa = 0.55).

CONCLUSION: 3-D representation software offers a plausible alternative for 3-D representation of conventional capsule endoscopy images (until optics technology matures enough to allow hardware enabled-"real" 3-D reconstruction of the gastrointestinal tract).

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Key words: Capsule endoscopy; Small-bowel; Threedimensional; Software; Algorithm; Reconstruction; Technology; Advance

Core tip: Accurate three-dimensional (3-D) reconstruction of the gastrointestinal tract requires the use of stereo-cameras that can simulate human binocular vision. In the absence of such technology in capsule endoscopy, we rely on software approaches [such as the Shape-from-Shading (SfS) algorithms] to obtain 3-D representation of digestive tract structures. In the present study, we evaluated the use of 4 publically available SfS in capsule endoscopy. 3 experienced/experts reviewers concluded that Tsai's approach is the best of the four available algorithms.

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INTRODUCTION

Capsule endoscopy (CE) has changed our diagnostic approach for small-bowel diseases^[1,2]. Although more accurate and of higher diagnostic yield than other modalities^[3,4], there are still occasions where pathology is either missed or misinterpreted^[5,7]. Furthermore, reports have shown that three-dimensional (3-D) reconstruction can facilitate diagnosis by enhancing textural features of mucosal structures or intestinal abnormalities^[8,9]. However, accurate 3-D reconstruction of the gastrointestinal (GI) tract requires the use of stereoscopic cameras that can simulate human binocular vision^[10,11]. With the current level of technological investment in CE though *i.e.*, camera size, packaging constraints and power consumption, accurate 3-D imaging of the intestinal lumen in small-bowel capsule endoscopy (SBCE) is still unfeasible^[9,12].

Therefore, software approaches that offer 3-D representation of conventional monocular two-dimensional (2-D) CE frames have been developed[13] and proposed for use in CE^[14]. Such approaches e.g., Shape-from-Shading (SfS) algorithms, are members of a family of shape recovery algorithms called shape-from-X techniques (Figure 1)[13]. Given a single 2-D image, these algorithms recover the shape of objects using the gradual variation of shading^[13]. Essentially, surface "reconstruction" with SfS is achieved through a mathematical representation that is inverted in order to recover dense surface distance and normal information by the gradual variation of shading[13]. We were able to retrieve 4 publicly available SfS algorithms [15-18]. To the best of our knowledge, no comparative study with images obtained during clinical SBCE has been performed to date^[19]. We aimed to evaluate the 3-D representation performance of 4 publicly available SfS algorithms by comparing them with their equivalent 2-D images of small-bowel structures/lesions obtained during SBCE, in order to identify the algorithm more helpful in facilitating identification and distinction between lesion and surrounding mucosa.

MATERIALS AND METHODS

Between January 2011 and January 2012, 262 SBCE procedures were performed at the Royal Infirmary of Edinburgh (tertiary referral centre for CE for the southeast of Scotland, United Kingdom) in 249 patients (mean age: 52.6 ± 12.1 years), as already described elsewhere^[9]. Out of them, 140 were performed with PillCam*SB2 (Given *Imaging Ltd., Yokneam, Israel) and 122 with MiroCam* (IntroMedic*Co, Seoul, South Korea). A total of 54 were selected images (27 obtained with MiroCam* and 27

with PillCam*SB) on the basis of the overall quality *i.e.*, brightness, absence of air bubbles, debris, or opaque luminal fluid and clarity of findings (lesions or structures). Thereafter, images were classified in the following image groups: (1) vascular lesions *i.e.*, angioectasias (n = 16); (2) inflammatory lesions *i.e.*, ulcers, erosions, aphthae, cobblestone, fold and/or villous oedema (n = 18); and (3) protruding lesions/structures *i.e.*, polyp/mass, nodular lymphoid hyperplasia, cluster of focal lymphangiectasia, chylous cysts, and ampulla of Vater, (n = 20).

3-D image representation software

All selected images were reconstructed in 3-D by means of all 4 SfS algorithms. Three reviewers (Rondonotti E, Mandelli G, Koulaouzidis A) with extensive CE experience and blinded to each other participated in this study. In order to facilitate the evaluation process, a Mathworks' Matlab program with a graphic user interface (GUI) was developed (Figure 2; a video presenting the evaluation process is provided as supplementary material via this link: https://dl.dropboxusercontent.com/u/7591304/ EvaluationVideo.mov). The program consisted of two windows in which the conventional 2-D SBCE image (Figure 2, single frame at the right side/window of the GUI screen) and its corresponding 3-D represented images (four, one for each of the 4 SfS under evaluation) are presented to the reviewer (Figure 2, left side/window of the GUI screen).

The 3-D SfS representations appeared in random order. The reviewers had the ability and freedom to rotate and zoom in each of the 3-D represented images. At the bottom of the GUI screen, a single "task request": "Choose the 3-D representation you consider most helpful in distinguishing the finding (seen in 2-D) from the surrounding mucosa" appeared. This prompted reviewers to choose one among the four 3-D 'reconstructed' images, each generated by a different 3-D algorithm. After selecting the best SfS representation, the reviewer had to click "next" to proceed to the next case. This process was repeated until the program reached the last case after which each separate evaluation was concluded.

Outcome measures

Reviewers were asked to evaluate 54 images. The following subgroup analyses were performed: (1) evaluation of 3-D representation according to the type of finding (vascular vs inflammatory vs protruding); and (2) evaluation according to the system generating the 2-D image (PillCam* vs Mirocam*). Furthermore, inter-observer agreement was calculated.

Ethics consideration

This study was conducted in accordance with United Kingdom research ethics guidelines. After review by the local ethics committee further specific ethical review and approval were not required, as the study was considered an evaluation of previously collected endoscopy images, using data already obtained as part of regular clinical care^[20].



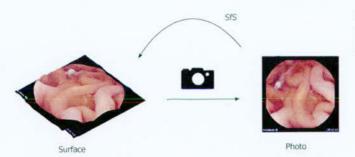


Figure 1 Shape-from-Shading function. Capturing a surface using a camera removes depth information. Shape-from-Shading (SfS) techniques try to reproduce the missing depth information from a given two-dimensional (2-D) image.

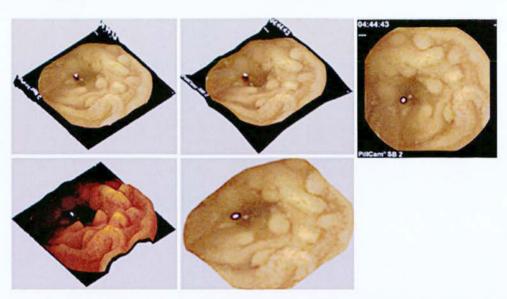


Figure 2 For the evaluation phase, a Mathworks® Matlab program with a graphic user interface was developed. The program consists of two windows in which the conventional two-dimensional capsule endoscopy image (single frame at the right side/window of the graphic user interface screen) and its corresponding three-dimensional represented images (four, one for each of the 4 shape-from-shading under evaluation) were presented to the reviewer.

Table 1 Results of the Shape-from-Shading method per lesion category

SfS method	Va	scular	Inflan	nmatory	Protrusion		
	PillCam®	MiroCam ^e	PillCam	MiroCam*	PillCam*	MiroCam	
Tsai	7	7	7	6	8	10	
Ciuti	1	0	1	0	1	4	
Torreão	0	0	1	0	0	0	
Barron	0	0	0	0	0	0	
None selected	0	1	0	0	0	0	

SfS: Shape-from-Shading.

Statistical analysis

For numerical variables, values are presented as mean \pm SD. Where necessary, the Fisher exact test was calculated. A two-tailed P value < 0.05 was considered statistically significant. Inter-observer agreement was calculated using an online kappa calculator (available from http://justus-randolph.net/kappa/) which provides the calculation of Randolph's free-marginal multirater kappa (21), applicable

when raters are not forced to assign a certain number of cases to each category. Values of *kappa* can range from -1.0 to 1.0, with -1.0 indicating perfect disagreement below chance, 0.0 indicating agreement equal to chance, and 1.0 indicating perfect agreement above chance. More specifically, the inte is classified per *kappa* as poor < 0.20, fair 0.2-0.40, good 0.41-0.60, very good 0.61-0.80 and, excellent $0.81-1.00^{[22]}$. All other statistical analyses were performed using a statistical package, StatsDirect, StatsDirect Ltd, Altrincham, Cheshire, United Kingdom.

RESULTS

Of the 4 SfS algorithms, Tsai's 3-D algorithm outperformed the rest (selected as best in 45/54 images), followed by Ciuti's (best performing SfS in 7/54 images) and Torreão's (in 1/54 images); there was a single image for which each reviewer selected (as best performing) a different 3-D representation algorithm. Of note, not once was Barron's 3-D algorithm selected as best performing (Table 1, Figure 3).

In 26/54 images, Tsai's algorithm was unanimously



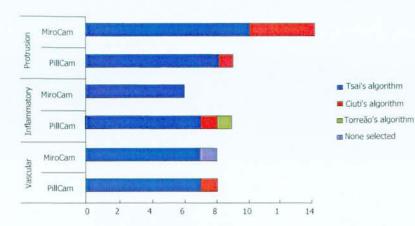


Figure 3 Assessment results for the 4 Shape-from-Shading algorithms per lesion category.

selected as the best performing 3-D representation SfS software. Tsai's 3-D algorithm superiority was independent of lesion category (protrusion/inflammatory/vascular; P = 0.678) and/or CE system used to obtain the 2-D images (MiroCam*/PillCam*; P = 0.558). Lastly, the inter-observer agreement was good (kappa = 0.55).

DISCUSSION

In the present study, we compared the performance of 4 publicly available 3-D "reconstruction" algorithms [15-18] (SfS software) using 54 conventional 2-D CE images. The evaluation criterion was subjective i.e., perceived visualisation improvement (3-D representations offered over the corresponding conventional 2-D images) by 3 experienced CE reviewers. Based on this evaluation, Tsai's algorithm is the 3-D representation model recommended for use in CE. This outcome directly supports Tsai's SfS model theoretical advantages: (1) able to produce good results for round surfaces, which are the case for most digestive tract shapes; and (2) it behaves quite well with bright surfaces^[13].

Depth information is an important aspect of human vision; it helps human brain to analyse and comprehend the surrounding environment. Images captured with conventional (non-stereoscopic) cameras "discard" the 3rd dimension (depth) as conventional cameras can only save 2 dimensions (height and width). Therefore depth information is lost; and moreover, most imaging algorithms perform less efficiently.

To date, engineers have not been able to equip capsule endoscopes with stereoscopic cameras for the following reasons: (1) packaging/space limitations; (2) low depth resolution of stereoscopic or time-of-flight cameras [22-24], and (3) power consumption issues. However, it is almost certain that in the foreseeable future these hardware-related limitations will be overcome [13] and eventually 3-D CE will be a commodity. Nevertheless, until hardware changes are widely implemented, several efforts have been made to convert 2-D images into 3-D images (3-D representation or "reconstruction") through software and dedicated algorithms. There are software algorithms that

offer a fair trade-off between 2-D images and hardwareenabled 3-D images. These algorithms are part of a family of shape recovery algorithms called Shape-from-X techniques^[13]. Basically a Sf8 algorithm recovers the shape of objects, given a single monocular image, using the gradual variation of shading^[8,13].

Sf8 algorithms can be divided into four groups: (1) minimization approaches [16-18], (2) propagation approaches; (3) local approaches; and (4) linear approaches [15]. It is important to remember that each of the 4 Sf8 algorithms evaluated herein utilizes a different approach to recover the shape from a conventional 2-D image.

More specifically, Tsai et al 15 described an repetitive update of the depth using a linear approximation of the reflectance function. Ciuti et al¹⁶ used a camera model with perspective projection and a light source close to the surface and away from the optical centre to measure depth. Torreão et al¹⁷ applied a linear-nonlinear biological model that mimics neuronal responses to estimate shape. Finally, Barron et at 18 proposed a unified model for recovering shape, reflectance and optional illumination while using local smoothness, global scarcity or entropy, and the absolute colour of each pixel. Although Tsai's [14,15] method is very straightforward and to an extent simplistic, it provides satisfying results. Cuiti's et al^[16] algorithm, on the other hand, uses a more advanced model (incorporating a camera model with perspective projection) that makes things in the background appear further back than in Tsai's model (Figure 4).

Since for a given 2-D image, light source and surface shape are not known, these algorithms try to model how the 2-D image was created from the 3-D environment to finally produce an approximation this 3-D depth. The above modelling has a significant impact on the resulting 3-D representation. During SfS process additional constraints need to be applied on the surface shape parameters or the light conditions to find the surface characteristics.

In conclusion, we showed previously that 3-D representation software offers a plausible alternative for 3-D representation of conventional CE images (until optics technology matures enough to allow a hardware enabled"real" 3-D reconstruction of the GI tract)^[9]. In the pres-

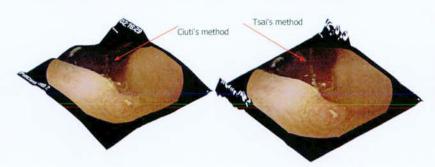


Figure 4 Ciuti's algorithm (left) and Tsai's method (right). Although Tsai's method is very straightforward and to an extent simplistic, it provides satisfying results. Ciuti's et al. algorithm, on the other hand, uses a more advanced model that makes things in the background appear darker than in Tsai's model.

ent study we compared 4 publicly available SfS methods. 3-D reconstruction is attracting interest in capsule endoscopy [8,9,14,25-28], especially as newly developed and/or under development CE become available, with greater potential (due to imager and optics) for 3-D software [30].

COMMENTS

Background

Over the past decade, conventional endoscope technology has advanced with the use of three-dimensional (3-D) cameras offering increased diagnostic and interventional capabilities. Unfortunately, due to hardware limitations, 3-D small-bowel capsule endoscopy (SBCE) is still an open technological challenge. It is aspired that 3-D SBCE will be able to offer similar benefits to conventional 3-D endoscopy. Therefore, information technology engineers suggested the use of software techniques (Shape-from-Shading, SfS) methods that simulate 3-D reconstruction i.e., 3-D representation in SBCE images. To date, various SfS approaches have been proposed; each aims to retrieve depth information from 2-D images (shape recovery) through different mathematical transformations, hence offering different shape approximations.

Research frontiers

The authors aimed to evaluate the 3-D representation performance of 4 publicly available SfS algorithms by comparing them with their equivalent 2-D images of small-bowel structures/lesions obtained during SBCE, in order to identify the algorithm more helpful in facilitating identification and distinction between the lesion and the surrounding mucosa.

Innovations and breakthroughs

This study, in conjunction with further similar work in the field, is useful in the assessing the potential validity of integrating 3-D representation in capsule endoscopy reviewing software.

Applications

Software-enabled 3-D representation is a promising approach that enables 3-D imaging at no additional cost. The authors have shown that SfS application leads to improved visualisation in SBCE and is it likely to be of use in certain clinical scenarios, like the 'mass or bulge' question.

Peer review

An interesting paper dealing with software and capsule endoscopy.

REFERENCES

- Iddan G, Meron G, Glukhovsky A, Swain P, Wireless capsule endoscopy. *Nature* 2000; 405: 417 [PMID: 10839527 DOI: 10.1038/35013140]
- 2 Eliakim R. Video capsule endoscopy of the small bowel. Curr Opin Gastroenterol 2013; 29: 133-139 [PMID: 23221650 DOI: 10.1097/MOG.0b013e32835bdc03]
- 3 Mata A, Llach J, Bordas JM. Wireless capsule endoscopy. World J Gastroenterol 2008; 14: 1969-1971 [PMID: 18395893 DOI: 10.3748/wjg.14.1969]
- 4 Koulaouzidis A, Rondonotti E, Karargyris A. Small-bowel capsule endoscopy: a ten-point contemporary review. World J Gastroenterol 2013; 19: 3726-3746 [PMID: 23840112 DOI:

10.3748/wjg.v19.i24.3726]

- Mavrogenis G, Coumaros D, Renard C, Bellocq JP, Defta D, Charneau D, Leroy J. Jejunal gastrointestinal stromal tumor missed by three capsule endoscopies. *Endoscopy* 2011; 43: 735-736, author reply 737 [PMID: 21811941 DOI: 10.1055/ s-0030-1236573]
- 6 Hakim FA, Alexander JA, Huprich JE, Grover M, Enders FT. CT-enterography may identify small bowel tumors not detected by capsule endoscopy: eight years experience at Mayo Clinic Rochester. Dig Dis Sci 2011; 56: 2914-2919 [PMID: 21735085 DOI: 10.1007/s10620-011-1773-0]
- 7 Triantafyllou K, Papanikolaou IS, Papaxoinis K, Ladas SD. Two cameras detect more lesions in the small-bowel than one. World J Gastroenterol 2011; 17: 1462-1467 [PMID: 21472105 DOI: 10.3748/wjg.v17.i11.1462]
- Koulaouzidis A, Karargyris A. Three-dimensional image reconstruction in capsule endoscopy. World J Gastroenterol 2012;
 18: 4086-4090 [PMID: 22919239 DOI: 10.3748/wjg.v18.i31.4086]
- 9 Koulaouzidis A, Karargyris A, Rondonotti E, Noble CL., Douglas S, Alexandridis E, Zahid AM, Bathgate AJ, Trimble KC, Plevris JN. Three-dimensional representation software as image enhancement tool in small-bowel capsule endoscopy: A feasibility study. *Dig Liver Dis* 2013; 45: 909-914 [PMID: 23849802 DOI: 10.1016/j.dld.2013.05.013]
- Stereo camera. Available from: URL: http://en.wikipedia. org/wiki/Stereo_camera
- 11 Kolar A, Romain O, Ayoub J, Viateur S, Granado B. Prototype of video endoscopic capsule with 3-d imaging capabilities. *IEEE Trans Biomed Circuits Syst* 2010; 4: 239-249 [PMID: 23853370 DOI: 10.1109/TBCAS.2010.2049265]
- Fisher LR, Hasler WL. New vision in video capsule endoscopy: current status and future directions. Nat Rev Gastroenterol Hepatol 2012; 9: 392-405 [PMID: 22565098 DOI: 10.1038/nrgastro.2012.88]
- 13 Zhang R, Tsai PS, Cryer JE, Shah M. Shape from Shading: A Survey. IEEE Trans Pattern Anal Mach Intell 1999; 21: 690-706 [DOI: 10.1109/34.784284]
- 14 Karargyris A, Karargyris O, Bourbakis N. 3D Representation of the Digestive Tract Surface in Wireless Capsule Endoscopy Videos. BIBE; 2010 May 31-Jun 3; Philadelphia, United States. New Jersey. IEEE International Conference on Bioinformatics and BioEngineering. In: Proceedings of the 2010 IEEE xplore, 2010: 279-280
- Tsai PS, Shah M. Shape from shading using linear approximation. Comput Vis Image 1994; 12: 487-498 [DOI: 10.1016/j.bbr.2011.03.031]
- 16 Ciuti G, Visentini-Scarzanella M, Dore A, Menciassi A, Dario P, Guang-Zhong Y. Intra-operative monocular 3D reconstruction for image-guided navigation in active locomotion capsule endoscopy. Biomedical Robotics and Biomechatronics (BioRob), 2012 4th IEEE RAS & EMBS International Conference June 2012: 768-774, 24-27 [DOI: 10.1109/BioRob.2012.6290771]
- 17 Torreão JRA, Fernandes JL. Linear-nonlinear neuronal model for shape from shading. Pattern Recognit Lett 2011; 32:



- 1223-1239 [DOI: 10.1016/j.patrec.2011.03.017]
- 18 Barron JT, Malik J. Color constancy, intrinsic images, and shape estimation. Computer Vision-ECCV 2012. Berlin Heidelberg: Springer, 2012: 57-70
- 19 Koulaouzidis A, Karargyris A. Application of 3D-Representation Algorithms in Small-Bowel Capsule Endoscopy. Glob J Gastroenterol Hepatol 2013; 1: 2-3 [DOI: 10.12970/2308-6483.20 13.01.01.1]
- 20 Warrens MJ. Inequalities between multi-rater kappas. Adv Data Anal Classif 2010; 4: 271-286 [DOI: 10.1007/s11634-010-0073-4]
- Online Kappa Calculator. Available from: URL: http://justusrandolph.net/kappa/
- 22 Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; 33: 159-174 [PMID: 843571]
- 23 Blais F. Review of 20 years of range sensor development. J Electron Imaging 2004; 13: 231-243 [DOI: 10.1117/1.1631921]
- 24 Wikipedia. Stereo camera. Available from: URL: http://en.wikipedia.org/wiki/Stereo_camera
- 25 Ciaccio EJ, Tennyson CA, Bhagat G, Lewis SK, Green PH. Use of shape-from-shading to estimate three-dimensional

- architecture in the small intestinal lumen of celiac and control patients. Comput Methods Programs Biomed 2013; 111: 676-684 [PMID: 23816252 DOI: 10.1016/j.cmpb.2013.06.002]
- 26 Ciaccio EJ, Tennyson CA, Bhagat G, Lewis SK, Green PH. Implementation of a polling protocol for predicting celiac disease in videocapsule analysis. World J Gastrointest Endosc 2013; 5: 313-322 [PMID: 23858375 DOI: 10.4253/wjge.v5.i7.313]
- Prasath VBS, Figueiredo IN, Figueiredo PN, Palaniappan K. Mucosal region detection and 3D reconstruction in wireless capsule endoscopy videos using active contours. Proceedings of the Engineering in Medicine and Biology Society (EMBC), 2012 IEEE Annual International Conference; 2012 Aug 28-Sep 1; San Diego, CA, USA. Engineering in Medicine and Biology Society (EMBC), 2012: 4014-4017 [DOI: 10.1109/EMBC.2012.6346847]
- Fu Y, Zhang DW, Liu H, Meng MQH. 3-D shape recovery of luminal wall from WCE image. Proceedings of the Automation and Logistics (ICAL), 2012 IEEE International Conference; 2012 Aug 15-17; Zhengzhou, China. Automation and Logistics (ICAL), 2012: 300-303 [DOI: 10.1109/ ICAL.2012.6308215]

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LETTERS TO THE EDITOR

Use of enhancement algorithm to suppress reflections in 3-D reconstructed capsule endoscopy images

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Author contributions: Koulaouzidis A and Karargyris A conceived and drafted the study, collected data, prepared and edited the final version of this manuscript.

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Key words: Capsule endoscopy; Three-dimensional reconstruction; Phantom; Experiment; PillCam; Software; Accuracy

Core tip: In an attempt to approximate a threedimensional (3-D) reconstruction of the digestive tract surface, a software that recovers information-using gradual variation of shading - from monocular twodimensional capsule endoscopy images has been proposed. Light reflections on the surface of the digestive tract are still a significant problem. Therefore, a phantom model and simulator has been constructed in an attempt to check the validity of a highlight suppression algorithm. Our results confirm that 3-D representation software performs better with simultaneous application of a highlight reduction algorithm. Furthermore, 3-D representation follows a good approximation of the real distance to the lumen surface.

Koulaouzidis A, Karargyris A. Use of enhancement algorithm to suppress reflections in 3-D reconstructed capsule endoscopy images. *World J Gastrointest Endosc* 2013; 5(9): 465-467 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i9/465. htm DOI: http://dx.doi.org/10.4253/wjge.v5.i9.465

Abstract

In capsule endoscopy (CE), there is research to develop hardware that enables "real" three-dimensional (3-D) video. However, it should not be forgotten that "true" 3-D requires dual video images. Inclusion of two cameras within the shell of a capsule endoscope though might be unwieldy at present. Therefore, in an attempt to approximate a 3-D reconstruction of the digestive tract surface, a software that recovers information-using gradual variation of shading-from monocular two-dimensional CE images has been proposed. Light reflections on the surface of the digestive tract are still a significant problem. Therefore, a phantom model and simulator has been constructed in an attempt to check the validity of a highlight suppression algorithm. Our results confirm that 3-D representation software performs better with simultaneous application of a highlight reduction algorithm. Furthermore, 3-D representation follows a good approximation of the real distance to the lumen surface.

TO THE EDITOR

In capsule endoscopy (CE), there is research to develop hardware that enables "real" three-dimensional (3-D) video by using an infrared projector and a CMOS camera ^[1,2]. However, it should not be forgotten that "true" 3-D requires dual video-images; furthermore, the inclusion of two cameras within the shell of a capsule endoscope might be unwieldy at present ^[3]. Therefore, major drawbacks at present are size, power consumption and packaging issues ^[4]. In an attempt to approximate a 3-D reconstruc-



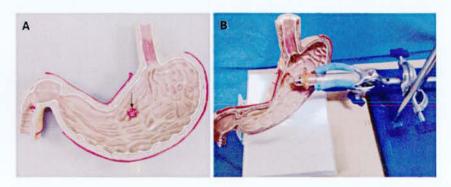


Figure 1 Phantom model (A) and task simulator setting (B). A: The arrow points to the gastric ulcer ("1/2 diameter and 3/16" depth).

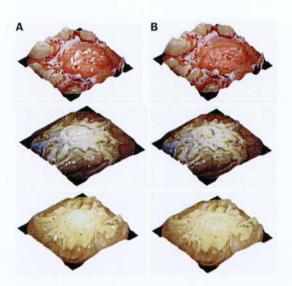


Figure 2 Three-dimensional representation of images captured for the 3 models: red, white and yellow. A: Original three-dimensional (3-D) represented images; B: The processed 3-D represented images using the highlight suppression algorithm.

tion of the digestive tract surface, Koulaouzidis et at^[4] and Karargytis et at^[8] proposed the use of a software [Shape-from-Shading (S/S)] that utilizes monocular CE frames. Essentially, S/S algorithms recover information -using gradual variation of shading [6] - on the shape of objects given a single two-dimensional (2-D) image. 3-D representation may be helpful in conjunction with other image enhancement tools e.g., virtual chromoendoscopy (FICE) [7] and/or color (blue) mode analysis of CE videos [8].

However, light reflections on the surface of the digestive tract are still a significant problem, not only for 3-D representation but also for traditional 2-D CE. When light falls on to a surface, some of the beams are reflected back straightaway -specular reflection- while the rest of the beams penetrate it before reflected (diffuse reflection). As most digestive tract structures/surfaces are di-electric and homogeneous, they display both types of reflections ^[4]. To reduce reflections, a highlight suppres-

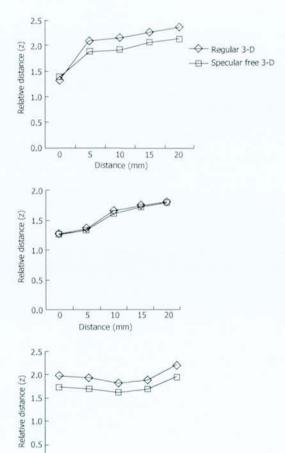


Figure 3 Relative distance of three-dimensional representation calculated over images taken from various distances of the capsule from the models.

15

20

sion algorithm[9] has been applied onto CE images.

10

Distance (mm)

0

To test this algorithm, a phantom task simulator was created. A Stomach Ulcer Anatomical Model (manufacturer: Anatomical Chart Company G200) was used; the



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stomach model has an red-colored base ulcer (1/2"diameter and 3/16"depth; Figure 1A); the latter was thereafter colored buttercup yellow using quick-drying spray paint (Tor Coatings*Ltd., United Kingdom) and white (using flat white spray from Plasti-Kote*Ltd.). A PillCam*SB2 (Given*Imaging Ltd., Yoqneam, Israel) was mounted on a plastic tube and held (with the use of regular lab stand) at 0, 5, 10, 15 and 20 mm from the ulcer base (usual working distance of the CE *in vivo*, Figure 1B). The images were uploaded to a workstation and they were categorized based on distance and ulcer base color (red, yellow and white). We aimed to check whether the ulcer models appear closer or further based on their 3-D representation.

Tsai's \$\int_{\infty}^{(9,10]}\$ algorithm was applied on each image in order to reconstruct its 3-D representation with (Figure 2A) or without (Figure 2B) software highlight suppression [9]. Tsai's \$\int_{\infty}^{(9)}\$ algorithm cannot measure the real distance of the camera to the model's surface but it gives the relative distance (z) to the black frame background. For each image, we selected the region of interest (ROI) of the ulcer model on the 3-D representation and we calculated the average depth (z) for each ROI.

The results (charts, Figure 3) confirm that the distance of the camera from the model surface increases so does the relative distance (z) on the 3-D representation. This effect is more evident for the white and yellow ulcer models. However, relative distance does not follow a similar trend for the red-based ulcer model. This is likely due to the saturation of the red color creating variations to the shading: red color appears darker or lighter. Finally, from the charts we conclude that the highlight suppression algorithm improved the quality of the images.

In conclusion, 3-D representation software seems to perform better with simultaneous application of a highlight reduction algorithm. Furthermore, 3-D representation follows a good approximation of the real distance to the lumen surface.

REFERENCES

- Stereovision. Available from: URL: http://www.visionsense.com/Stereo_Vision.html
- Kolar A, Romain O, Ayoub J, Viateur S, Granado B. Prototype of video endoscopic capsule with 3-d imaging capabilities. *IEEE Trans Biomed Circuits Syst* 2010; 4: 239-249 [PMID: 23853370 DOI: 10.1109/TBCAS.2010.2049265]
- 3 Fisher LR, Hasler WL. New vision in video capsule endoscopy: current status and future directions. Nat Rev Gastroenterol Hepatol 2012; 9: 392-405 [PMID: 22565098 DOI: 10.1038/ nrgastro.2012.88]
- 4 Koulaouzidis A, Karargyris A. Three-dimensional image reconstruction in capsule endoscopy. World J Gastroenterol 2012; 18: 4086-4090 [PMID: 22919239 DOI: 10.3748/wjg.v18.i31.4086]
- Karargyris A, Bourbakis N. Three-dimensional reconstruction of the digestive wall in capsule endoscopy videos using elastic video interpolation. *IEEE Trans Med Imaging* 2011; 30: 957-971 [PMID: 21147593 DOI: 10.1109/TMI.2010.2098882]
- 6 Zhang R, Tsai PS, Cryer JE, Shah M. Shape from Shading: A Survey. IEEE Trans Pattern Anal Mach Intell 1999; 21: 690-706 [DOI: 10.1109/34.784284]
- 7 Krystallis C, Koulaouzidis A, Douglas S, Plevris JN. Chromoendoscopy in small bowel capsule endoscopy: Blue mode or Fuji Intelligent Colour Enhancement? *Dig Liver Dis* 2011; 43: 953-957 [PMID: 21893436 DOI: 10.1016/j.dld.2011.07.018]
- 8 Koulaouzidis A, Douglas S, Plevris JN. Blue mode does not offer any benefit over white light when calculating Lewis score in small-bowel capsule endoscopy. World J Gastrointest Endosc 2012; 4: 33-37 [PMID: 22347530 DOI: 10.4253/wjge.v4.i2.33]
- 9 Tan RT, Ikeuchi K. Separating reflection components of textured surfaces using a single image. *IEEE Trans Pattern* Anal Mach Intell 2005; 27: 178-193 [PMID: 15688556 DOI: 10.1007/978-0-387-75807_17]
- 10 Koulaouzidis A, Karargyris A, Rondonotti E, Noble CL, Douglas S, Alexandridis E, Zahid AM, Bathgate AJ, Trimble KC, Plevris JN. Three-dimensional representation software as image enhancement tool in small-bowel capsule endoscopy: A feasibility study. *Dig Liver Dis* 2013; Epub ahead of print [PMID: 23849802 DOI: 10.1016/j.dld.2013.05.013]

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Digestive Endoscopy

Three-dimensional representation software as image enhancement tool in small-bowel capsule endoscopy: A feasibility study



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ABSTRACT

Background: Three-dimensional imaging in capsule endoscopy is not currently feasible due to hardware limitations. However, software algorithms that enable three-dimensional reconstruction in capsule endoscopy are available.

Methods: Feasibility study. A phantom was designed to test the accuracy of three-dimensional reconstruction. Thereafter, 192 small-bowel capsule endoscopy images (of vascular: 50; inflammatory: 73; protruding structures: 69) were reviewed with the aid of a purpose-built three-dimensional reconstruction software. Seven endoscopists rated visualisation improved or non-improved. Subgroup analyses performed for diagnostic category, diagnosis, image surface morphology and colour and SBCE equipment used (PillCam® vs. MiroCam®).

Results: Overall, phantom experiments showed that the three-dimensional reconstruction software was accurate at 90% of red, 70% of yellow and 45% of white phantom models. Enhanced visualisation for 56% of vascular, 23% of inflammatory and <10% of protruding structures was noted (*P*=0.007, 0.172 and 0.008, respectively). Furthermore, three-dimensional software application enhanced 53.7% of red, 21.8% of white, 17.3% of red and white, and 9.2% of images of lesions with colour similar to that of the surrounding mucosa, *P* < 0.0001.

Conclusions: Application of a three-dimensional reconstruction software in capsule endoscopy leads to image enhancement for a significant proportion of vascular, but less so for inflammatory and protruding lesions. Until optics technology allows hardware-enabled three-dimensional reconstruction, it seems a plausible alternative.

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1. Introduction

Over the past decade, capsule endoscopy (CE) has revolutionised the evaluation of small-bowel diseases [1,2]. In recent years, research has been carried out to produce three-dimensional (3D) reconstruction of the gastrointestinal (GI) tract in conventional video endoscopy using stereoscopic cameras [3,4]; several reports

have shown that it can facilitate diagnosis by enhancing mucosal textural features and abnormalities [5,6].

However, due to current technological limitations of capsule endoscopes (i.e. packaging and size constraints, power consumption) hardware enabled 3D reconstruction of the intestinal lumen in small-bowel capsule endoscopy (SBCE) is yet to be available. Therefore, a software-based approach [Shape-from-Shading (SfS)] has been proposed that helps approximate a 3D representation from monocular two-dimensional (2D) images. These algorithms recover the shape of objects from 2D images using gradual variation of shading [7]. Eventually, amongst 4 publicly available SfS algorithms [8–11], Tsai's method performed better based on preliminary results (unpublished authors' data).

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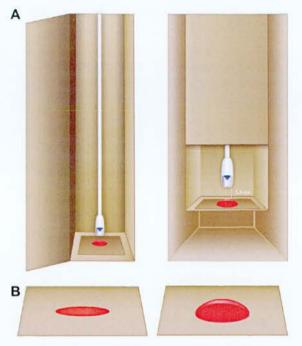


Fig. 1. Phantom simulator (A) and phantom models (B).

We conducted a two-phase, feasibility study in order to assess:

- The accuracy of 3D representation, by using CE images from phantom paradigms (phase 1).
- Whether 3D representation improves visualization (of surface/textural aspects) of small-intestine structures/lesions, by using of a group of selected SBCE images from clinical practice (phase 2).

2. Methods

2.1. Phase 1 - phantom simulator

For the accuracy assessment of the software, a task simulator was constructed; 2D images of phantom models were obtained by using CE and compared with their 3D representation counterparts. Overall, the simulator was designed based on the following principles: (a) to be constructed with readily available materials, e.g. cardboard boxes and stationary office supplies; (b) to allow minimal external light for simulation of clinical CE; and lastly (c) phantom models to be representative of the variety of colours and shapes of structures/lesions encountered in SBCE. A cuboid cardboard box (12 cm × 30 cm × 45 cm) was used to simulate abdominal wall and allow placement of CE sensors for video capture. A frame was cut open at the top side of the box to allow insertion of a cardboard cuboid tube (6 cm × 9 cm × 42 cm) which was to act as the main function chamber/bowel simulator. Furthermore, a 4 cm × 6 cm rectangular frame was cut open in the lower part the side of the tube facing the open lids of the box. This was done to allow placement of the phantom-models plates on the reviewing surface during CE video capture (Fig. 1A). Finally, following placement of CE sensors, a real-time viewer was used to monitor progress of video/images capture.

A PillCam®SB2 CE was mounted on a small hemispheric plastic cap with Pritt® sticky fixer and a commercial cotton string was used to suspend the capsule 1.5 cm above the phantom object plates. As

aforementioned, phantoms were made with commercially available stationary material. Therefore, red, yellow and white coloured, flat-headed drawing pins (Fig. 1B), as well as blocks of white, red and yellow Pritt® sticky tack (Henkel AG & Co. KGaA, Dusseldorf, Germany) and a ibuprofen tablet (Nurofen® 400 mg) were used as phantom models. Phantoms were placed on cardboard panels of equal size in such a way that the model would be either protruding or at a level with the plate surface. From the video obtained, 60 2D images of high quality (20 for each of the 3 colours, i.e. red, yellow and white) were selected by one of the authors (AK), converted in 3D images and reviewed for evaluation by the second co-author (AK) who was unaware of the surface type of each image, i.e. if the imaged object was flat or protruding.

2.2. Phase 2 - clinical study

2.2.1. SBCE 2D images: patients, image selection and classification

From January 2011 to January 2012, 262 SBCE procedures in 249 patients (67 males/182 females; mean age: 52.6 ± 12.1 years) have been performed at the Royal Infirmary of Edinburgh (University Hospital and referral centre for CE for the southeast of Scotland, UK). Out of those, 140 were performed with PillCam® (Given®Imaging Ltd., Yokneam, Israel) and 122 with MiroCam® (IntroMedic® Co., Seoul, South Korea). An experienced SBCE provider (SD), familiar with both aforementioned SBCE systems, selected and de-identified a group of images by reviewing the thumbnails of all 262 videos. Images were selected on the basis of their overall quality, i.e. brightness, no bubbles and/or luminal debris or opaque luminal fluid and findings (lesions or structures) clarity. An expert CE reviewer (ER) acted as second selector. Eventually, only images for which there was complete agreement between the 2 reviewers in terms of image quality, colour and type of depicted finding were included.

Therefore, a total of 192 SBCE images (84 obtained with PillCam®SB2/108 obtained with MiroCam®), covering a wider spectrum of findings seen in SBCE, entered 3D reconstruction. These images were classified as per:

- Predominant colour of the depicted structure/lesion into 4 image-groups: red, white, mixed (red+white) and a group with lesion colour similar to that of the surrounding mucosa.
- 2. Surface morphology of the depicted structure/lesion into the following groups: (a) Convex surface morphology, i.e. polyp/neoplastic, chylous cysts, NLH, fold oedema, and AoV (n=67); (b) flat or concave surface morphology, i.e. mucosal ulcer, erosion, aphthae, villous oedema and angioectasias (n=103); and (c) combi-surface morphology, i.e. cobblestone and lymphangiectasias (n=22).
- Diagnostic category into the following groups: (a) vascular, i.e. angioectasias (n = 50), (b) inflammatory, i.e. ulcers, erosions, aphthae, cobblestone, fold/villous oedema (n = 73), and (c) luminal protrusion, i.e. polyp/neoplastic, nodular lymphoid hyperplasia (NLH), cluster of focal lymphangiectasias, chylous cysts, and ampulla of Vater (AoV) (n = 69) (Table 1).
- 4. Lastly, each diagnosis was examined separately.

2.2.2. SBCE procedures

The technical characteristics of capsules, CE procedure and methodology for review of CE images have been described in detail previously [12,13]. In essence, SBCE was performed with PillCam®SB2 and MiroCam® capsule endoscopes using an established for our unit procedure protocol, i.e. strict liquid diet the day prior to the test, combined with purge (2 I polyethylene glycol; Moviprep®, Norgine Ltd., Middlesex, UK) and overnight fast. The capsule is ingested with 100 mg of anti-foam (Simethicone) and 5 mg of liquid prokinetic suspension (Domperidone), unless

Table 1
Evaluated images, in total and per SBCE system used (PillCam®/MiroCam®); AoV: ampulla of Vater; N: number; SBCE: small-bowel capsule endoscopy.

Diagnostic category	N	SBCE PillCam®-MiroCam®	P value
VASCULAR (N=50)		25-25	1.0
Angioectasias	50	25-25	
INFLAMMATORY (N = 73)		28-45	0.359
Mucosal cobblestone	9	4-5	
Mucosal breaks/aphthae	21	11-10	
Mucosal ulcers	25	7-18	
Mucosal fold/villous oedema	18	6-12	
PROTRUDING (N = 69)		31-38	0.435
Lymphomas	3	0-3	
Polyps	10	5-5	
Chylous cysts	11	5-6	
Lymphangiectasias	13	8-5	
Lymphoid hyperplasia	15	5-10	
AoV	17	8-9	

in exceptional circumstances. The patients are allowed to drink clear fluids after 2 h and consume a light meal/snack after 4 h. Written informed consent was obtained from all patients prior to the procedure as part of their regular clinical care.

2.2.3. 3D image representation software

visualisation software was developed in Mathworks®Matlab; it can process a 576 × 576 image in less than 2 s. The software allows a reviewer to load capsule endoscopy images from a folder. Then the software processes each image and exports its corresponding 3D represented image in a proprietary format of Matlab® (.fig extension). For the evaluation process, another Matlab® programme with a user interface was devised. The programme consists of two windows in which the conventional 2D SBCE image and its corresponding 3D represented image are given (Fig. 2). The reviewer can rotate and zoom in the 3D images. At the bottom of the screen, a single question regarding the efficiency of the 3D representation is given. Five possible answers to choose from are also presented. After selecting the desired answer the reviewer clicks next to proceed to the next case. This process is performed until the programme reaches the last case after which each separate evaluation is concluded.

2.2.4. Raters and outcome measures

Seven reviewers – each with substantial experience in GI endoscopy but variable experience in interpretation of SBCE images – participated in phase 2. Reviewers were unaware to each other's evaluation.

Each of the 3D representation images were scored for textural enhancement of the depicted finding and therefore categorized as improved/non improved. To evaluate whether the 3D representation tool improves visualisation of SBCE images, reviewers were asked to compare each 3D represented image with a corresponding 2D counterpart and to rate it according to the following scale: +2 (definitely improved), +1 (somewhat improved), 0 (no different or equivalent to conventional 2D image), -1 (somewhat worse), -2 (definitely worse) [14]. Thereafter, reviewers' scores were tallied and the average score for each image was calculated. To simplify analysis the data are presented into three categories:

- improved if average score ≥1;
- same if average score was 0.99 to -0.99; and,
- worse if average score ≤-1.

The following subgroup analyses were performed: evaluation of 3D representation according to groups described above, i.e. predominant colour of depicted structure, surface morphology,

diagnostic category and diagnosis; the equipment generating the 2D image (PillCam® vs. Mirocam®); and, the CE experience of raters. Inter-observer agreement was calculated for each image group (vascular, inflammatory and protuberant).

Furthermore, reviewers were advised to leave each 3D image at an angle most consistent with their grading so that mean angles for right/left and up/down (for each image group) could be calculated.

2.3. Ethics consideration

This study was conducted in accordance with UK research ethics guidelines. After review by the local ethics committee further specific ethical review and approval were not required, as the study was considered an evaluation of previously collected images, using data already obtained as part of regular patient care.

2.4. Statistical analysis

For numerical variables, values are expressed as mean (\pm standard deviation, SD). The *t*-test for continuous variables and the chi-square (χ^2) test for categorical variables were used. A two-tailed *P* value <0.05 was considered statistically significant. Pearson's agreement correlation was used for phase 1 of this study.

For phase 2, inter-observer agreement was measured by free-marginal multirater kappa statistics [15], using an online Kappa Calculator, available at http://justusrandolph.net/kappa/(retrieved November 24, 2012). A sample size of 192 images provides a margin of error of 7.04% (as calculated by and online sample size calculator, available at http://www.raosoft.com/samplesize.html). kappa <0.4 was considered as slight agreement whereas between 0.41 and 0.6 as moderate, 0.61–0.80 substantial and 0.81–1.00 as excellent agreement. All other statistical analyses were performed using a statistical package, StatsDirect, StatsDirect Ltd., Altrincham, Cheshire, UK.

3. Results

3.1. Phase 1

Overall, phantom experiments showed that the SfS algorithm was 90, 70 and 45% (P=0.14) accurate in interpreting the protruding or non-protruding surface nature of red, yellow and white phantom models, respectively (Figure S1). Sensitivity and specificity of the above evaluation was 80 and 100% for red-coloured objects; 81.3 and 25% for yellow-coloured objects; 100 and 21.3% for white-coloured objects. Lastly, Pearson's correlation was 0.93, 0.63 and 0.35 for red, yellow and white, respectively.

3.2. Phase 2

3.2.1. Selected images

The number of images selected for each category, according to the SBCE system used and the type of findings is tabulated in Table 1. Overall, there was no statistically significant difference in the number of images included per diagnostic category for vascular, inflammatory and protruding structures/lesions (P = 1.0, 0.359, 0.435, respectively).

3.2.2. 3D images evaluation

For the entire image group (n=192) and all (n=7) reviewers, 51/192 (27.6%) were evaluated as improved (better) with 3D representation and 141/192 (73.4%) as equivalent to their 2D counterparts.

Sub-analysis per predominant colour revealed that 3D representation improved red, white, mixed and lesions with colour similar

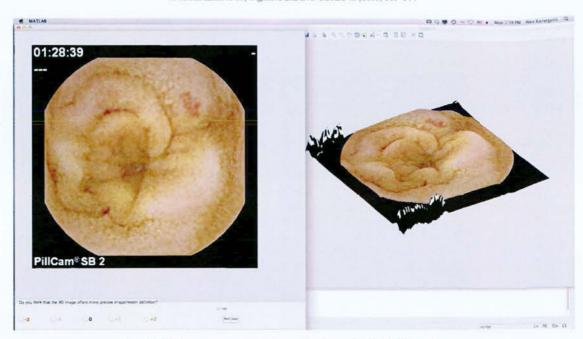


Fig. 2. The 3D image representation software evaluation interface in a Matlab® environment.

to the surrounding mucosa in 53.7% (29/54), 21.8% (12/55), 17.3% (5/29) and 9.2% (5/54) of cases (P<0.0001).

Sub-analysis per surface morphology showed that 3D representation was felt to improve evaluation in 14/67~(20.9%) of convex findings, 33/103~(32%) of flat/concave findings and 4/22~(18.2%) of combi-surface morphology findings, P=0.1929.

Sub-analysis per diagnostic category; 56% (28/50) of vascular, 23.2% (16/69) of protruding, and 9.6% (7/73) of inflammatory lesions were evaluated as showing enhanced textural features on 3D representation (Figure S2–5, Table 2).

Sub-analysis per diagnosis revealed that evaluation of angioectasias with 3D representation showed improved visualisation in 56% (28/50); chylous cysts 36.36% (4/11); polyps/neoplastic lesions 30.76% (4/13), LNH 26.6% (4/15), mucosal cobblestone 22.2% (2/9), lymphangiectasias 15.38% (2/13), AoV 11.76% (2/17), mucosal ulcers/erosions/aphthae 8.69% (4/46) and villous/fold oedema 5.55% (1/18) (P<0.0001).

Sub-analysis per SBCE system revealed that 3D representation led to enhanced visualisation in 20.2% (17/84) of images obtained

Table 2 Image enhancement with the three-dimensional image representation software, as per small-bowel capsule endoscopy system, image group and colour of structure/finding.

All readers	$n/N(\mathcal{X})$
SBCE system MiroCam® PillCam®	34/108 (31.5) 17/84 (20.2)
Type of finding Vascular Protuberant Inflammatory	28/50 (56.0) 16/69 (23.2) 7/73 (9.6)
Colour of finding Red White Mixed (Red + White) Colour similar to mucosa	29/54 (53.7) 12/55 (21.8) 5/29 (17.3) 5/54 (9.2)
Overall	51/192 (26.6)

with PillCam® and 31.5% (34/108) of images captured by Mirocam®, P = 0.099

Sub-analysis per CE reviewer experience (for the entire image series); there was statistically significant difference between the rating from experienced CE and non-CE readers (77/192 vs. 51/192, P < 0.007). For both evaluators' sub-groups though, no image was perceived as worse to its 2D equivalent. The results of the comparison between CE and non-CE readers according to type of lesion and SBCE equipment generating the 2D images are summarized in Table 3.

Inter-observer agreement was at <0.4 for the entire group of images, as well as when each diagnostic category was examined separately. The kappa statistics for all raters, CE-readers and non-CE readers is presented in Table 4.

4. Discussion

Hardware-based reconstruction is based on stereoscopic vision, where multiple image sensors are used to provide the necessary information for depth retrieval. Stereoscopic approaches utilise at least two Images - of the same target - at two different angles of view. Hence, a typical 3D-imaging system comprises two independent cameras, each camera contributing one viewpoint. However, inclusion of two cameras within a CE device to create a stereo-image can be unwieldy [2]. Therefore, a couple of important 3D hardware-enabled endoscopy technologies have been proposed. Kolar et al. [16] presented a system that can give - in real time - both 3D and texture information using an infrared projector and a CMOS camera; the major disadvantages of this system are its size and power consumption. Shahinian et al. [17] reported a promising new technique for endoscopic 3D imaging that uses a single lens system. This technique creates two viewpoints in a single-lens camera by placing a bipartite-filter at the limiting aperture, but this is still to be incorporated in a SBCE device.

Therefore, in the current absence of a hardware-enabled 3D reconstruction, Karargyris et al. [18] recently proposed the use of a 3D software-enabled technique (SfS) for CE videos. The algorithm is

 Table 3

 Sub-groups analyses performed for capsule endoscopy and non-capsule endoscopy readers.

Type of finding	Capsule endoscopy readers (%)	Non-capsule endoscopy readers (%)	P value
Vascular	38/50 (76.0)	24/50 (48.0)	0.007
Protuberant	31/69 (44.9)	12/69 (17.4)	0.008
Inflammatory	8/73 (10.9)	15/73 (20.5)	0.172
Overall	77/192 (40.1)	51/192 (26.6)	0.006

^{&#}x27; Statistically significant.

very fast and "behaves" reasonably well with specular textures [19]. Eventually, all SfS techniques, such as the linear method of Tsai, take a single 2D input-signal, i.e. a conventional SBCE image and through a series of mathematical transformations (energy minimization) produce a corresponding 3D representation image. Strictly from a mathematical point of view, since 3D represented images are derived from monocular 2D conventional CE images, only visualization change. Essentially, this means that the image information does not change.

In order to assess the usefulness of this 3D representation approach in SBCE, we conducted a feasibility study including (a) a task simulator and (b) a clinical part. In the latter, we included reviewers from a wider endoscopic audience and not only CE readers. Moreover, the clinical SBCE images we selected cover a wide range of findings in CE and they were categorised as per group/type of finding and type of SBCE system used to produce the 2D image. Overall, the simulator showed that 3D representation software gives a 90, 70 and 45% accuracy when it comes to predicting the protruding or not nature of red, yellow and white phantom models, respectively. Furthermore, the clinical study showed that using 3D representation software in images obtained from SBCE, about a quarter (26%) of them present enhanced visualisation features, as compared to their 2D conventional counterparts. This effect is independent to the type of SBCE system used, Table 2.

Having observed increased accuracy of the 3D software for red coloured phantoms and less so for yellow and white, it is surprising that major improvement is observed for vascular lesions (56%). whereas moderate (23%) and low (<10%) is noted for inflammatory and protruding findings, respectively. Recently, Liao et al. [20] showed that vascular lesions represent the majority of small-bowel pathology identified by means of capsule endoscopy and account for about 50% of SCBE diagnostic yield in patients with obscure GI bleeding. An improved visualization using 3D reconstruction was showed only for vascular lesions. It is of course to an extent inopportune that findings presenting better delineation with 3D enhancement, i.e. angioectasias are those most easy to recognize using a standard visualization. This is likely due to the fact that vascular lesions, even those of small size, present a clear margin, a well-defined lesion border and a definite colour difference with the surrounding mucosa. One could argue that by regularly implementing this image enhancement tool in SBCE, could lead to improved vascular lesion detection. Furthermore, perhaps it would be clinically relevant to further investigate whether 3D representation may provide a classification of such lesions in order to identify those at higher risk of bleeding [21].

Table 4
Inter-observer agreement for all reviewers (and per CE reviewing experience groups) for all images and per diagnostic category; CE: capsule endoscopy.

Raters groups	All images	Diagnostic category				
		Vascular	Inflammatory	Protruberant		
All raters (n = 7)	0.182	0.163	0.193	0.185		
CE-readers $(n = 3)$	0.164	0.358	0.115	0.082		
Non-CE readers $(n = 4)$	0.301	0.3	0.318	0.29		

The most difficult lesions to be visualized and categorized are flat/concave lesions and/or neoplastic lesions where the improvement of 3D reconstruction seems to be marginal. One might expect that a 3D representation would perform best in enhancing differences between flat and protruding lesions; certainly, the results of the task simulator were reassuring in this aspect. This has not become evident though in our second-stage (clinical) assessment. A plausible explanation is that real life protruding small-bowel structures or lesions are not necessarily entirely or solely red and more likely to have a mixed colour or similar to that of the surrounding mucosa (e.g. AoV, small-bowel polyps or masses, etc.). Furthermore, lack of insufflation in SBCE often causes a protruding lesion to appear only in part in the video frames as a "fold between folds", i.e. not as defined luminal protrusion. Even for experienced CE readers, protruding lesions often represent a significant diagnostic challenge, particularly when the distinction between masses and bulges is at stake [22]. Nevertheless, readers with CE experience noted a significantly higher improvement as compared to non-CE readers (44.9% vs. 17.4%).

Interestingly, when we analysed the evaluation results based on the assessors SBCE experience, it became obvious that physicians experienced in CE review, i.e. assessors most used to 2D SBCE images of small-bowel pathology, described a significantly higher image improvement with the use of the 3D enhancement tool, 38/50 vs. 24/50 (P=0.007) and 31/69 vs. 12/69 (P=0.008), for angioectasias and protruding findings, respectively. Conversely, in the inflammatory lesions image group, both CE and non-CE readers agreed that 3D offered only a limited textural/feature enhancement with 8/73 vs. 15/73, respectively, P=0.172. These results may simply reflect familiarity with SBCE reviewing software and/or image manipulation or merely enthusiasm bias. In that respect, we believe that including a diverse group of GI endoscopists - all with advanced image interpretation skills but variable experience in CE images interpretation - provides a more balanced evaluation of this enhancement tool.

The present study has few limitations; first, in order to test the performance of the 3D software, we selected high clarity SBCE images; hence, we do not know if our results can be reproduced with images obtained in the everyday SCBE practice, where the presence of intraluminal debris or opaque fluid can affect the overall visibility and a 3D representation of small-bowel findings. Second, the heterogeneous group of raters/assessors could be considered by some as potential limitation of this evaluation. Third, although we attempted a subgroup analysis per type of SBCE system, raters where not blinded to the brand of SBCE used to obtain the 2D image, as eventually the two SBCE systems produce images of different characteristics. Furthermore, some inherit limitations of the software should be taken into account, i.e. many objects in the real world are dielectric and homogeneous, hence displaying dual reflections. In fact, this might be responsible for the only fair interobserver agreement of this study. Most digestive structures fall into this category. Therefore, when the light beams fall on to such an object, some of them reflect back immediately creating the specular reflection; the rest first penetrate the object and then reflect creating the diffuse reflection. This phenomenon creates highlights, which distort the outcome of any 3D image representation.

Until optics technology matures enough to allow a hardwareenabled 3D reconstruction of the GI tract [23,24], 3D representation software offers a plausible alternative for 3D representation of conventional CE images. Work is underway on measuring its precision not by visual inspection but by strict mathematical approach. However, the present study is its first of its kind to examine the potential usefulness of 3D representation. Further studies are needed to evaluate the effect of this software in lesion detection and in patient management/clinical course.

Disclosure

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Conflict of interest statement

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/ j.dld.2013.05.013,

References

- [1] Iddan G, Meron G, Glukhovsky A, et al. Wireless capsule endoscopy. Nature
- [2] Fisher LR, Hasler WL, New vision in video capsule endoscopy: current status and future directions. Nature Reviews Gastroenterology & Hepatology 2012-9-392-405
- [3] Mueller-Richter U, Limberger A, Weber P, et al. Possibilities and limitations of current stereo-endoscopy. Surgical Endoscopy 2004;18:942-7.

 [4] Tsutsui A, Okamura S, Muguruma N, et al. Three-dimensional reconstruction of
- endosonographic images of gastric lesions: preliminary experience. Journal of Clinical Ultrasound 2005;33:112–8.
- Bhandari S, Shim CS, Kim JH, et al. Usefulness of three-dimensional, multidetector row CT (virtual gastroscopy and multiplanar reconstruction) in the evaluation of gastric cancer: a comparison with conventional endoscopy, EUS. and histopathology. Gastrointestinal Endoscopy 2004;59:619-26.

- [6] Taylor SA, Halligan S, Slater A, et al. Polyp detection with CT colonog-raphy: primary 3D endoluminal analysis versus primary 2D transverse analysis with computer-assisted reader software. Radiology 2006;239: 759-67
- [7] Zhang R, Tsai P-S, Cryer JE, et al. Shape from shading: a survey. IEEE Transactions
- on Pattern Analysis and Machine Intelligence 1999;21:690–706.

 [8] Barron JT, Malik J. Color constancy, intrinsic images, and shape estimation. In: Andrew Fitzgibbon, Svetlana Lazebnik, Pietro Perona, Yoichi Sato, Cordelia Schmid, editors. Proceedings of the 12th European conference on Computer Vision – Volume Part IV (ECCV'12), Vol. Part IV. Berlin, Heidelberg; Springer-Verlag; 2012. p. 57-70.

 [9] Visentini-Scarzanella M, Stoyanov D, Yang GZ. Metric depth recovery from
- monocular images using shape-from-shading and specularities. In: IEEE International Conference on Image Processing (ICIP) 2012. 2012 (in press).

 [10] Torreão JRA, Fernandes JL. Linear-nonlinear neuronal model for shape from
- shading, Pattern Recognition 2011;32:1223-39.
- [11] Tsai PS, Shah M. Shape from shading using linear approximation. Image and
- Vision Computing 1994;12:487–98.

 [12] Koulaouzidis A, Yung DE, Lam JH, et al. The use of small-bowel capsule endoscopy in iron-deficiency anemia alone; be aware of the young anemic patient. Scandinavian Journal of Gastroenterology 2012;8–9:
- [13] Metzger YC, Adler SN, Shitrit AB, et al. Comparison of a new PillCamTM SB2 video capsule versus the standard PillCamTM SB for detection of small bowel disease. Reports of Medical Imaging 2009;2:7–11.
 [14] Imagawa H, Oka S, Tanaka S. et al. Improved visibility of lesions of the small
- intestine via capsule endoscopy with computed virtual chromoendoscopy. Gastrointestinal Endoscopy 2011;73:299–306.

 [15] Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statis-
- tic Family Medicine 2005:37:360-3
- [16] Kolar A, Romain O, Ayoub J, et al. A system for an accurate 3D reconstruction in video endoscopy capsule. EURASIP Journal on Embedded Systems 2009;71631:7, http://dx.doi.org/10.1155/2009/716317.
- [17] Korniski R, Bae SY, Shearn M, et al. 3D imaging with a single-aperture 3mm objective lens: concept, fabrication, and test. In: Proceedings of SPIE 8129/Novel optical systems design and optimization XIV, vol. 812904. 2011., http://dx.doi.org/10.1117/12.894110.
- [18] Karargyris A, Bourbakis N. Three-dimensional reconstruction of the digestive wall in capsule endoscopy videos using elastic video interpolation. IEEE Transactions on Medical Imaging 2011;30:957-71.
- [19] Koulaouzidis A, Karargyris A. Three-dimensional image reconstruc-tion in capsule endoscopy. World Journal of Gastroenterology 2012;18:
- [20] Liao Z, Gao R, Xu C, et al. Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. Gastrointestinal Endoscopy 2010;71:280-6.
 [21] Spada C, Hassan C, Costamagna G. Virtual chromoendoscopy: will it play a role
- in capsule endoscopy. Digestive and Liver Disease 2011;43:927–8.

 [22] Girelli CM, Porta P, Colombo E, et al. Development of a novel index to dis-
- criminate bulge from mass on small-bowel capsule endoscopy. Gastrointestinal Endoscopy 2011;74:1067–74.
- [23] Barkhoudarian G, Romero AD, Laws ER. Evaluation of the three-dimensional endoscope in transsphenoidal surgery. Neurosurgery 2013 [Epub ahead of
- Kolar A, Romain O, Ayoub J, et al. Prototype of video endoscopic capsule with 3-D imaging capabilities. IEEE Transactions on Biomedical Circuits and Systems 2010:4:239-49.



ORIGINAL ARTICLE: Clinical Endoscopy

Utility of 3-dimensional image reconstruction in the diagnosis of small-bowel masses in capsule endoscopy (with video)

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Background: In small-bowel capsule endoscopy (SBCE), differentiating masses (ie, lesions of higher probability for neoplasia) requiring more aggressive intervention from bulges (essentially, false-positive findings) is a challenging task; recently, software that enables 3-dimensional (3D) reconstruction has become available.

Objective: To evaluate whether "coupling" 3D reconstructed video clips with the standard 2-dimensional (s2D) counterparts helps in distinguishing masses from bulges.

Design: Three expert and 3 novice SBCE readers, blind to others and in a random order, reviewed the s2D video clips and subsequently the s2D clips coupled with their 3D reconstruction (2D+3D).

Setting: Multicenter study in 3 community hospitals in Italy and a university hospital in Scotland.

Patients: Thirty-two deidentified 5-minute video clips, containing mucosal bulging (19) or masses (13).

Intervention: 3D reconstruction of s2D SBCE video clips.

Main Outcome Measure: Differentiation of masses from bulges with s2D and 2D+3D video clips, estimated by the area under the receiver operating characteristic curve (AUC); interobserver agreement.

Results: AUC for experts and novices for s2D video clips was .74 and .5, respectively (P = .0053). AUC for experts and novices with 2D+3D was .70 (compared with s2D: P = .245) and .57 (compared s2D: P = .049), respectively. AUC for experts and novices with 2D+3D was similar (P = .1846). The interobserver agreement was good for both experts and novices with the s2D (k = .71 and .54, respectively) and the 2D+3D video clips (k = .58 in both groups).

Limitations: Few, short video clips; fixed angle of 3D reconstruction.

Conclusions: The adjunction of a 3D reconstruction to the s2D video reading platform does not improve the performance of expert SBCE readers, although it significantly increases the performance of novices in distinguishing masses from bulging. (Gastrointest Endosc 2014;80:642-51.)

Abbreviations: 2D, 2-dimensional; 3D, 3-dimensional; AUC, area under the (ROC) curve; CE, capsule endoscopy; MB, mucosal bulge; ROC, receiver operating characteristic; s2D, standard 2D; SBCE, small-bowel capsule endoscopy.

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Since its introduction in clinical practice in 2001, small-bowel capsule endoscopy (SBCE) has become a prime mode for the evaluation of the small bowel in several clinical settings, such as obscure GI bleeding and Crohn's disease. In this context, SBCE has a high yield of findings and a positive impact on diagnosis and patient management (ie, cost-effectiveness). The most common small-bowel findings (ie, angioectasias, ulcers, and/or luminal stenosis) are easy to recognize and are rarely missed. Conversely, large small-bowel protruding lesions (eg, small-bowel mass lesions) can be missed by capsule endoscopy (CE), and the value of a negative SBCE in excluding sinister small-bowel pathology remains unclear. Furthermore, those of us who routinely read SBCE studies can attest that luminal protrusions in SBCE are a common finding.

The presence of a "mass" can be the result of several processes, for example, mucosal disruption by underlying pathology, a lesion with intact overlying intact mucosa (either because of submucosal or extramural/extrinsic origin), and/or a false-positive finding from bowel contraction, loop angulation, or even intussusception. 10,11 Luminal protrusions with changes in color (erythema) and signs of mucosal disruption (exudates, erosions, and ulcers) are highly suggestive of a neoplastic process; however, in most cases the CE appearance of masses (ie, clinically significant lesions of higher probability for neoplasia) is not dissimilar to that of innocent mucosal bulges (MBs). MBs are defined as round, smooth, large-based luminal protrusions with ill-defined boundaries, resulting either from loop angulations and/or impression from adjacent loops/ structures. 10 They are benign endoscopic findings of no clinical significance, essentially false-positive findings. 1,12 Furthermore, a small-bowel lesion can be depicted only in few frames and/or a mass may only be seen tangentially, and it cannot be sampled or probed. 1.12 Therefore, an accurate distinction between masses and MBs is crucial, because missing a tumor can eventually jeopardize a curative resection and patient prognosis. On the other hand, misclassifying an innocent small-bowel MB as a neoplastic mass may lead to unnecessary, invasive, and-most of the time—expensive procedures. Girelli and Porta 10 noted that a smooth, round, protruding "mass" exhibits the following characteristics when it is associated with the innocent MB: (1) an ill-defined boundary with the surrounding mucosa, (2) a diameter larger than its height, (3) no visible lumen in the frames in which it appears, and (4) an image lasting less than 10 minutes. 10,1

Software tools (eg, flexible spectral imaging color enhancement, Blue mode, and/or suspected blood indicator) have been developed to assist capsule reviewers with so-called difficult to characterize small-bowel lesions. ¹³ Research has been carried out to produce 3-dimensional (3D) reconstruction of the GI tract using stereoscopic vision methods. ¹⁴ However, because of technologic limitations inherit to SBCE (ie, packaging in capsule-size endoscopes and power consumption constraints), ¹⁵ hardware-enabled

Take-home Message

- The distinction between masses and innocent mucosal bulging at small-bowel capsule endoscopy (SBCE) is a difficult task even for experienced readers. The adjunction of a 3D reconstruction software to the standard capsule endoscopy (CE) 2D view significantly improves the performance of novice readers in distinguish between masses and bulging.
- The use of a 3D reconstruction software could be useful in the training of novice CE readers.

3D reconstruction of the intestinal lumen is yet to be available. ¹⁶ Over the last few years, software that enables 3D representation/approximation (Shape-from-Shading) from monocular 2-dimensional (2D) SBCE images has been developed. ¹⁷ This software recovers the shape of objects from 2D images using gradual variation of shading. ¹⁸ Recently, we showed that application of such software in SBCE leads to image enhancement for a significant proportion of vascular and protruding small-bowel lesions. ¹⁹ However, to the best of our knowledge, this reconstruction has been applied only to still images (not to video segments); furthermore, most studies performed thus far focused more on technical aspects (ie, quality of images/visualization) ¹⁹⁻²¹ than on clinical issues (ie, reaching a diagnosis). ²²

In this 2-phase study we aimed to evaluate whether coupling the standard 2D (s2D) video clips with a 3D reconstruction enhanced the performance of SBCE readers (with different level of SBCE experience) in distinguishing masses from innocent MB.

METHODS

Phase 1: choosing the optimal angle for 3D video reconstruction

PillCam SB2 (Given Imaging Ltd, Yoqneam, Israel) captures two 2D frames per second. These images are displayed in sequence, as the relevant proprietary software (RAPID; Given Imaging Ltd, Yoqneam, Israel) generates a video that gives the impression of movement of the capsule through the small bowel. To re-create 3D video clips for the purpose of this study, short 2D video segments were selected and broken down into the frames that constituted them. Individual frames were 3D reconstructed and recompressed to respective 3D videos. For this task, dedicated 3D visualization software was developed in a Mathworks Matlab (MathWorks Inc, Natick, Mass, USA) environment. It should be noted that when a single image is reconstructed in 3D, the user can manipulate the viewing angle and rotate at 360 degrees and zoom in or out, whereas there is no freedom to rotate the viewing angle of all the 3D images stitched together in a 3D video. For this reason, before proceeding with the main evaluation, it was necessary to decide the optimal

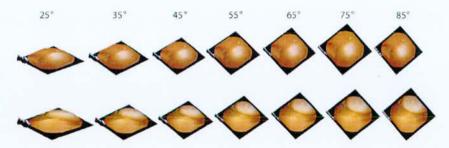


Figure 1. Two 2D SBCE frames reconstructed in 3D using the SfS algorithm at the 7 angles (25, 35, 45, 55, 65, 75, and 85 degrees). 2D, 2-dimensional; SBCE, small-bowel capsule endoscopy; 3D, 3-dimensional; SfS, Shape-from-Shading.

viewing angle for 3D reconstruction of individual frames before they were stitched back again into a 3D video.

To select the best angle for reconstruction, ten 3-minute 2D SBCE videos (containing about 360 frames each) depicting small-bowel luminal protrusions (small-bowel cancer, 1; polyps, 3; bulging, 4; ampulla of Vater, 2) were selected by an expert SBCE reviewer (G.M.), deidentified, and stored in a folder for further processing. For each s2D video clip, a corresponding 3D clip was reconstructed at 25, 35, 45, 55, 65, 75, and 85 degrees by using the aforementioned software. The angles were, to an extent, arbitrarily chosen, because evaluating the full spectrum of angles from 1 to 90 degrees would have been impractical and counterproductive. This resulted in a total of 70 short 3D video clips (Fig. 1).

Three reviewers (A.K., S.D., E.R.), all with extensive experience in SBCE and blinded to each other (but aware of the finding depicted in each video clip), reviewed the clips in random order. Prompted by the question, "Is this 3D reconstructed video clip helpful in facilitating the elevated lesion/structure from the surrounding mucosa in the clip?" they were asked to assign a number between 1 (not helpful) and 5 (very helpful), for each of the 7 different angles of 3D reconstruction of each 2D video. No time limit was used, and each reviewer was allowed to spend as much time as he or she needed to grade the videos. Thereafter, the scores were tallied (the maximum score for each group of ten 3D reconstructed videos, at a certain angle, was 50), and the 3D reconstruction angle with the higher score was used for the rest of 3D video reconstructions in phase 2 of this study (Fig. 2).

Phase 2: evaluation of 3D videos review

Video selection. For phase 2 of this study, 3 gastroenterologists who were experts in SBCE (C.G., M.S., L.F.) selected and deidentified short (5-minute) video clips (from an equal number of SBCE examinations performed in 2 centers: C.G. and L.F., Ospedale Busto Arsizio, Milano; M.S., Ospedale San Carlo Borromeo, Milan, Italy) containing either masses or MBs. If obvious endoscopic markers of possible malignancy (ie, mucosal disruption, surface ulceration, active bleeding) were identified, the videos were excluded. All SBCE examinations were performed with the capsule system used in the first phase of the study. SBCE was carried out after an overnight fast and bowel cleansing by 2 liters of polyethylene glycol solution taken the afternoon before the SBCE investigation. As per manufacturer protocol, liquids are allowed 2 hours into the study and a light meal 4 hours after the ingestion of the capsule endoscope.

Video evaluation. Videos clips were deidentified, encoded to ensure blind review, and stored in a dedicated Dropbox (Dropbox Inc, San Francisco, Calif, USA) folder. The Matlab software reconstructed the 3D videos at the optimal 3D viewing angle (as per the first phase of the study). These videos were uploaded to the shared folder on Dropbox. The folder was shared among the reviewers for easier access.

Two SBCE readers groups were involved in the evaluation: a group of SBCE experts (n = 3; all > 1000 SBCE reviews with > 10 years of experience) and a group of novice readers (n = 3; competent in conventional digestive endoscopy, familiar with the SBCE system, who received training on CE for the purpose of this study, but not completed > 10 SBCE reviews neither working with SBCE in routine clinical practice). The 2 readers groups, with diametrically opposite SBCE exposure, were chosen to examine the potential validity of 3D software as an adjunct tool through the realistic clinical scenarios of limited exposure/learning phase and expert SBCE review. To avoid any possible referral bias in evaluating the video clips, the readers were unaware of the clinical indication to SBCE.

All readers, blind to each other and in a random order, reviewed first the s2D SBCE videos (provided to them in Audio Video Interleave format) and then (5 to 7 days later to minimize the "recall" bias) the combined 2D+3D video clips. In the combined 2D+3D view the reader was able to visualize side to side the 2D and the reconstructed 3D video of the same patient; the reader was free to visualize them in sequence or at the same time and to repeat the visualization several times (Fig. 3, Video 1 [available online at www.giejournal.org]). No time limit was used in the video review phase, and each reviewer was allowed to spend as much time as needed with each video clip. For each case, the diagnosis (mass or MB) reached after

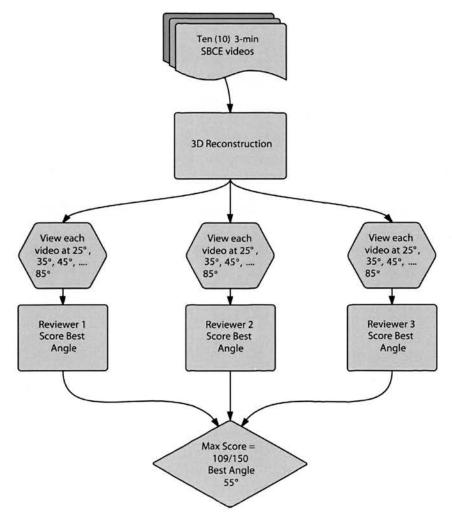


Figure 2. Flowchart of study phase 1. SBCE, small-bowel capsule endoscopy.

s2D and 2D+3D review by each individual reader and the group was compared with that of the reference standard (Fig. 4).

Reference standard

In our study, the presence of a small-bowel mass had to be confirmed by histology (reference standard for positive diagnosis) or excluded after a complete diagnostic workup and/or clinical follow-up (reference standard for negative diagnosis). Therefore, all included patients received an individualized diagnostic workup (including CT enterography and/or magnetic resonance enterography followed by deep enteroscopy or surgical exploration, as necessary) for evaluation of the entire small bowel and specifically the area of interest depicted in SBCE as possible mass/bulging. If after the diagnostic workup no mass was found, patients were clinically followed for a

period of 6 months before medical discharge, and the finding identified by SBCE was therefore defined as an innocent MB.

Statistics

Individual and per-reader group (experts and novices) sensitivity, specificity, and positive and negative likelihood ratios were calculated for each of the reviewers. Diagnostic accuracy (true positive + true negative/true positive + false positive + false positive + false positive + false positive) and precision (true positive/true positive + false positive) were also calculated. In addition, individual and summative receiver operating characteristic (ROC) analysis was undertaken. The ROC curve is initially constructed by plotting the sensitivity and the false positivity (1-specificity) for each reviewer. The ROC curve is constructed to fit these points. The area under the ROC curve (AUC) is then

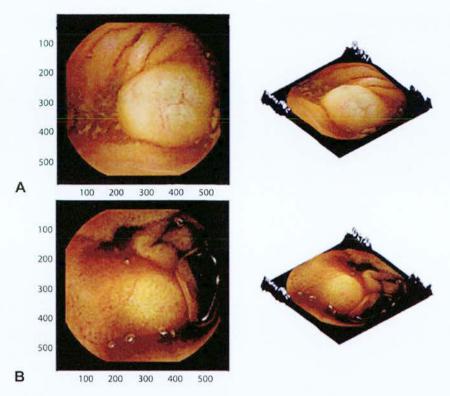


Figure 3. Two SBCE frames depicting a mass (A) and bulging (B) with their corresponding 55-degree 3D reconstruction. SBCE, small-bowel capsule endoscopy; 3D, three-dimensional.

calculated. An AUC close to 1.0 signifies that the test has near perfect discrimination, whereas an AUC close to .5 suggests poor discrimination. $^{\!\!\!\!2^{\!4}}$ The AUC comparison was performed by comparing the square of their standardized difference with the quartiles of the $\chi 2$ distribution. The analyses were performed with Stata 13 (Copyright 1996–2013 StataCorp LP, College Station, Tex) using the function "roccomp" as described in detail elsewhere. $^{\!\!\!\!\!25,20}$

Interobserver agreement, for each group and for each reviewing session, was measured by the kappa statistic using the Randolph's free-marginal multirater kappa; k). Brennan and Prediger²⁸ suggested using free-marginal k when raters are not forced to assign a certain number of cases to each category and using fixed-marginal k when they are. A negative value represents agreement worse than chance, whereas values in the range of 0 to .25, .25 to 0.50, .50 to .75, and .75 to 1.00 represent poor, fair, good and near-perfect agreement, respectively.²⁵

Ethics consideration

This study was conducted in accordance with established research ethics guidelines. After review by the local ethics committee, further specific ethical review and approval were not required because the study was considered an evaluation of previously collected endoscopy images, using data already obtained as part of regular

clinical care. Patients gave their written, informed consent for the studies undertaken a part of clinical workup.

RESULTS

Phase 1: choosing the optimal angle for 3D reconstruction

The 3D video reconstruction at 55 degrees obtained the highest score by each of 3 expert individually (38/50, 28/50, and 33/50, respectively) as well as summative (109/150) and mean score (3.7/5).

Phase 2: distinguishing between mass and bulge (with 3D review)

Thirty-two short videos were selected (25 contributed by C.G. and L.F. and 8 by M.S.). Thirteen of them were classified by the reference standard as depicting masses and 19 MBs. More specifically, 6 neuroendocrine tumors, 5 GI stromal tumors, and 2 adenocarcinomas were finally diagnosed.

The sensitivity, specificity, and positive and negative likelihood ratios for individual reviewers are presented in Table 1. In the 2D video review, the summative diagnostic accuracy/precision for experts and novices were .87/.65 and .79/.5, respectively. In the combined 2D+3D video review,

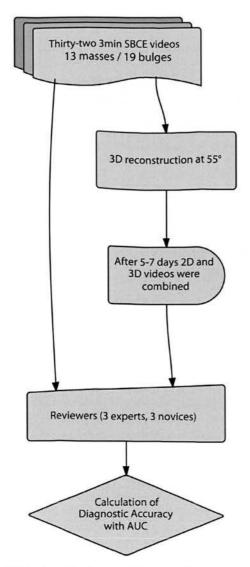


Figure 4. Flowchart of study phase 2. SBCE, small-bowel capsule endoscopy; AUC, area under the (ROC) curve.

the relevant values for experts and novices were .81/.52 and .87/.79, respectively.

The summative AUC for the experts and novices groups for s2D review was .74 and .5, respectively (P=.0053). The summative AUC for the expert and novice groups for combined 2D+3D review was .70 and .57, respectively (P=.1846). Comparing the 2D and the 2D+3D video review, no statistical difference in the AUC was observed among experts, (P=.245), whereas a significant improvement was observed among novices (P=.049). The AUCs (summative ROCs) for each of the 2 CE reviewer groups for the 2D and 2D+3D video reviews are showed in Figure 5 and details of individual assessments in Table 2. For the 2D review, the interobserver agreement (k) of experts and novices was .71 and .54, respectively. For the

2D+3D review, the k value for experts and novices was .58 for both groups.

DISCUSSION

The present study confirms that the distinction between masses and bulges, in the s2D SBCE videos, remains a challenging (even for expert SBCE readers) task; nevertheless, as expected, experienced readers performed better than novices. It is noteworthy that the adjunction of 3D reconstructed video clips to the s2D SBCE reading software did not improve performance of experts (AUC from .74 to .7; P = .245), whereas it significantly improved the performance of novice readers (AUC from .5 to .57; P = .049). However, it should be noted that when a false-negative diagnosis (per evaluation, not per case) was examined, 3D led to a marked reduction from 6 to 1 in the experts group, whereas in the novice group the application of 3D false negative resulted in an increase of false-negative evaluations by 13% (from 13 to 15). False negatives are considered to be crucial in this scenario, because they are likely to lead to a situation where further essential workup and therapy (for a clinically significant lesion) is held back. Of course, the spotlight here is on the expert group, because no one would expect that novices would have to read/interpret SBCE on their own, especially at this stage in their SBCE training.

Since the advent of wireless CE, the small-bowel tumor detection rate has risen to 2% to 9% in those presenting with obscure GI bleeding. The greatest increase was seen in carcinoid tumors, followed by lymphomas and adenocarcinomas. 12,30 Nevertheless, several studies showed that SBCE can miss large (often sinister) protruding mucosal lesions. 5.9 Moreover, it has been shown that both the interobserver agreement and the detection rate of significant findings are low, regardless of the readers' experience. 31,32 A plausible explanation is that in conventional endoscopy, air insufflation (together with the ability to probe and/or take biopsy specimens) is helpful in distinguishing between masses and innocent MBs, whereas in CE this "luxury" is lacking. Hence, false-positive findings are not uncommon, and the differentiation between masses and bulges in SBCE is still challenging. 12 This is clearly demonstrated in our study by the performance of expert reviewers in evaluating s2D video clips, where the summative diagnostic accuracy is high, albeit < 90%. This is even more evident in the novice group, with a significant lower accuracy and AUC than the experts, confirming that experience seems to be a key factor in CE, influencing the correct evaluation of difficult findings.

To overcome the aforementioned confounders, a couple of novel indices/scoring systems (aiming to discriminate a MB from a mass on CE) have been developed. Shyung et al³³ reported a score composed of 5 parameters (ie, bleeding, mucosal disruption, irregular surface, color,

TABLE 1. Performances (sensitivity, sp	ecificity, and positive and ne	gative likelihood ratios)	of novices and experts in reading 2D
and 2D+3D reconstructed videos			

Reviewer	2D	2D+3D	2D	2D+3D	2D	2D+3D	2D	2D+3D
	Sensitivity (%)	Sensitivity (%)	Specificity (%)	Specificity (%)	(+)LR	(+)LR	(-)LR	(-)LR
	s (95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
Expert 1	83	100	90	84	83	100	90	84
	(70.0-96.0)	(90.6-100.0)	(79.6-100.0)	(71.3-96.7)	(70.0-96.0)	(90.6-100.0)	(79.6-100.0)	(71.3-96.7)
Expert 2	83	100	90	63	83	100	90	63
	(70.0-96.0)	(90.6-100.0)	(79.6-100.0)	(46.3-79.9)	(70.0-96.0)	(90.6-100.0)	(79.6-100.0)	(46.3-79.9)
Expert 3	83	92	85	79	83	92	85	79
	(70.0-96.0)	(82.6-100.0)	(72.6-97.4)	(64.9-93.1)	(70.0-96.0)	(82.6-100.0)	(72.6-97.4)	(64.9-93.1)
Novice 1	85	69	68	84	85	69	68	84
	(72.6-97.4)	(53.0-85.0)	(52.8-84.0)	(71.3-96.7)	(72.6-97.4)	(53.0-85.0)	(52.8-84.0)	(71.3-96.7)
Novice 2	69	64	84	100	69	64	84	100
	(53.0-85.0)	(47.4-80.6)	(71.2-96.7)	(90.6-100.0)	(53.0-85.0)	(47.4-80.6)	(71.2-96.7)	(90.6-100.0
Novice 3	46	46	89	89	46	46	89	89
	(28.7-63.3)	(28.7-63.3)	(78.1-99.8)	(78.1-99.8)	(28.7-63.3)	(28.7-63.3)	(78.1-99.8)	(78.1-99.8)

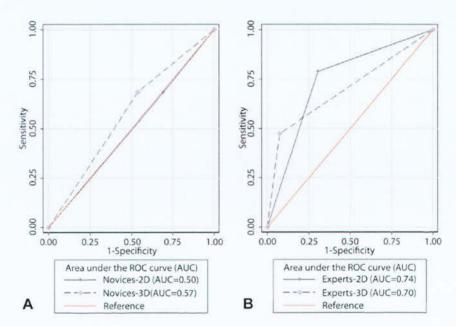


Figure 5. ROC curves of video reading with s2D and 2D+3D for novices (A) and experts (B), respectively. ROC, receiver operating characteristic; s2D, standard 2-dimensional; 3D, 3-dimensional.

and the presence of white villi). A small-bowel mass lesion is probable with a score ≥ 4 , whereas a score ≤ 2 indicates a low probability of a sinister lesion. However, this index takes into account "high-risk" features such as bleeding, mucosal disruption, and irregular mucosal surface (ie, clear endoscopic markers of malignancy, adopted in the consensus statement [2006/2007] of a panel of international experts in CE as helpful discriminators 11). Girelli et al $^{5+}$ proposed the Smooth Protruding Index on Capsule

Endoscopy score ¹² in which a score > 2 has 83% sensitivity and 89% specificity for tumors. Other attempts to differentiate tumors on CE include an automated scale that uses wavelet-based analysis in CE images; this has a reported 95% sensitivity and specificity. ^{12,35} Conversely, flexible spectral imaging color enhancement offers no benefit in this setting over the standard reviewing mode. ^{55,36}

Therefore, we thought that software offering 3D reconstruction, and hence emphasizing certain endoscopy

Video case	Expert 1		Expert 2		Expert 3		Novice 1		Novice 2		Novice 3	
REVIEW mode	s2D	2D+3D										
Bulge	0			0		•	0	0	0		0	
Bulge	0	0	•		0		0	•	•	•	0	0
Bulge	0		0	0	0	0	0		•		0	0
Bulge	0		0		0	0	0	0		0	0	0
Bulge		0		0	0	0	0	0	0	•		0
Bulge	0		0		0		0		•	0		
Bulge	-				0		•	0		0		0
Bulge	0		0	0	0	•	0	0	9	0		0
Bulge				0	0	•		0		0		0
Bulge	0	0	0	•	0	•	0	0	0	0	0	0
Bulge	0	0	0	0	0	0	0	•	0	0	0	
Bulge	0	0	0	0	0		0		0	0	0	0
Bulge	0		0	0	0	0	0	•	0	0	•	0
Bulge	0	0	0		0	0		0	0	0	0	0
Bulge	•		•		0		0		0			
Bulge					0		0		•			
Bulge	0		0		0		•	0	•		0	0
Bulge			0		0							
Bulge	0					0				0	•	
Mass	-0-		0		-		-		-		-	0
Mass	0	0	0	0	. 0	0	0	0	0	0	0	0
Mass	0	0	0	0	0	0	0	0	•	0	0	0
Mass	0	0	0	0	0	0	0	0	0	0	0	0
Mass	0		0	0	0	0	0		0	0	0	0
Mass	0	•	0	0	0	•	0	0		0	0	0
Mass	0	0	•			0	0	•		0	0	0
Mass	0	0	•	0	0	•	0		0	0	0	0
Mass		•	0	0	0	0		0	•	0		
Mass			0	0	0	0	0		0	0	•	0
Mass		0	0	0	0	0	0	0	0	0	0	0
Mass	_0_											
Mass	0		0	0		0		•	0	0	0	0

features such as the perception of depth and volume differences between the objects, could allow resolution of diagnostic dilemmas in such a setting. Furthermore, to the best of our knowledge, all previous studies on 3D reconstruction were performed with individual frames/images. Most of these studies focused on technical issues (ie, image quality, visualization) rather than on clear clinical issues. ¹⁹⁻²¹ It is well known that in CE the video component

is as crucial in final interpretation (MB flattens with peristalsis) as cautious reviewing of still frames. Our data suggest that although 3D software does not have any significant impact on accurately discriminating masses from bulges (when expert readers are involved), it can potentially allow them to reduce the false-negative evaluations by 83%. One can argue that the level of expertise of those involved in this study (experts > 1000 SBCE

reviews and > 10 years clinical experience) negatively biased the contribution of the new software in this subgroup. Furthermore, the fact that they are accustomed to working with the s2D software explains why the new feature might be challenging.³⁷

On the other hand, we selected novices who were already familiar with the s2D and received training similar to that proposed by ASGE²³ but were beginners at using CE. Therefore, our results suggest that although the new software cannot substitute clinical and SBCE experience (even after the 3D reconstruction, novices' performance was poorer than those of experts), it may be helpful in the training phase by potentially shortening the learning curve. Furthermore, the combination of other enhancement tools such as Blue mode³⁸ might improve the performance of 3D reconstruction. Moreover, similar to the inclusion of the Lewis Score calculator, we recommend that an atlas and scoring systems (ie, Smooth Protruding Index on Capsule Endoscopy) are embedded in commercially available reading software to assist expert and novice readers in achieving higher performance.

This study has some limitations, including small sample size (a consequence of the relative rarity of small-bowel tumors) and the inflexibility of the selected video clips review (short video clips in Audio Video Interleave format; it was not possible to modify review speed or change the angle of view). In addition, we decided to include only patients whose diagnosis was confirmed by a widely accepted "hard" reference standard. Consequently, we selected cases by excluding all those with endoscopic high-risk "stigma" of mass lesions. Another possible limitation is a bias introduced by the combined evaluation of the 3D reconstruction and the s2D, instead of the 3D reconstruction alone, of which we were fully aware. Nevertheless, we decided to combine 2D with 3D because the reconstruction of an 8-hour-long video in 3D would require considerable time and resource.

Our goal was to simulate a clinical scenario, similar to that of other advanced endoscopic features (ie, narrow-band imaging [NBI], iSCAN, flexible spectral imaging color enhancement) where the reader evaluates the video in the s2D mode and applies the new feature (in our study, 3D reconstruction) to a region of interest. The first phase of the study was performed to overcome issues with image angle of view. However, we cannot be certain that the angle chosen for 3D applies to all lesions depicted in this current study. Nevertheless, this means there are areas of future research in the use of 3D alone or in combination with other software tools.³⁹

In conclusion, the results of the present study confirm that the distinction between masses and MBs in SBCE is still a challenging task even for experienced readers. In this situation, review experience seems to have a primary role. However, the adjunct of 3D reconstruction to the s2D video reading software significantly improves the performance of novice SBCE readers in distinguishing masses

from MBs, thus potentially shortening their learning curve and leading to a reduced rate of false-negative diagnoses in expert hands. Further studies are needed to test the feasibility of 3D reconstruction in clinical practice and to evaluate the impact on the reviewing process in terms of both time and diagnostic yield.

REFERENCES

- ASGE Technology Committee, Wang A, Banerjee S, Barth BA, et al. Wireless capsule endoscopy. Gastrointest Endosc 2013;78:805-15.
- Gerson LB. Small bowel endoscopy: cost-effectiveness of the different approaches. Best Pract Res Clin Gastroenterol 2012;26:325-35.
- Marmo R, Rotondano G, Rondonotti E, et al. Capsule enteroscopy vs. other diagnostic procedures in diagnosing obscure gastrointestinal bleeding: a cost-effectiveness study. Eur J Gastroenterol Hepatol 2007;19:535-42.
- Lewis BS, Eisen GM, Friedman S. A pooled analysis to evaluate results of capsule endoscopy trials. Endoscopy 2005;37:960-5.
- Postgate A, Despott E, Burling D, et al. Significant small-bowel lesions detected by alternative diagnostic modalities after negative capsule endoscopy. Gastrointest Endosc 2008;68:1209-14.
- Ross A, Mehdizadeh S, Tokar J, et al. Double balloon enteroscopy detects small bowel mass lesions missed by capsule endoscopy. Dig Dis Sci 2008:53:2140-3.
- Baichi MM, Arifuddin RM, Mantry PS. Small-bowel masses found and missed on capsule endoscopy for obscure bleeding. Scand J Gastroenterol 2007;42:1127-32.
- Chong AK, Chin BW, Meredith CG. Clinically significant small-bowel pathology identified by double-balloon enteroscopy but missed by capsule endoscopy. Gastrointest Endosc 2006;64:445-9.
- Zagorowicz ES, Pietrzak AM, Wronska E, et al. Small bowel tumors detected and missed during capsule endoscopy: single center experience. World J Gastroenterol 2013;19:9043-8.
- Girelli CM, Porta P. Bulge or mass? A diagnostic dilemma of capsule endoscopy. Endoscopy 2008;40:703-4.
- Mergener K, Ponchon T, Gralnek I, et al. Literature review and recommendations for clinical application of small-bowel capsule endoscopy, based on a panel discussion by international experts. Consensus statements for small-bowel capsule endoscopy, 2006/2007. Endoscopy 2007;39:895-909.
- Islam RS, Leighton JA, Pasha SF. Evaluation and management of smallbowel tumors in the era of deep enteroscopy. Gastrointest Endosc 2014;79:732-40.
- Koulaouzidis A, Rondonotti E, Karargyris A. Small-bowel capsule endoscopy: a ten-point contemporary review. World J Gastroenterol 2013;19: 3726-46.
- Kolar A, Romain O, Ayoub J, et al. Prototype of video endoscopic capsule with 3-d imaging capabilities. IEEE Trans Biomed Circuits Syst 2010;4:239-49.
- Woods SP, Constandinou TG. Towards a micropositioning system for targeted drug delivery in wireless capsule endoscopy. Conf Proc IEEE Eng Med Biol Soc 2011;2011:7372-5.
- Koulaouzidis A, Karargyris A. Three-dimensional image reconstruction in capsule endoscopy. World J Gastroenterol 2012;18:4086-90.
- Karargyris A, Bourbakis N. Three-dimensional reconstruction of the digestive wall in capsule endoscopy videos using elastic video interpolation. IEEE Trans Med Imaging 2011;30:957-71.
- Karargyris A, Rondonotti E, Mandelli G, et al. Evaluation of 4 threedimensional representation algorithms in capsule endoscopy images. World J Gastroenterol 2013;19:8028-33.
- Koulaouzidis A, Karargyris A, Rondonotti E, et al. Three-dimensional representation software as image enhancement tool in small-bowel capsule endoscopy: a feasibility study. Dig Liver Dis 2013;45:909-14.
- Prasath VB, Figueiredo IN, Figueiredo PN, et al. Mucosal region detection and 3D reconstruction in wireless capsule endoscopy videos using active contours. Conf Proc IEEE Eng Med Biol Soc 2012;2012:4014-7.

- Fan Y, Meng MQ, Li B. 3D reconstruction of wireless capsule endoscopy images. Conf Proc IEEE Eng Med Biol Soc 2010;2010:5149-52.
- Ciaccio EJ, Tennyson CA, Bhagat G, et al. Use of shape-from-shading to estimate three-dimensional architecture in the small intestinal lumen of celiac and control patients. Comput Methods Programs Biomed 2013;111:676-84.
- ASGE Training Committee 2011-2012, Rajan EA, Pais SA, et al. Smallbowel endoscopy core curriculum. Gastrointest Endosc 2013;77:1-6.
- Harrell FE Jr, Lee KL, Mark DB. Tutorial in biostatistics multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361-87.
- DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837-45.
- Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983:148:839-43.
- Randolph JJ. Online kappa calculator. Available at: http://justus.randolph. name/kappa, 2008.
- Brennan RL, Prediger DJ. Coefficient kappa: some uses, misuses, and alternatives. Educ Psychol Measure 1981;41:687-99.
- Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-74.
- Rondonotti E, Pennazio M, Toth E, et al. Small-bowel neoplasms in patients undergoing video capsule endoscopy: a multicenter European study. Endoscopy 2008;40:488-95.

- Rondonotti E, Soncini M, Girelli CM, et al. Can we improve the detection rate and interobserver agreement in capsule endoscopy? Dig Liver Dis 2012;44:1006-11.
- Zheng Y, Hawkins L, Wolff J, et al. Detection of lesions during capsule endoscopy: physician performance is disappointing. Am J Gastroenterol 2012;107:554-60.
- Shyung LR, Lin SC, Shih SC, et al. Proposed scoring system to determine small bowel mass lesions using capsule endoscopy. J Formos Med Assoc 2009;108:533-8.
- Girelli CM, Porta P, Colombo E, et al. Development of a novel index to discriminate bulge from mass on small-bowel capsule endoscopy. Gastrointest Endosc 2011;74:1067-74.
- Kobayashi Y, Watabe H, Yamada A, et al. Efficacy of flexible spectral imaging color enhancement on the detection of small intestinal diseases by capsule endoscopy. J Dig Dis 2012;13: 614-20.
- Duque G, Almeida N, Figueiredo P, et al. Virtual chromoendoscopy can be a useful software tool in capsule endoscopy. Rev Esp Enferm Dig 2012;104:231-6.
- Prasad V, Cifu A. Medical reversal: why we must raise the bar before adopting new technologies. Yale J Biol Med 2011;84:471-8.
- Krystallis C, Koulaouzidis A, Douglas S, et al. Chromoendoscopy in small bowel capsule endoscopy: Blue mode or Fuji Intelligent Colour Enhancement? Dig Liver Dis 2011;43:953-7.
- lakovidis DK, Maroulis DE, Karkanis SA. An intelligent system for automatic detection of gastrointestinal adenomas in video endoscopy. Comput Biol Med 2006;36:1084-103.

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