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**Small-bowel capsule endoscopy: A Ten-table contemporary review**

Koulaouzidis A *et al*. Tabulated review on capsule endoscopy

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**Abstract**

The introduction of capsule endoscopy (CE) in clinical practice increased the interest for the study of the small-bowel. Consequently, in about 10 years, an impressive quantity of literature -on indications, diagnostic yield (DY), safety profile and technical evolution of CE- has been published as well as several reviews. At present time, there are 5 small-bowel capsule enteroscopy (SBCE) models in the worldwide market. Head-to-head trials have showed –in the great majority of studies- comparable results in terms of DY, image quality and completion rate. CE meta-analyses formed the basis of national/international guidelines; these guidelines place CE in a prime position for the diagnostic work-up of patients with OGIB, known and/or suspected Crohn’s and possible small-bowel neoplasia. A 2-l PEG-based purge, administered the day before the procedure, is the most widely practiced preparation regimen. Whether this regimen can be further improved (*i.e.,* by further decreasing its volume, changing the timing of administration, coupling it with prokinetics and/or other factors) or if it can really affect the DY, is still under discussion. Faecal calprotectin has been used in SBCE studies in two settings: in patients taking NSAIDs, to evaluate the type and extent of mucosal damage and, more importantly from a clinical point of view, in patients with knowNSuspected Crohn’s disease for assessment of inflammation activity. Although there is still a lot of debate around the exact reasons of SBCE poor performance in various small-bowel segments, it is worth to remember that the capsule progress is non-steerable, hence more rapid in the proximal than in lower segments of the small-bowel. Capsule aspiration -a relatively unexpected complication- has been reported with increasing frequency. This is probably related with the increase in the mean age of patients undergoing CE. CE video review is a time-consuming procedure. Therefore, several attempts have been made to develop technical software features, in order to make CE video analysis easier and shorter (without jeopardizing its accuracy). Suspected Blood Indicator (SBI), QuickView and FICE are some of the software tools that have been checked in various clinical studies to date.

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**Key words:** Capsule endoscopy; Calprotectin; Meta-analysis; Review; Preparation; Reading software; Complication; Indications

**Core tip:** This innovative, concise and “unique” review (structured as Q and A with several tables that make this paper very easy to read and hopefully enjoyable), keeps narrative text to the necessary minimum, in order to guide the reader to consult the wealth of information included in tabulated form. These tables are the outcome of the authors’ personal endeavor to compile in a detailed, yet easy to refer way, information that has often been overlooked by the plethora of similar reviews and/or info on contentious issues in capsule enteroscopy. We believe that this document can be used as reference for study, in reference lists of future manuscript and as important guide for future clinical research on the field.

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**INTRODUCTION**

An early conceptual abstract on capsule endoscopy (CE), entitled “An endorobot for flexible endoscopy, a feasibility study”, was published in 1994[1]. Then, in 1997 two groups of pioneers, initially working independently in Israel and London, joined forces to achieve wireless endoscope[2]. Three years later, in the Digestive Disease Week meeting of the millennium and almost concurrently in Nature[3], Paul Swain presented the world’s first wireless capsule endoscope.

Indeed, the brainchild of Iddan *et al*[4] has revolutionised the field of gastrointestinal (GI) diagnostics, turning into reality the concept of painless and wireless endoscopy. Furthermore, the introduction of CE in clinical practice increased the interest for the study of the small-bowel. Consequently, in about 10 years, an impressive quantity of literature -on indications, diagnostic yield (DY), safety profile and technical evolution of CE- has been published as well as several reviews. Therefore, we aim to focus readers’ attention on some current and contentious issues, often missed from similar reviews on the field. We herein present (in a comprehensive yet user-friendly manner) a systematic review of the current literature in a form of question-and-answer. We expect CE readers, of all experience levels, will find this review useful as a source of further reading and reference.

**WHICH ARE THE DIFFERENCES AMONG THE CURRENT COMMERCIALLY AVAILABLE CAPSULES?**

Since 2001, the year of approval by the FDA of the first video capsule with the prophetic, yet slightly unfortunate, brand name mouth-to-anus (M2A®; Given®Imaging, Yoqneam, Israel), a total of more than 2000000 capsules have been ingested worldwide[5]. Furthermore, over the last decade, technology has improved in the field of CE as competition has become quite stiff. At present time, there are 5 small-bowel capsule enteroscopy (SBCE) models in the market worldwide (Table 1)[5,6]. Although similar in size and shape, they differ on several technical aspects. Of the 5 SBCE, four are in widespread use, although most of the published literature studies are with PillCam®. Nevertheless, head-to-head trials have showed –in the great majority of studies– comparable results in terms of DY, image quality and completion rate (CR) (Table 2)[7-11].

**DO HIGH-GRADE EVIDENCE SUPPORT THE USE OF CAPSULE ENDOSCOPY IN CLINICAL PRACTICE?**

In recent years, many authors[12-14] reviewed systematically the validity of SBCE in clinical practice. Out of this evidence base, it clearly emerges that in daily practice the leading indications for CE are: gastrointestinal (GI) bleeding of obscure origin (OGIB accounts for 60%-70% of all SBCE examinations world-wide), and Crohn's disease (CD; known and/or suspected). Other clinical indications, although less common, are coeliac disease and clinical suspicion of small-bowel neoplasia[15,16]. Therefore, we decided to summarize (Table 3) [17-32],the results of the more robust -from a methodological point of view- publications which addressed the role of CE in the field of OGIB, CD and coeliac disease. These meta-analyses have formed the basis of national/international guidelines, which place CE in a prime position for the diagnostic work-up of patients with OGIB, known and/or suspected CD and possible small-bowel neoplasia[33-36].

**WHICH IS THE BEST PREPARATION REGIMEN FOR SMALL-BOWEL CAPSULE ENDOSCOPY?**

This certainly is one of the most contentious issues in CE. Since the introduction of CE in clinical practice, it was clear that small-bowel cleanliness is one of the key factors (as in fact is often the case for endoscopic examinations) to guarantee high diagnostic performance. Thus far, several studies have been performed in order to test whether the administration of different purgatives and/or prokinetics would impact on small-bowel cleanliness. It is noteworthy that these studies are rather heterogeneous in terms of type of laxatives administered, dosages and/or administration schedule (Table 3)[22,25,30]. Furthermore, in some studies laxatives and prokinetics were administered concurrently, which is probably a further source of bias. Essentially, the current evidence base suggests that a preparation regimen based on laxatives (more specifically polyethylene glycol; PEG) is more effective -than fasting alone- in improving the small-bowel mucosa visualization. Among the PEG-based laxatives, a low volume schedule seems to be at least equally effective than high volume regimens[25,30]. Therefore, a 2-l PEG-based purge, administered the day before the procedure, is the most widely practiced preparation regimen. Whether this regimen can be further improved (*i.e.,* by further decreasing its volume, changing the timing of administration, coupling it with prokinetics and/or other pharmaceutical factors) or if it can really affect the DY, is still under discussion[37].

**IS THERE A ROLE FOR FAECAL CALPROTECTIN AS “SELECTION TEST” FOR CAPSULE ENDOSCOPY?**

Due to its high DY and its negative predictive value (NPV), CE has shown remarkable cost-effectiveness[38]. However, CE still remains less widely available and likely more expensive, when compared to other diagnostic modalities for the small-bowel[39]. Furthermore, although CE is generally considered overall a safe modality, it can lead to severe complications (capsule retention in some patients’ subgroups is reported as high as 15%[13-15, 40]. Consequently, any tool or methods that allows selection of candidates, hence a more targeted and/or smooth “delivery” of SBCE, is a welcome approach. However, any pre-CE selection tool should be easy to perform, safe, inexpensive and fast[41]. In light of all these issues, faecal inflammation tests[of which, faecal calprotectin (FC) is the more widely available] have been proposed. In fact, FC has been used in SBCE studies in two settings: in patients taking NSAIDs, to evaluate the type and extent of mucosal damage (Table 4)[41-44] and, more importantly from a clinical point of view, in patients with knowNSuspected Crohn’s disease for assessment of inflammation activity (Table 4)[45-48]. In these patients, although there is no clear agreement on a cut-off level, faecal calprotectin seems to be a cost-effective “screening test”, able to identify those with higher possibility to present small-bowel lesions.

**HAS CAPSULE ENDOSCOPY THE SAME DIAGNOSTIC CAPABILITY ACROSS THE SMALLBOWEL?**

There are several papers, mostly case presentations and/or case series, reporting patients in whom capsule endoscopy failed to identify small-bowel lesions which were subsequently diagnosed by other modalities[49-52]. Such missed lesions (including neoplastic pathology) were occasionally large and often located in the proximal small-bowel[50, 51]. Although there is still a lot of debate around the exact reasons of poor SBCE performance[53], it is worth to remember that the non-steerable capsule progress is more rapid in the proximal than in lower segments of the small-bowel[53]; furthermore, opaque bile secretions and/or intra-luminal content might consequently hamper/prevent detailed mucosa visualization. Table 5 summarises all studies reporting the number of exams in which one of the few small-bowel landmarks, the ampulla of Vater (AoV), was visible during CE[54-66]. Hence, this evidence base provides an indirect confirmation of the limitations of SBCE in evaluating the proximal small-bowel. Interestingly, even in earlier studies[54] which have not been confirmed since by other investigators, the AoV was missed in >50% of SBCE examinations. This is obviously an important drawback, especially when SBCE is used as surveillance tool, in patients with small-bowel polyposis syndromes.

**CAPSULE ENDOSCOPE ASPIRATION, HOW COMMON IS THIS COMPLICATION?**

Capsule enteroscopy is generally considered safe, having an overall complication rate of about 1%-3%[13,14]. Undoubtedly, the most feared complication of CE is capsule retention in the small bowel (overall retention rate 1.5%-2%), which seems directly related with the clinical indication for SBCE[13,14,40]. Interestingly enough, other possible complications -which were postulated at the time of CE introduction (*i.e.,* retention inside colonic diverticula, interaction with pacemakers etc.) to represent potential hurdles for the method, were shown to be very infrequent and/or without clinically relevant consequences[67-71]. Conversely, capsule aspiration -a relatively unexpected complication- has been reported with increasing frequency (Table 6)[72-93]. Overall, this is probably related with the increase in the mean age of patients undergoing CE. In fact, capsule aspiration occurs in 1 out of 800-1000[88] procedures, mostly in elderly male patients with co-morbidities and/or swallowing disorders. In the majority of cases capsule aspiration resolves quickly, because patients expectorate the capsule. However, in selected cases, emergency bronchoscopy is required. Thus far, only one fatality-directly associated with capsule aspiration- has been reported[90].

**CAN WE SHORTEN OUR READING TIME IN CAPSULE ENDOSCOPY?**

Few will disagree with the notion that CE is a time-consuming procedure. In fact, although capsule administration and swallowing requires only a couple of minutes, SBCE transit through the small bowel -although variable- on overage lasts about 2-5 h[93]. This results in 14400-72000 frames, depending on capsule frame rate (Table 1). This large amount of visual information requires careful evaluation by the CE reader. In addition, any small-bowel lesion may only be visible in just a few or even in a single frame[94]. Therefore, focused and undivided attention is required for the entire duration of each CE video evaluation. 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 jeopardising its accuracy). The first software feature designed for this purpose was the Suspected Blood Indicator (SBI), 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-coloured lesions. Nevertheless, the accuracy profile of this tool (Table 7) is suboptimal and, at present time, it can be used only as supportive tool[95-101].

Given®Imaging Ltd. has also introduced another software tool, which aims specifically at shortening the CE reading time, the Quick View. This sampling tool is able to select one frame every **X** CE frames (the sampling rate can be set by the reader) and therefore present, with the click of a tag-button, a shortened CE video which can be reviewed in a few minutes. Although the sampling method of the Quick View system is only quantitative**,** it has showed a promising sensitivity and specificity in identifying small-bowel lesions (Table 8), and reveals promising potential when coupled with other image enhancing systems[102-111]. Olympus has similar software function (express mode) and we are aware of a single relevant study with very similar results[112].

In the last few years, Given®Imaging Ltd, through a collaboration with Fujinon Inc., Japan introduced the electronic chromo-endoscopy (FICE: Fujinon Intelligent Chromo Endoscopy) in the field of capsule enteroscopy. Data available thus far, show that application of FICE in SBCE videos, leads to improved image quality and definition of the surface texture of small-bowel lesions (Table 9)[113-118]. Although this seems to facilitate the detectability of small-bowel findings, it is still under question whether it proves to be clinically significant[119]. Similar function from Olympus Inc., shows promising results[120].

**WHAT’S NEW ON THE FIELD OF SMALL-BOWEL CAPSULE ENDOSCOPY?**

As aforementioned, there are differences among different capsule models (Table 1). Since its introduction in clinical practice in 2001, CE technology has been significantly. For instance, battery life is longer, image capture frame rate has increased, angle of view is now wider, light control has been optimized, and many real time viewing systems are now available. Nevertheless, these impressive advancements, do not allow overcoming the main current limitation of CE, *i.e.,* uncontrolled propulsion; CE relies totally on natural bowel peristalsis *i.e.,* it still remains a rather “passive” diagnostic technique.

Several research groups are working to design brand new capsules able to actively move or to be remotely manoeuvred through their descent in the small bowel[123]. These new capsules would allow not only recognizing a small bowel lesion but also, in a near future, to collect targeted tissue samples or to deliver drugs (Table 10)[124-141].

**CONCLUSION**

Since CE introduction in clinical practice in 2001, over 1500 papers -focused on SBCE- have been published (PubMed search 17/03/2012; keyword term: "small bowel capsule endoscopy"; available from <http://www.ncbi.nlm.nih.gov/pubmed/?term=small+bowel+capsule+endoscopy>).

Out of those, <20% are clinical trials; case reports and reviews account for about 40% of published evidence. As the amount of information has increased exponentially –and in fact continues to do so-[12], it is often difficult for the busy clinician to retrieve and filter data or extract answers to questions arising from the daily clinical practice. In the present review, we opted to answer certain pertinent questions on contentious and important issues in CE through comprehensive tables. Essentially, we aim to present an easy-to-read review with all the necessary evidence to support opinions expressed herein.

The analysis of the publications listed in the tables clearly demonstrates how SBCE, although much "younger" than other endoscopic techniques, has found a definite role in the diagnostic work-up of certain patient-subgroups. Further success of this modality depends not only on continuous technological progress (*i.e.,* introduction of new capsule models, improved battery life and /or development of new reading software features)[142] but also on the search for new diagnostic strategies, aiming to select for SBCE those patients with higher potential for positive DY[32,45,81,111,117].

Certain issues (*i.e.,* best small-bowel preparation for CE[143], occurrence of some potentially life-threatening complications, visualisation quality of the proximal small-bowel) remain open and they will –surely- be the target of further clinical studies and technical improvements.

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**P-Reviewer** Driscoll D **S-Editor** Wen LL  **L-Editor**  **E-Editor**

**Table 1 Available types of small-bowel capsule endoscopes and operating characteristics**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Capsule device** | **Company** | **Country** | **Field of view (°)** | **Lens** | **LEDs** | **Image sensor** | **Transmission** | **Frames per second (fps)** | **Dimensions (mm)** | **Weight (g)** | **Battery life (h)** | **Real-time imager** | **FDA approval** | **Reviewing software** | **Optical**  **enhancements** |
| PillCam®SB2 | Given®Imaging, Yokneam | Israel | 156 | Multi-element | 4 | CMOS | Radiofrequency | 2-41 | 11 × 26 | 3.45 | 9->11.5**2** | yes | yes | *Rapid*®v7 | Blue-mode  FICE 1,2,3 |
| MiroCam®v2 | IntroMedic®Co., Seoul | Korea | 170 | N/A | 4 | CMOS | EFP | 3 | ø11 × 24 | 3.2 | 12 | yes | yes | MiroView®v2 | ALICE  Colour-Mode |
| EndoCapsule® | Olympus© Co., Tokyo | Japan | 145 | N/A | 4 | CCD | Radiofrequency | 2 | ø11 × 26 | 3.45 | 10 | yes | yes | OLYMPUS®WS-1 | Contrast imaging |
| OMOM®  (SmartCapsule) | Chongding Jinshan Science and Technology Co., Beijing | China | 140 | N/A | 4 | CCD | Radiofrequency | 2 (variable) | 13 ×27.9 | 6 | 8 | yes | no | OMOM® workstation | N/A |
| CapsoCam®SV1 | CapsoVision® Inc., Saratoga | USA | 360 | N/A | 16 | N/A | On-board EPROM Flash Memory (USB) | 16 (4 per camera) | 11 × 31 | N/A | 15 | no | no | CapsoView® | N/A |

1PillCam®SB2 (L) captures 2 fps - PillCam®SB2-4 captures 4fps; 2PillCam®SB2 (L) battery life > 11.5h - PillCam®SB2-4 battery life 8 h. CMOS: Complementary metal–oxide–semiconductor; CCD: Charge-coupled device; FDA: Food and Drug Administration; FICE: Fujinon Intelligent Chromo Endoscopy; EFP: Electric Field Propagation; ALICE: colour mode for MiroView; USB: Universal Serial Bus. N/A: Not available.

**Table 2 Head-to-head trials of small-bowel capsule endoscopy systems**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Country** | **Centre** | **Objective/s** | **Study type** | **Design** | **CE type** | **Outcome/s** | **Conclusion** |
| Hartmann *et al*[7] | Germany | Single centre | Head-to-head evaluation of technical performance and DY of two CE systems (PillCam®SB *vs* EndoCapsule®) | Prospective | ►OGIB pts  ►Pts randomized to undergo 2 CEs using different CE in random order | ►PillCam®SB (Given®Imaging, Yoqneam, Israel)  ►EndoCapsule® (Olympus© America, Allentown, Pa) | ►Pts enrolled: 40  ►CR: PillCam®SB 33/40 (82%); EndoCapsule® 40/40 (100%); *P*=NS  ►Overall DY: PillCam®SB 26/50 (52%); EndoCapsule® 29/50 (58%); *P*=NS  ►DY (SB P2): PillCam®SB 22/50 (44%); EndoCapsule® 25/50 (50%); *P*=NS  ►In all discordant SB P2findings (not detected by the PillCam®SB but detected by EndoCapsule®), PillCam® SB examinations were incomplete | ►Statistically non-significant trend for EndoCapsule® to detect more bleeding sources in pts with suspected small-bowel bleeding than PillCam®SB  ►This is (likely) due to the longer recording time with EndoCapsule® |
| Cave *et al*[8] | USA | Multicentre  (4 centres) | Comparison of performance  (DY in pts with OGIB):  EndoCapsule® *vs* PillCam®SB | Prospective | ►OGIB pts  ►EndoCapsule® and PillCam®SB swallowed by each participant 40 min apart  ►Ingestion of CEs in randomized order  ►Head-to-head comparison of CEs | ►EndoCapsule® (Olympus© America, Allentown, Pa) ►PillCam®SB  (Given®Imaging, Yoqneam,Israel) | ►Pts with OGIB (transfused or with haematocrit <31% (males) or <28% (females): 63  ►Available data 51/63; 9 pts excluded for technical reasons + 3 pts for protocol violation  ►24 videos read as normal; 14 as abnormal (from both CEs). Disagreement occurred in 13  ►No adverse events reported for either CE. Overall agreement: 38/51 (74.5%); κ=0.48, *P*=0.008  **Limitations:** Although ingestion randomized, videos reading not blind (different shape of the image margin) | ►Both devices are safe and have comparable DY within the previously reported range  ►Subjective difference in image quality favouring the EndoCapsule®  ►Lack of electromechanical interference between 2 different CEs |
| Kim HM *et al*[9] | Korea | Single centre | Head-to-head evaluation of technical performance DY and of two capsule systems (PillCam® SB *vs* MiroCam®) | Prospective | ►Pts referred to CE for various indications  ►Each pt was randomly assigned to swallow 1 of 2 CEs; the second CE was swallowed once fluoroscopy indicated that first CE had reached the SB | ►MiroCam®  (IntroMedic Co. Ltd,Seoul,Korea) ►PillCam®SB (Given®Imaging, Yoqneam,Israel) | ►Pts enrolled: 24  ►Mean operating time: MiroCam®  702 min; PillCam® SB 446 min; *P*<0.001  ►CR: MiroCam®  20/24 (83%); PillCam® SB 14/24 (59%); *P*=0.031  ►DY: MiroCam®  11/24 (45.8%); PillCam® SB10/24 (41.7%); *P*=1.0  ►DY (additive of both capsules): 12/24 (50%)  ►Concordance of findings among the two capsule systems 87.5%; κ=0.74 | ►MiroCam shows a longer operating time and a higher CR  ►Nevertheless, the 2 capsule systems showed comparable efficiency  ►Sequential capsule endoscopy with the MiroCam and PillCam SB produced slight (but NS) increase in DY |
| Pioche *et al* [10] | France | Multicentre | Head-to-head evaluation of the diagnostic concordance (κ value):  PillCam® SB SB2 *vs* MiroCam® | Prospective | ►OGIB pts  ►Each pt ingested 2 CEs at a 1 h interval in a random order  ►Videos read in a random order by 2 experienced (>200 CEs) readers  ►Image-by-image review of cases of disagreement between the readers was performed by 3 expert readers | ►MiroCam®  (IntroMedic Co. Ltd, Seoul,Korea) ►PillCamSB2 (Given®Imaging, Yoqneam, Israel) | ►83 pts; drop-outs explained (10 technical issues); 73 pts/videos analysed  ►31 concordant (-) ve cases (42.4%) and 30 concordant (+) ve cases (41.1%)  ►Satisfactory diagnostic concordance between the 2 systems (κ=0.66)  ►DY similar among the 2 CE systems(PillCam®SB 2 *vs* MiroCam®: 46.6% *vs* 56.2%, respectively; *P*=0.02)  ►SBTT longer with MiroCam® *vs* PillCam®SB (mean SBTT: 268 *vs* 234 min, *P*<0.05)  ►Reading time longer with MiroCam® *vs* PillCam®SB (mean reading time 40 *vs* 23 min; *P*<0.05)  ►(+) ve diagnosis obtained in 46.6% *vs* 56.2% of pts with PillCam®SB2 *vs* MiroCam®, respectively  ►PillCam®SB2 *vs* MiroCam® CEs identified 78.6%*vs* 95.2% of (+) ve cases, respectively; *P*=0.02 | ► MiroCam® showed a slightly higher DY; difference not statistically significant  ►The 2 CE systems showed comparable efficiency for the diagnosis of OGIB |
| Dolak *et al* [11] | Austria | Single centre | Head-to-head comparison (MiroCam® *vs* EndoCapsule®) of:  -CR of SB examinations  -DY in SB disease | Prospective | ►Pts referred to CE for various indications  ►Each pt was randomly assigned to swallow either MiroCam® first, followed by the EndoCapsule® 2 h later, or vice versa  ►All videos analysed by two investigators independently | ►MiroCam®  (IntroMedic Co. Ltd, Seoul,Korea)  ►EndoCapsule® (Olympus America, Allentown, Pa) | ►Pts enrolled: 50  ►CR: MiroCam® 48/50 (96%) *vs* EndoCapsule® 45/50 (90%); *P*=0.38  ►DY in SB: MiroCam® 25/50 (50%) *vs* EndoCapsule® 24/50 (48%); *P*>0.99  ►Concordance of findings among the two CE systems: 68%; κ=0.50 | ►The two capsule endoscopy systems were not statistically different with regards to CR and DY  ►Moderate concordance, mainly caused by missed pathological findings (which affected both devices), needs consideration in clinical practice |

DY: Diagnostic yield; OGIB: Obscure Gastrointestinal Bleeding; pts: Patients; CE: Capsule endoscope/y; CR: Completion rate; NS: Not significant (statistically); SB: Small-bowel; P2: Refers to grading of angioectasias; SBTT: Small-bowel transit time.

**Table 3 Available meta-analysis and systematic reviews in the field of small-bowel capsule endoscopy**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Title** | **Search**  **Start - end date** | **Type** | **Subject** | **Data extractors** | **Total Titles found** | **Titles entered meta-analysis** | **Individuals included** | **Outcome/Conclusion** |
| Marmo *et al*[17] | Meta-analysis: capsule enteroscopy *vs* conventional modalities in diagnosis of SB diseases | Jan 1966 – Mar 2005 | Meta-analysis of diagnostic test accuracy | DY/safety of SBCE *vs* alternative modalities  (PE, SBBaR or enteroclysis) in SB disease | 2 | 187 | 17 | 526 pts  (289 OGIB)  (237 CD) | ►17 studies (526 patients) met inclusion criteria  ►Overall; the rate difference for SB disease (*i.e.,* the absolute pooled difference in the rate of positive findings) of SBCE *vs* alternative modalities was 41% (95%CI: 35.6-45.9)  For OGIB; 37% (95%CI: 29.6-44.1); for Crohn's disease 45% (95%CI: 30.9-58.0)  ►Incomplete SBCE occurred in 13%, more often in OGIB (17%) than in pts with CD (8%) (*P*<0.006)  ►Adverse events: 29 pts (6%)  ►Capsule retention more frequent in pts with CD (3% *vs* 1%, OR 4.37) |
| Triester *et al* 18] | A meta-analysis of the yield of CE compared to other diagnostic modalities in patients with OGIB | NS – April 2005 | Meta-analysis of diagnostic test accuracy | Incremental yield (IY) (yield of CE–yield of comparative modality) and 95%CI: of CE over comparative modalities | 2 | 80 | 14 | 396 (CE – PE)  88 (CE – SBBaR) | ►14 studies (*n =* 396) compared DY CE *vs* PE in OGIB; 63% *vs* 28%, respectively (IY=35%,*P*<0.00001,95%CI: 26–43%)  For clinically significant findings (*n =* 376) DY was 56% (CE) *vs* 26% (PE); IY=30%,*P*<0.00001,95%CI: 21–38%  ►3 studies (*n =* 88) compared DY of CE *vs* SBBaR; 67% *vs* 8%, respectively (IY=59%,*P*<0.00001,95%CI: 48–70%)  For clinically significant findings DY was 42% (CE) *vs* 6% (SBBaR); IY =36%,*P*<0.00001,95%CI: 25–48%  ► NNT to yield one additional clinically significant finding with CE over either modality: 3 (95%CI: 2–4)  ►1 study compared DY (significant findings) of CE *vs* intraoperative enteroscopy (*n =* 42,IY=0%,*P*=1.0,95%CI: -16–16%)  ►1 study compared DY (significant findings) of CE *vs* CT enteroclysis (*n =* 8,IY=38%,*P*=0.08,95%CI: -4–79%)  ►1 study compared DY (significant findings) of CE *vs* mesenteric angiogram (*n =* 17,IY=-6%,*P*=0.73,95%CI: -39–28%)  ►1 study compared DY (significant findings) of CE *vs* SB MRI (*n =* 14, IY=36%,*P*=0.007,95%CI: 10–62%)  CE–DY *vs* PE (vascular lesions): 36% *vs* 20% (IY=16%,*P*<0.00001,95%CI: 9–23%)  CE–DY *vs* PE (inflammatory lesions): 11% *vs* 2% (IY=9%,*P*=0.0001,95%CI: 5–13%)  CE–DY *vs* PE (tumours or "other" findings): no difference |
| Leighton *et al*, 2006,[19] | Capsule endoscopy: A Meta-analysis for use with OGIB and CD | NS – April 2005 | Meta-analysis of diagnostic test accuracy | DY and safety of SBCE *vs* alternative modalities (PE, SBBaR or enteroclysis) in SB disease | 2 | 80 | 20 | 537 pts | ►CE superior to PE/SB radiography for diagnosing SB pathology in pts with OGIB (yield comparable to intraoperative endoscopy)  ►Incremental yield of CE over PE/SB radiography is > 30% for clinically significant findings, due to visualization of additional vascular, inflammatory lesions by CE  ►CE was also superior to SB radiography, colonoscopy+ileoscopy, CT enterography, PE for diagnosing non-stricturing SB CD  ►Marked improvement in yield with the use of CE over all other methods in pts who had established CD and were evaluated for SB recurrence  ►Unknown whether these results will translate into improved pt outcomes with the use of CE *vs* alternate methods |
| Triester et al[20] | A meta-analysis of the yield of CE compared to other diagnostic modalities in patients with non-stricturing SB Crohn’s Disease | NS – Aug 2005 | Meta-analysis of diagnostic test accuracy |  | 2 | 82 | 9 | 250 | ►9 studies (*n =* 250) compared DY CE *vs* SBBaR in CD; 63% *vs* 23%, respectively (IY=40%, *P*<0.001, 95%CI:=28–51%)  ►4 studies (*n =* 114) compared DY CE *vs* C+IL in CD: 61% *vs* 46%, respectively (IY=15%, *P*=0.02, 95%CI:=2–27%)  ►3 studies (*n =* 93) compared DY CE *vs* CT enterography/enteroclysis: 69% *vs* 30%, respectively (IY=38%, *P*= 0.001, 95%CI:=15–60%)  ►2 studies compared DY CE *vs* PE: (IY=38%, *P*<0.001, 95%CI: =26–50%)  ►1 study compared DY CE *vs* SBMRI: (IY=22%, *P*=0.16, 95%CI:=-9–53%)  **Sub-analysis** (pts with suspected CD): no difference in DY CE *vs* SBBaR (*P*=0.09), C+IL (*P*=0.48), CT enterography (*P*=0.07) or PE (*P*=0.51)  **Sub-analysis** (pts with established CD): difference in DY CE *vs* SBBaR (*P*<0.001 C+IL (*P*=0.002), CT enterography (*P*<0.001) and PE (*P*<0.001) |
|
| Pasha *et al*[21] | DBE and CE Have Comparable DY in SB Disease: A Meta-Analysis | NS – Dec 2006 | Meta-analysis of diagnostic test accuracy | Comparison of DY of CE *vs* DBE | 2 | 113 | 11 | 397 | ►Pooled DY CE *vs* DBE: 60% *vs* 57% (IYW: 3%; 95%CI: -4−10%; *P* = 0.42; FEM)  ►Pooled DY CE *vs* DBE (vascular findings, 10 studies): 24% *vs* 24% (IYW: 0%; 95%CI: -5−6%; *P* = 0.88; REM)  ►Pooled DY CE *vs* DBE (inflammatory findings, 9 studies): 18% *vs* 16% (IYW: 0%; 95%CI: -5−6%; *P* = 0.89; FEM)  ►Pooled DY CE *vs* DBE (polyps/tumours, 9 studies): 11% *vs* 11% (IYW: -1%; 95%CI: -5−4%; *P* = 0.76; FEM)  ►SB disease: CE *vs* DBE have comparable DY, including OGIB  CE should be the initial diagnostic test for determining the insertion route of DBE |
| Niv [22] | Efficiency of bowel preparation for capsule endoscopy examination: a meta-analysis | NS – July 2007 | Meta-analysis of RCTs and cohort studies | Purgative use *vs* fasting alone for SBCE | 1 | 6 | 8 | 130 (bowel prep)  107 (fasting) | ► 237 pts, 130 with and 107 without preparation  ►Seven out of 8 studies included a comparison of GTT, SBTT and CR  ►SBCE CR: 76% in pts with preparation *vs* 68% without prep (difference did not reach statistical significance)  ►No statistically significant difference between CEs performed with or without preparation in GTT (pooled effect size, -0.054; 95%CI: -0.418–0.308) or  SBTT (pooled effect size, -0.327; 95%CI: -1.419 – -0.765) |
| El-Matary *et al*[23] | Diagnostic characteristics of given video capsule endoscopy in diagnosis of celiac disease: a meta-analysis |  | Meta-analysis of diagnostic test accuracy | Coeliac and CE | 2 | N/A | 3 | 107 pts | ►3 studies (*n =* 107; 63 pts with CD/44 without) met inclusion criteria  ►Pooled SBCE (overall) Sens and Spec: 83% (95%CI: 71–90%) and 98% (95%CI: 88–99.6%), respectively  ►No major complications reported  ►Costs mentioned only in 1 study. Overall, diagnostic characteristics of SBCE, could not justify the routine use of SBCE as alternative to biopsy |
| Chen *et al*[24] | A meta-analysis of the yield of CE compared to DBE in pts with SB diseases | NS – Feb 2007 | Meta-analysis of diagnostic test accuracy | Comparison of DY of CE *vs* DBE | 2 | 163 | 8 | 277 | ►8 studies (*n =* 277 pts) prospectively compared the yield of CE and DBE were included  ►No difference between the yield of CE and DBE[170/277 *vs* 156/277, OR 1.21 (95%CI: 0.64-2.29)]  ►Sub analysis: yield of CE significantly higher than that of DBE without combination of oral+anal insertion approaches[137/219 *vs* 110/219, OR 1.67 (95%CI: 1.14-2.44), *P*<0.01), but not superior to the yield of DBE with combination of the two insertion approaches[26/48 *vs* 37/48, OR 0.33 (95%CI: 0.05-2.21), *P*<0.05)]  ►Focused meta-analysis of the fully published articles concerning OGIB showed similar results wherein the yield of CE was significantly higher than that of DBE without combination of oral+ anal insertion approaches[118/191 *vs* 96/191, fixed model: OR 1.61 (95%CI: 1.07-2.43), *P*<0.05)] and the yield of CE was significantly lower than that of DBE by oral+ anal combinatory approaches[11/24 *vs* 21/24, fixed model: OR 0.12 (95%CI: 0.03-0.52), *P*<0.01)] |
| Rokkas *et al*[25] | Does purgative preparation influence the diagnostic yield of small bowel video capsule endoscopy?: A meta-analysis | NS – Feb 2008 | Meta-analysis of RCTs and cohort studies | Purgative use *vs* fasting alone for SBCE | 2 | 194 | 12 | 718 pts purgative  444 controls | ►12 eligible studies (6 prospective/6 retrospective), including 16 sets of data  ►Significant difference in DY between pts prepared with purgatives(*n =* 263) *vs* pts prepared with clear liquids(*n =* 213):  OR=1.813 (95%CI: 1.251–2.628, *P*=0.002)  ►Significant difference in SBVQ between pts prepared with purgatives(*n =* 404) *vs* pts prepared with clear liquids(*n =* 249):  OR=2.113 (95%CI: 1.252–3.566, *P*=0.005)  There was no statistically significant difference regarding CR rate. Purgatives did not affect VCE gastric transit time (GTT) or VCE small bowel transit time (SBTT) |
| Liao *et al*[13] | Indications, detection, completion, and retention rates of SBCE:  a systematic review | 2000 – Jan 2009 | Systematic review of evidence base | Indications, DR,  CR and RR of SBCE | 2 | 227 | 227 | 22,753 (Pts)  22,840 (CE) | ►Most common indications: OGIB (66.0%); investigation of clinical symptoms (10.6%); definite/suspected CD (10.4%)  ►Pooled DRs for overall, OGIB, CD, neoplasia: 59.4%, 60.5%, 55.3%, 55.9%, respectively  ►Commonest cause for OGIB: angiodysplasia (50.0%)  ►Pooled CRs (overall): 83.5%; breakdown 83.6% (OGIB), 85.4% (clinical symptoms), 84.2% (CD)  ►Pooled RRs (overall): 1.4%; breakdown 1.2% (OGIB), 2.6% (clinical symptoms), 2.1% (CD)  Hence, most common indication for SBCE is OGIB, with high DR and low RR  A relatively high RR is associated with definite/suspected CD and neoplasms |
| Dionisio *et al*[26] | CE has a significantly higher DY in patients with suspected and established small-bowel CD: a meta-analysis | 2000 – May 2009 | Meta-analysis of diagnostic test accuracy | DY of CE *vs* modalities in patients with suspected/ established CD | 2 | 291 | 12 | 428 | ►8 studies (*n =* 236 pts) compared CE *vs* C+IL, 4 (*n =* 119 pts) CE *vs* CTE, 2 (*n =* 102 pts) *vs* PE, 4 (*n =* 123 pts) *vs* MRE  ►For suspected CD, several comparisons met statistical significance; Yields in this subgroup were:  CE *vs* SBR: 52 *vs* 16% (IYw=32%, *P*<0.0001, 95%CI:=16-48%)  CE *vs* CTE: 68 *vs* 21% (IYw=47%, *P*<0.00001, 95%CI:=31-63%)  CE *vs* C+IL: 47 *vs* 25% (IYw=22%, *P*=0.009, 95%CI:=5-39%)  ►For established CD, statistically significant yields for CE *vs* an alternate diagnostic modality in patients were seen:  CE *vs* PE: 66 *vs* 9% (IYw=57%, *P*<0.00001, 95%CI:=43-71%)  CE *vs* SBR: 71 *vs* 36% (IYw=38%, *P*<0.00001, 95%CI:=22-54%)  CE *vs* CTE: 71 *vs* 39% (IYw=32%, *P*≤0.0001, 95%CI:=16–47%) |
| Wu *et al*[27] | Systematic review and meta-analysis of RCTs of Simethicone for GI endoscopic visibility | NS – Nov 2009 | Meta-analysis of RCTs | Simethicone and CE | 2 | 128 | 4 | 121 | ►Adequate or excellent/good SB mucosa visualization in pts receiving Simethicone *vs* those who did not (66.1 *vs* 37.2%)  ►Pooled OR=2.84 (95%CI:1.74–4.65, *P*=0.00); no significant heterogeneity (*P*=0.16, *I2*=38.8%) or publication bias (*P*=0.251)  ►Sens analysis: studies stratified by factors such as bowel preparation (purgative *vs* fasting):  Significant results for bowel preparation + fasting (OR=4.43, 95%CI: 1.82–10.76, *P* =0.00) with *P* =0.78, *I2*=0.0%  No significant results for bowel preparation + purgative (OR=1.59, 95%CI: 0.78–3.27, *P* =0.203) with *P* =0.20, *I2*=38.9% |
| Cohen and Klevens[28] | Use of CE in diagnosis and management of pediatric patients, based on meta-analysis | Jan 2001 – May 2010 | Systematic review of evidence base | Systematic compilation of data on indications and outcomes of CE in paediatric patients | 2 | N/A | 15 | 740 examinations  723 pts | ► Most common indication for CE (in pts<18 years): suspicion or evaluation of IBD (overall 54%)  Breakdown: suspected CD (34%), known CD (16%), UC (1%), indeterminate colitis (3%)  ►CR and RR: 86.2% (95%CI: 81.5–90.3%) and 2.6% (95%CI: 1.5–4.0%), respectively  ►CE RR (gastric and SB): 0.5% and 1.9%, respectively; similar to those of adults, by indication  ►CE with positive findings: 65.4% (95%CI: 54.8–75.2%)  ►CE resulting in new diagnosis: 69.4% (95%CI: 46.9–87.9%); CE leading to change in therapy: 68.3% (95%CI: 43.6–88.5%) |
| Teshima *et al*[29] | DBE and CE for OGIB:  an updated meta-analysis | NS – June 2010 | Meta-analysis of diagnostic test accuracy | OGIB;  CE or DBE | 2 | 147 | 10 | 651 CE  642 DBE | ►Pooled DY for CE: 62% (95%CI:47.3–76.1%)  ►Pooled DY for DBE 56% (95%CI:48.9–62.1%); OR for CE *vs* DBE of 1.39 (95%CI:0.88–2.20; *P* =0.16)  **Subgroup analyses**  ►DBE–DY after (+)ve CE: 75.0% (95%CI:60.1–90.0%)  ►DBE–DY after (-)ve CE: 27.5% (95%CI:16.7–37.8%)  ►DBE–OR (for successful diagnosis after (+)ve CE) compared with DBE: 1.79 (95%CI:1.09–2.96; *P* = 0.02)  In OGIB CE and DBE have similar DY; DBE–DY significantly higher when performed in pts with prior positive CE |
| Belsey *et al*[30] | Meta-analysis: efficacy of SB preparation for SBCE | Jan 2000 – Dec 2010 | Meta-analysis of RCTs | Purgative use *vs* fasting alone for SBCE | 2 | 33 | 8 | 291 pts (PEG)  133 pts (NaP)  322 pts (fasting) | ►8 studies, using PEG or NaP-based bowel cleansing regimens  ►Any form of purgative significantly better visibility than fasting alone (OR=2.31; 95%CI: 1.46–3.63; *P*<0.0001)  ►Similar results on DY (OR=1.88; 95%CI: 1.24–2.84; *P*=0.023)  **Subgroup analyses (per cleansing regimen used):**  ►PEG-based regimens showed benefit (OR=3.11; 95%CI: 1.96–4.94; *P*<0.0001)  ►NaP-based regimens no significant difference from fasting alone (OR=1.32; 95%CI: 0.59–2.96; *P*<0.0001)  ►Use of purgatives (alongside fasting) is recommended in SBCE; PEG-based regimens offer a clear advantage over NaP  ►Lower volume PEG regimens as efficacious as higher volumes traditionally used for colonoscopy preparation |
| Rokkas and Niv[31] | The role of video CE in the diagnosis of coeliac disease: a meta-analysis | N/A – April 2011 | Meta-analysis of diagnostic test accuracy | Coeliac and CE | 2 | 461 | 6 | 166 | ►Pooled CE Sens: 89% (95%CI:82–94%) and Spec: 95% (95%CI:89–98%); AuROC:0.9584  ►Although not as accurate as pathology, CE a reasonable alternative method of diagnosing Coeliac Disease |
| Koulaouzidis *et al*[32] | Diagnostic yield of SBCE in patients with IDA: a systematic review | Jan 2001 – Nov 2011 | Systematic review of evidence base | IDA and CE | 2 | 1,225 | 24 | 1,960 | ►Pooled SBCE–DY in IDA: 47% (95%CI: 42–52%), with significant heterogeneity among included studies (*I2*=78.8%, *P<*0.0001)  ►Pooled SBCE–DY (subgroup 1: 4 studies focused solely on IDA pts): 66.6% (95%CI: 61.0–72.3%; *I2*=44.3%)  ►Pooled SBCE–DY (subgroup 2: 20 studies not focusing only on IDA pts): 44% (95%CI: 39–48%; *I2*=64.9%)  ►SBCE in **subgoup 1**: more vascular (31% *vs* 22.6%, *P*=0.007), inflammatory (17.8% *vs* 11.3%, *P*=0.009), neoplastic (7.95% *vs* 2.25%, *P*<0.0001) lesions detected |

CE: Capsule endoscopy; N/A: Not available or not applicable; Sens: Sensitivity; Spec: Specificity; AuROC: Area under Receiver operation characteristics curve; DBE: Double-balloon enteroscopy; OGIB: Obscure gastrointestinal bleeding; DY: Diagnostic Yield; pts: Patients;

**Table 4** **Studies evaluating the clinical application of faecal calprotectin in the setting of small-bowel capsule endoscopy**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Country** | **Centre** | **Study type** | **Design** | **Participants** | **FC** | **CE** | **Objective/s** | **Outcome/s** |
| Goldstein *et al*[41] | USA | Multicentre | Prospective | Double-blind,  triple-dummy,  placebo controlled | 334, healthy subjects | N/A | M2A®;  Given®Imaging, Yokneam, Israel | Evaluate incidence of SB injury and correlation with FC in healthy subjects on celecoxib or ibuprofen+omeprazole | ►Mean increase in FC higher in subjects on ibuprofen+omeprazole compared with celecoxib alone (*P*<0.001)  ►No correlation between FC and SB mucosal breaks |
| Hawkey *et al*[42] | Germany  UK | Multicentre | Prospective | Double-blind,  double-dummy,  placebo controlled | 139, healthy subjects | Phical Calprotectin Test Kit NovaTec  ImmunodiagnosticaGmbH  Dietzenbac, Germany | M2A®;  Given®Imaging, Yokneam, Israel | Investigate SB injury  lumiracoxib reduces *vs* naproxen+omeprazole | ►More SB mucosal breaks on naproxen+omeprazole (77.8 *vs* 40.4%,*P*<0.001)  ►Furthermore, higher FC *vs* placebo (96.8 *vs* 14.5 μg/g, *P*<0.001)  ►27.7% on lumiracoxib had SB mucosal breaks (*vs* placebo, *P*=0 .196; *vs* naproxen, *P*<0.001)  ►No increase in FC (–5.7 μg/g; *vs* placebo*, P*=0.377; *vs* naproxen*, P*<0.001) |
| Smecuol *et al*[43] | Argentina  Spain  Canada | Multicentre | Prospective | Non-blinded study | 20, healthy subjects | Calprest  Eurospital S.p.A  Trieste, Italy | M2A®;  Given®Imaging, Yokneam, Israel | Determine SB damage by low-dose ASA (on a short-term basis) | ►Short-term administration of low-dose ASA associated with mucosal abnormalities of the SB mucosa  ►Median baseline FC (6.05μg/g; range, 1.9–79.2) increased significantly after ASA use |
| Werlin *et al*[44] | USA  Israel  UK | Multicentre | Prospective | N/A | 42 pts with CF**\*** (aged 10-36); 29 had pancreatic insufficiency | Calprest  Eurospital S.p.A  Trieste, Italy | PillCam®SB; Given®Imaging, Yokneam, Israel | Examine the SB of pts with CF without overt evidence of GI disease using CE | ►Varying degrees of diffuse areas of inflammatory findings in the SB: oedema, erythema, mucosal breaks and frank ulcerations  ►No adverse events recorded  ►FC markedly high in pts with pancreatic insufficiency, 258µg/g (normal <50) |
| Koulaouzidis *et al*[45] | UK | Single centre | Retrospective | Chart review | 70 pts with suspected CD and (-)ve bi-directional endoscopy | CALPRO NovaTec  ImmunodiagnosticaGmbH  Dietzenbac, Germany | 1. PillCam®SB; Given®Imaging, Yokneam, Israel  2. MiroCam®; IntroMedic Co., Seoul, Korea | Value of FC as selection tool for further investigation of the SB with SBCE, in a cohort of pts with suspected CD | ►FC=50-100μg/g: normal SBCE, despite symptoms suggestive of IBD  ►FC >100μg/g: good predictor of positive SBCE  ►FC >200μg/g: associated with higher SBCE DY(65%); confirmed CD in 50%  ►Measurement of FC prior SBCE: useful tool to select patients for referral. If FC <100μg/g: SBCE is not indicated (NPV 1.0) |
| Jensen *et al*[46] | Denmark | Single centre | Prospective | Blinded study | 83 pts from GI OPD clinics with suspected CD | Calprotectin ELISA, BÜHLMANN LaboratoriesAG,  Basel, Switzerland | PillCam®SB; Given®Imaging, Yokneam, Israel | Determine FC levels in CD restricted to SB compared to colonic CD, in pts on first diagnostic work-up  Assess the sens and spec of FC in suspected CD | ► In pts with SB or colonic CD FC is equal: median 890μg/g *vs* 830 mg/kg, respectively (*P*=1.0)  ►FC cut-off =50μg/g: 92% and 94% sens for SB and colonic CD, respectively  ►Overall, sens and spec for FC: 95% and 56%  ►CD was ruled out with NPV of 92%  ►In suspected CD, FC is effective marker to r/o CD and select patients for endoscopy |
| Koulaouzidis *et al*[47] | UK | Single centre | Retrospective | Chart review | 49 pts; known or suspected CD | CALPRO NovaTec  ImmunodiagnosticaGmbH  Dietzenbac, Germany | PillCam®;  Given®Imaging, Yokneam, Israel  MiroCam®; IntroMedic Co., Seoul, Korea | Assess performance of 2 SBCE inflammation scoring systems (LS and CECDAI) correlating them with FC  Define threshold levels for CECDAI | ►LS performs better than CECDAI in describing SB inflammation, especially at FC <100μg/g  ►CECDAI levels of 3.8 and 5.8 correspond to LS thresholds of 135 and 790, respectively |
| Sipponen *et al*[48] | Finland | Single centre | Prospective | Blinded study | 84 pts; known or suspected CD | Calprest®,  Eurospital S.p.A  Trieste, Italy | PillCam®;  Given®Imaging, Yokneam, Israel  MiroCam®; IntroMedic Co., Seoul, Korea | Study the role of FC and S100A12 in predicting SB inflammatory lesions | ►CE abnormal in 35/84 (42%)pts:  14 CD, 8 NSAID-enteropathy, 8 angioectasias,  4 polyps/ tumours, 1 ischemic stricture  ►Median FC/S100A12: 22μg/g (range 2-342)/0.048μg/g(range 0.003-1.215)  ►FC significantly higher in CD pts (median 91, range 2-312) compared with pts with normal CE or other abnormalities (*P*=0.008)  ►Faecal S100A12(0.087μg/g, range 0.008-0.896): no difference between the groups (*P*=0.166)  Sens, spec, PPV, NPV in detecting SB inflammation; FC (cut-off 50μg/g): 59%,71%,42%,83%; S100A12(cut-off 0.06μg/g): 59%, 66%, 38%, 82%, respectively |

CF: Cystic Fibrosis; CD: Crohn’s disease; GI: Gastrointestinal; OPD: Out-Patient Department; SB: small-bowel; FC: faecal calprotectin; ASA: acetyl-salycylic acid; CE: capsule endoscopy/e; Pts: patients; Sens: Sensitivity; Spec: Specificity; SBCE: small-bowel capsule endoscopy; LS: Lewis Score; CECDAI: Capsule endoscopy Crohn’s Disease Activity Index; NPV: Negative Predictive Value; PPV: Positive Predictive value.

**Table 5 Studies looking at the identification rate of the ampulla in capsule endoscopy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **CE (N)** | **Type of CE model; Company** | **AoV seen *n* (%)** | **Reviewers (N)** | **Reviewing speed (fps)** | **Frames AoV visible( Mean ±SD)** | **Comments** |
| Wijeratne and Condon<B21>, </C>[53]1 | 138 | NS | 9 (6) | 1 | NS | NS | 4 FAP patients (AoV not seen) |
| Kong *et al*[54] | 110 | M2A®; Given®Imaging Ltd | 48 (43.6) | 2 | 15 | 3.5 ±2.5 |  |
| Clarke *et al*[55] | 125 | M2A®; Given®Imaging Ltd | 13 (10.4) | 2 | 5 | NS |  |
| Iaquinto *et al*[56] | 23 | PillCam®SB; Given®Imaging Ltd | 0 (0) | 2 | NS | N/A | FAP patients (11/23 had duodenal polyps) |
| Metzger *et al*<B20> [57] | 20 | PillCam®SB1; Given®Imaging Ltd | 1 (5) | NS | NS | NS | Repeat examinations |
| PillCam®SB2; Given®Imaging Ltd | 5 (25) | NS | NS | NS |  |
| Katsinelos *et al*[58] | 14 | NS | 0 (0) | 1 | NS | N/A | FAP patients |
| Nakamura *et al*</[59] | 96 | PillCam®SB1; Given®Imaging Ltd | 18 (18) | 2 | 10 | NS |  |
| Karagiannis *et al*<B25></C[60] | 10 | PillCam®Colon; Given®Imaging Ltd | 6 (60) | NS | NS | NS | **Two-headed PillCam®** |
| Lee *et al*[61]1 | 30 | PillCam®SB; Given®Imaging Ltd | 13 (43.3) | NS | NS | NS |  |
| 30 | PillCam®SB2; Given®Imaging Ltd | 15 (50.0) | NS | NS | NS |  |
| Selby and Prakoso<B23>,, </C>[62] | 50 | PillCam®SB1; Given®Imaging Ltd | 0 (0) | 2 | NS | N/A |  |
| 50 | PillCam®SB2; Given®Imaging Ltd | 9 (18) | 2 | NS | NS |  |
| 8 | PillCam®ESO1; Given®Imaging Ltd | 0 (0) | 2 | NS | N/A | **Two-headed PillCam®** |
| 12 | PillCam®ESO2; Given®Imaging Ltd | 1 (8) | 2 | NS | NS | **Two-headed PillCam®** |
| Koulaouzidis *et al*[63] | 11 | PillCam®ESO1; Given®Imaging Ltd | 4 (36.4) | 1 | 7 | NS | **Two-headed PillCam®** |
| 7 | PillCam®ESO2; Given®Imaging Ltd | 1 (14.3) | 1 | 9 | NS | **Two-headed PillCam®** |
| Park *et al*[64] | 30 | PillCam®SB; Given®Imaging Ltd | 13 (43.3) | 6 | 7 | 3.1 ±1.1 |  |
| 30 | PillCam®SB2; Given®Imaging Ltd | 15 (50.0) | 6 | 9 | 3.1 ±1.5 |  |
| Koulaouzidis *et al*[65] | 262 | PillCam®SB1; Given®Imaging Ltd | 28 (10.7) | 1 | 6 | 36.35 ±73.24 |  |
| 148 | PillCam®SB2; Given®Imaging Ltd | 13 (8.8) | 1 | 6 | 42.46 ±69.3 |  |
| 209 | MiroCam®; IntroMedic Ltd | 18 (8.6) | 1 | 6 | 87.20 ±248.4 |  |
| Sieg *et al*[66] | 25 | CapsoCam®SV1; Capsovision Ltd | 22 (71) | 3 | NS | 3.1 ±1.8 |  |

CE: Capsule endoscopy; NS: Not stated; AoV: Ampulla of Vater; fps: Frames per second; FAP: Familial adenomatous polyposis syndrome; 1Publishedonly as abstracts.

**Table 6** **Case reports of aspiration of capsule endoscopes**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Case**  **age/gender** | **Comorbidities** | **CE model/company** | **Swallowing Difficulties** | **No of attempts to swallow CE/**  **gagging or coughing** | **Aspiration time (s, min or h)/**  **Where in bronchial tree CE seen** | **Capsule removal (if employed)** | **Final diagnosis** |
| Schneider *et al*[72] | 64/male | Mechanical MV on phenprocoumon,  BMI 15.5 | M2A®;  Given®Imaging Ltd | No Hx of dysphagia | 4/Gagging and spitting capsule – last attempt recurrent coughing (aspiration presumed) | 2 min/trachea –bronchi | Spontaneous resolution | Ns |
| Fleischer *et al*[73] | 76/male | HHT | M2A®;  Given®Imaging Ltd | No Hx of dysphagia | 1/lodged in his throat - no respiratory difficulty, could talk, vital signs normal | 60 min/cricopharyngeous | Endoscopy - Roth net  6 days post-dilation, patient ingested capsule with no problem | Spasticity, prominence of cricopharyngeous  Endoscopy and oesophageal dilation 1 week later |
| Sinn *et al*[74] | 69/female | On phenprocoumon | M2A®;  Given®Imaging Ltd | No Hx of dysphagia | 1/Coughed several times | 50 s/bifurcation of the trachea | Spontaneous resolution | Ns |
| Tabib *et al*[75] | 87/female | Recent onset IDA  CHF, IHD, AF, bladder cancer, CRF | M2A®;  Given®Imaging Ltd | No Hx of dysphagia  Pre-CE barium meal | 2/Choking, dyspnoea  CE felt lodged in the throat | Ns /Right main-stem bronchus - bronchus intermedius | Rigid bronchoscopy | Ns |
| Buchkremer *et al*[76] | 74/male | Recent diagnosis of Coeliac Disease  Past Hx of ankylosing spondylitis | M2A®;  Given®Imaging Ltd | No Hx of dysphagia | Ns/Dyspnoea started after CE ingestion | Ns /Right main-stem bronchus | Flexible bronchoscopy | Ns |
| Rondonotti *et al*[77] | Ns | Ns | M2A®;  Given®Imaging Ltd | Ns | Ns/Coughed several times | Ns / Ns | Spontaneous resolution | Ns |
| Nathan and Biernat[78] | 93/male | No significant past medical Hx | M2A®;  Given®Imaging Ltd | No Hx of dysphagia | 1/Coughed hours post-ingestion | ~8 h/bronchial tree | Spontaneous resolution | Ns |
| Shiff *et al*[79] | 75/male | Ns | M2A®;  Given®Imaging Ltd | No Hx of dysphagia | 2/some Coughing | Ns/bronchi | Spontaneous resolution  Eventually, CE endoscopic placement | Ns |
| Sepehr *et al*[80] | 67/male | HTN, DM, CVA | ns | Hx of dysphagia (intermittent) | 1/Cough, tachypnoea, and tachycardia | Ns/trachea | Endoscopy - Roth net | Ns |
| Koulaouzidis *et al*[81] | 76/male | Ns | PillCam®SB;  Given®Imaging Ltd | No Hx of dysphagia | 1/coughed weakly | 15 s/trachea | Spontaneous resolution | Ns |
| Guy *et al*[82] | 90/male | Ischaemic CVA | Ns | No Hx of dysphagia | Ns/no symptoms | Ns/ bronchial tree | Rigid bronchoscopy – stone retrieval basket | Ns |
| Leeds *et al*[83] | 85/male | Ns | Ns | No Hx of dysphagia | Ns/Difficulty swallowing CE, slightly painful | 8 h/lobar bronchus | Spontaneous resolution | Ns |
| Bredenoord *et al*[84] | 65/male | Sigmoid colectomy for diverticulae;  Ileal carcinoid resected | Ns | Hx of dysphagia  (intermittent) | Lengthy swallowing attempt /coughing noted | Ns/right main bronchus | Spontaneous resolution  Eventually, CE was swallowed on same session | Normal small-bowel |
| Choi *et al*[85] | 75/male | Prior CVA | PillCam®SB;  Given®Imaging Ltd | No Hx of dysphagia | Ns/coughed several times | 2 h/Left main bronchus | Flexible bronchoscopy – Roth net and bronchial wall irrigation to induce cough | Ns  Patient declined further investigations |
| Depriest *et al*[86] | 90/male | IHD,AF,PVD(warfarin+clopidogrel) | PillCam®SB;  Given®Imaging Ltd | No Hx of dysphagia | Ns/some cough | Ns/Left main bronchus; then Right main bronchus | Chest percussive therapy + postural drainage  Flexible bronchoscopy + extraction basket + Roth net | Ns |
| Kurtz *et al*[87] | 73/male | Renal cell cancer, MV(bovine)  hyperlipidaemia, melaena | Ns | No Hx of dysphagia | Sips of water, 1st attempt, 2 min later non-productive cough (20 s) | Level of carina; then Right main stem bronchus | Bronchoscopy – retrieval basket  (multiple spontaneous ejections from trachea prior bronchoscopy) | Ns |
| Lucendo *et al*[88] | 80/male | Advanced PD, DM  Walking + speech difficulties | PillCam®SB;  Given®Imaging Ltd | No Hx of dysphagia | Several attempts/persistent coughing and some dyspnoea | 20 s/tracheobronchial tree | Spontaneous resolution | Oesophageal ulcer + Ileal Ulcer |
| Pezzoli *et al*[89] | 82/male | Unexplained anemia, HTN | Ns | No Hx of dysphagia | Ns/asymptomatic (minimal cough) | 3 d / in the right bronchus | Spontaneous resolution | Ns |
| Parker *et al*[90] | 77/female | Hysterectomy | Ns | No Hx of dysphagia | Initial attempt unsuccessful/chocking episode  CE coughed-up | Ns/Ns | Spontaneous resolution  Endoscopic placement with AdvanCE® device | Patient suffered intracranial bleed; eventually succumbed |
| Despott *et al*[91] | 65/male | COPD, Cirrhosis, Pancreatitis | Ns | No Hx of dysphagia | Ns/asymptomatic | Ns/Right main bronchus | Rigid bronchoscopy - Roth net | Endoscopic placement with AdvanCE® device |
| 73/male | COPD | Ns | Ns | Ns/brief coughing | Ns/Left main bronchus | Bronchoscopy – snare + Roth net | Endoscopic placement with AdvanCE® device |
| 81/male | Ns | Ns | Ns | Ns/ fleeting choking sensation | Ns/Right main bronchus | Rigid bronchoscopy – crocodile grasping forceps | Ns |
| Girdhar *et al*[92] | 83/male | COPD, GORD | PillCam®SB;  Given®Imaging Ltd | No Hx of dysphagia | Difficult, requiring multiple sips of water/  some cough, after 1 h mild shortness of breath | Ns/Left main bronchus | Flexible bronchoscopy + rat-tooth alligator forceps+  Stiff-Wire Basket with a Pin-Vise Handle | Ns |
| Yarlagadda *et al*[93] | 80/male | AF, IHD, CVA, on anti-coagulants, anaemia+melaena | M2A®;  Given®Imaging Ltd | Ns | Ns | 24 h/  Left main stem bronchus; then Right bronchus | Flexible bronchoscopy + net + snare forceps + tripod  Eventually, grasped with basket | Ns |

MV: Mitral valve; BMI: Body Mass Index; HHT: Hereditary Haemorrhagic Telangiectasia; IDA: Iron Deficiency Anaemia; CHF: Chronic Heart Failure; IHD: Ischaemic Heart Disease; AF: Atrial Fibrillation; CRF: Chronic Renal Failure; Hx: History; Ns: Not stated; HTN: Hypertension; DM: Diabetes Mellitus; CVA: Cerebrovascular Accident; PVD: Peripheral Vascular Disease; PD: Parkinson’s disease; COPD: Chronic Obstructive Pulmonary Disease; GORD: Gastro-Oesophageal Reflux Disease; CE: capsule endoscopy.

**Table 7** **Studies looking at the clinical validity of Suspected Blood Indicator, feature of capsule endoscopy reading software, in small-bowel capsule endoscopy**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Country** | **Centre** | **Objective/s** | **Study type** | **Design** | **CE type** | **Outcome/s** | **Conclusions** |
| Gross *et al*[95] | USA | Single centre | Accuracy of SBI  to number of blood transfusions | Retrospective | ►Gold standard  Lesions detected by experienced CE reviewer | M2A  Given® Imaging Ltd | ►Gold standard: 72 pts  ►pts received blood transfusions ranging between 0–16 units  ►Overall: A total of 17 pts had positive SBI. Active bleeding in 16 pts, who were transfused  an average of 8 units before the study.  ►55 pts had a negative SBI and no active bleeding was seen on their capsule studies. In this group, the average number of PRBC transfused was 1 unit.  There was one patient who had a false positive SBI with no active bleeding seen in the capsule study review. | Pts receiving blood transfusions are more likely  to have a positive SBI correlating with the localization of active bleeding |
| Liangpunsakul *et al*[96] | USA | Single centre | Assess  accuracy of SBI | Retrospective | ►Gold standard  Lesions detected by experienced CE reviewer  ►Significant lesions considered  AVMs, ulcers, erosions, active bleeding  ►Reviewing speed: 15fps | M2A  Given® Imaging Ltd | ►Gold standard: 109 lesions  ►SBI: 31 potential areas of blood; correctly identified lesions: 28  ►Overall:  SBI (Sens, PPV, accuracy): 25.7%, 90%, 34.8%, respectively  ►For actively bleeding SB lesions only:  SBI (Sens, PPV, accuracy): 81.2%, 81.3%, 83.3%, respectively | ► SBI has good sens andPPV for actively bleeding SB lesions |
| D'Halluin *et al*[97] | France | Multicentre  (7 centres) | Assess  sens/spec of SBI  (in OGIB) | Retrospective | ►Gold standard  Lesions detected by experienced CE reviewer  SBI tags marked by another investigator  ►Significant lesions considered  Bleeding or having a bleeding potential: high (P2), low (P1), or absent (P0)  ►Concordance: same time code in frames selected by expert reader and those tagged by SBI  ►Reviewing speed: NS | M2A  Given® Imaging Ltd | 156 SBCE recordings evaluated:  ►In 83 (normal): either no lesion (*n =* 71) or P0 lesion (*n =* 12)  ►In 73 abnormal: P2 (*n =* 114) and P1 (*n =* 92) lesions  ►154 red tags analysed:  SBI (Sens, spec, PPV, NPV) for P2 or P1: 37%, 59%, 50%, 46%, respectively | ► SBI-based detection of SB lesions (with bleeding potential) is of limited clinical value |
| Singnorelli *et al* [98] | Italy | Single centre | Assess sens/spec of SBI per lesion, overall, according to red findings (identified by the reader), and per patient | Retrospective | ►Gold standard  Lesions detected by four experienced CE reviewers  ►Outcomes : sens, spec and accuracy calculated both per lesion/patient  ►Reviewing speed: NS | M2A  Given® Imaging Ltd | ►95 patients; 209 red findings  ►Overall sens: 28%  ►Sens higher for identification of blood (61 %) than for nonbleeding “red” findings e.g. AVMs (26 %)  ►Per-patient sens, spec: 41%, 70%, respectively | ► SBI has low sens/spec in per-lesion and per-patient SBCE evaluation  ► Complementary/rapid screening tool  ► Complete review of the recordings is still necessary |
| Ponferrada *et al*[99] ❖ | Spain | Single centre | Assess accuracy/performance of SBI | Prospective | ►Gold standard  Lesions detected by experienced CE reviewers | M2A  Given® Imaging Ltd | ►57 consecutive patients  ►Indications:  OGIB (64.9%), CD (14%), malabsorption (14%), suspicion of SB tumour (7.1%)  ►SBI Sens, spec, PPV, NPV: 58.3%, 75.5%, 38.8%, 87.2%, respectively |  |
| Buscaglia *et al*[100] | USA | Single centre | Assess accuracy/performance of SBI according to CE indications | Retrospective | ►Gold standard  Lesions detected by experienced CE reviewer  ►Significant lesions:  AVMs, varices, venous ectasias, red spots, ulcers, erosions, blood, blood clots  ►Concordant and discordant findings between CE reviewer and SBI  ►Reviewing speed: 8-15fps | M2A  Given® Imaging Ltd | ►CE indications: OGIB (*n =* 112), suspected CD (*n =* 122), anaemia of unknown origin (*n =* 53), other (*n =* 4)  ►221 lesions with bleeding potential  ►Overall: SBI (sens, spec, PPV, NPV): 56.4%, 33.5%, 24.0%, 67.3%, respectively  ►For actively bleeding lesions: SBI (sens, PPV): 58.3%, 70%, respectively  ►For suspected CD: SBI (sens, NPV): 64%, 80.4%, respectively  ►For OGIB: SBI sens 58.3%  ►For anaemia: SBI sens 41.3% | ► SBI performance characteristics suboptimal/insufficient to screen for SB lesions with bleeding potential  ► Even in pts with active intestinal bleeding, SBI sens was only <60% |
| Park *et al*[101] | S. Korea | Single centre | Investigate whether SBI is affected by background colour and CE velocity | Experimental | ►Paper-made phantom SB models in a variety of colours to simulate the background colours observed in CE  ►Red spots were attached inside them  ►CE manually passed through models  ►SBI red spots detection rate was evaluated based on colours of SB models and CE velocities (0.5, 1, 2 cm/s) | M2A  Given® Imaging Ltd | ►SBI red spots detection rate differed significantly per background colour of SB model, *P* <0.001  ►SBI red spots detection rate highest for very pale magenta, burnt sienna, yellow background  ►SBI red spots detection rate lowest for dark brown, very pale yellow background  ►SBI red spots detection rate decreases at rapid CE passage (1-2 cm/s) compared to slower (0.5 cm/s) for very pale yellow (*P* =0.042), yellow (*P* =0.001), very pale magenta (*P* =0.002), burnt sienna (*P* =0.001) background.  ►Red spots detection rate no different according to velocity for light greyish pink (*P* =0.643) or dark brown (*P* =0.396) background. | ► SBI sens affected by background colour and capsule passage velocity in the models |

PRBC: Pack red blood cells; fps: Frames per sec; SBI: Suspected blood indicator; CE: Capsule endoscopy; AVM: Arterio-venous malformations; SB: Small-bowel; sens: Sensitivity; spec: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; OGIB: Obscure gastrointestinal bleeding; CD: Crohn’s disease.

**Table 8** **Studies looking at the clinical validity of QuickView, feature of capsule endoscopy reading software, in small-bowel capsule endoscopy**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **QuickView sampling rate** | **QuickView reading frame mode/**  **Reading Speed (fps)** | **Average reading time (mean)** | **Comparison with/**  **Reading frame mode/**  **Reading speed used (fps)** | **Rapid®Reader**  **version** | **No of reviewers** | **No of cases (Total)** | **No of cases**  **(OGIB)** | **No of cases**  **(CD)** | **No of cases**  **(polyposis)** | **No of cases**  **(other)** | **QuickView**  **Sensitivity (%)** | **QuickView**  **Specificity (%)** | **Lesionsmissed**  **(No of cases)** |
| Schmelkin[101]❖ | NS | NS | NS | NS | 4.0 | 1 | 47 | 47 | N/A | N/A | N/A | 100 | 100 | N/A |
| Diaz *et al*[102]❖ | NS | NS  25, 15, 5 | NS | NS | NS | 2 | 57 | 37 | 12 | N/A | 8 | NS | NS | NS |
| Ponferrada  *et al*[97]❖ | NS | 25, 15, 5 | NS | Conventional/ns/15,15,5 |  | 2 | 57 | 37 | 8 | N/A | 12 | 91.2(25fps); 93(15fps); 96.5(5fps) | NS | NS |
| Appalaneni *et al*[103]❖ | NS | Single frame  25 | 3 min | NS | NS | 2 | 50 | NS | NS | NS | NS | NS | NS | 2 |
| Westerhof *et al*[104] | High (17) | NS | 4.4 min(median) | Conventional/Dual View/18 | 4.0 | 2 | 100 | 56 | 30 | 2 | 12 | NS | NS | 13 |
| Shiotani *et al*[105] | High (17) | Single  6 | 17.9 min | NS | 5.0 | 3 | 44 | NS | NS | NS | 14 | NS | NS | 10 |
| Hosoe *et al*[106] | Normal | NS | NS | NS | 5.0 | 3 | 45 | NS | NS | NS | 14 | NS | NS | NS |
| Saurin *et al*[107] | NS | NS | 11.6 min | Conventional/NS/NS | 5.0 | 12 | 106 | 106 | N/A | N/A | N/A | 89.2 | 84/7 | 8 |
| Shiotani *et al*[108] | 5, 15, 25, 35 | Single  NS | NS | NS | 6.5 | 4 | 87 | NS | NS | NS | NS | NS | NS | NS |
| Koulaouzidis *et al*[109] | 35 | Dual View (WL+BM)  18 | 475 s (QuickView WL)  450 s (QuickView BM) | Conventional/Single or Dual View/12-20 | 7.0 | 1 | 200 | 106 | 81 | 4 | 9 | 92.3 (QVWL P1+P2)  91 (QVBM P1+P2) | 96.3 ( QVWL P1+P2)  96 (QVBM P1+P2) |  |
| Kyriakos *et al*[110] | NS | NS  3 | 16.3 min (6.7) | Conventional /NS/NS | 5.0 | 2 | 100 | 55 | 22 | 3 | 20 | NS | NS | 12 |

NS: Not stated; NA: Not applicable; fps: Frames per second; QVWL; QuickView with white light; QVBM: QuickView with blue mode; OGIB: Obscure gastrointestinal bleeding; CD: Crohn’s disease; P1,P2: classification as per probability of bleeding.

**Table 9 Studies looking at the clinical validity of Fujinon® Intelligent Chromo endoscopy Enhancement /Blue Mode, feature of capsule endoscopy reading software, in small-bowel capsule endoscopy**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Country** | **Centre** | **Study type** | **Objective/s** | **Design** | **Images** | **FICE** | **CE** | **Outcome/s** |
| Imagawa *et al*[112] | Japan | Single Centre | Retrospective | Assess whether visualization of SB lesions improves with FICE | ►5 experienced readers compared CE-WL images to their FICE counterparts | ►Angioectasias (*n =* 23)  ►Erosion/ulcers(*n =* 47  ►Tumour(*n =* 75) | FICE 1,2,3 | PillCam®SB1;  Given®Imaging Ltd | ►FICE 1:  AVMs: improvement in 87%(20/23) cases  Erosion/ulceration: improvement 53.3%(26/47) cases  Tumour images: improvement 25.3%(19/75) cases  ►FICE 2:  AVMs: improvement in 87%(20/23) cases  Erosion/ulceration: improvement in 25.5%(12/47) cases  Tumour images: improvement in 20.0%(15/75) cases  ►FICE 3:  All images groups: only equivalence achieved in all cases.  Intra-observer agreement: good to satisfactory( 5.4 or higher) |
| Imagawa *et al*[113] | Japan | Single Centre | Prospective | Assess whether FICE improves detection rate of SB lesions in CE | ►A CE reader  reviewed CE-WL videos  ►Another reader, reviewed CE-FICE videos with FICE 1,2,3 | 50 pts | FICE 1,2,3 | PillCam®SB1;  Given®Imaging Ltd | ►Angioectasias detection  CE-WL: 17 AVMs  CE-FICE 1: 48 AVMs  CE-FICE 2: 45 AVMs  CE-FICE 3: 24 AVMs  Significant CE-FICE 1and2 (*P*=0.0003 and <0.0001, respectively)  ►Detection rate for erosion, ulceration and tumour did not differ statistically between CE-WL and CE-FICE 1,2,3  ►Similar interpretation time (CE-WL: 36±6.9min; CE-FICE 1: 36±6.4min; FICE 2: 38±5.8min; FICE 3: 35±6.7min) |
| Gupta *et al*[114] | Belgium | Single Centre | Retrospective | Assess potential benefit of FICE for SB lesion detection in patients with OGIB | ►CE videos analysed by 2 GI fellows with and without FICE 1,2,3  ►Reference standard:  Senior consultant described findings as  P0, P1 and P2 lesions | 60 pts with OGIB | FICE 1,2,3 | PillCam®SB1;  Given®Imaging Ltd | ►Overall, 157 lesions diagnosed with CE-FICE *vs* 114 with CE-WL (p=0.15).  ►For P2 lesions; CE-FICE Sens/Spec: 94%/95% vs CE-WL Sens/Spec: 97%/96%, respectively  5/ 55 AVMs better characterized with CE-FICE than CE-WL  ►More P0 diagnosed by CE-FICE than CE-WL(39 *vs* 8, p<0.001)  ►Intra-class kappa correlations between fellows and reference: CE-FICE *vs* CE WL for P2 lesions: 0.88 *vs* 0.92  CE-FICE *vs* CE WL for P1 lesions: 0.61 *vs* 0.79 |
| Krystallis *et al*[115] | UK | Single Centre | Retrospective | Assess FICE and BLUE Mode visualisation of SB lesions in CE | ►2 experienced reviewers CE-WL images to  FICE/BLUE Mode counterparts | ►Angioectasias (*n =* 18)  ►Erosion/ulcers(*n =* 60  ►Villi oedema (*n =* 17)  ►Cobblestone(*n =* 11)  ►Blood lumen (*n =* 15)  ►LICS/other(*n =* 46) | BLUE Mode  FICE 1,2,3 | Pillcam®SB1/SB2; Given®Imaging Ltd | ►Total of 167 images; for all lesion categories:  ►BLUE Mode *vs* WL: image improvement in 83%; k: 0.786  ►FICE 1 *vs* WL: image improvement in 34%; k: 0.646  ►FICE 2 *vs* WL: image improvement in 8.6%; k: 0.617  ►FICE 3 *vs* WL: image improvement in 7.7%; k: 0.669 |
| Duque *et al*116] | Portugal | Single Centre | Prospective | Assess reproducibility and diagnostic accuracy of CE-FICE | ►4 physicians reviewed 150 FICE images  ►2 experienced physicians analysed 20 CE. One interpreted CE-WL; the other, CE-FICE videos | 20 patients with OGIB | BLUE mode  FICE 1,2,3 | PillCam®SB2;  Given®Imaging Ltd | ►Concordance between the 4 gastroenterologists: 0.650  ►CE-WL identified 75 findings and the CE-FICE 95  ►CE-FICE did not miss any lesions identified by CE-WL and allowed the identification of a higher number of AVMs (35 *vs* 32) and erosions (41 *vs* 24) |
| Nakamura *et al*[117] | Japan | Single Centre | Prospective | Assess preview of angioectasias by CE-FICE preview  (compared to CE-WL) | ►One experienced physician analysed CEs in QuickView mode  ►Mean reading time, sensitivity and specificity for angiodysplasia detection were evaluated including SBI | 50 pts with angiodysplasia were randomly assigned to 2 equally sized groups of CE-WL reading and  CE-FICE reading | SBI  BLUE mode  FICE 1,2,3 | PillCam®SB2;  Given®Imaging Ltd | ►Mean reading time: 14min for both CE-WL and CE-FICE reading  ►The two previews for angiodysplasia were significantly superior to the function of SBI (*P*<0.01)  ►Sens and spec of CE-WL: 80% and 100%, respectively  ►Sens and spec of CE-FICE: 91% and 86%, respectively  ►FICE reading was superior in sens, while it resulted in more false (+) ve lesion findings and lower spec |
| Sakai *et al*[118] | Japan | Single Centre | Prospective | ►Assess whether CE-FICE improves detectability of SB lesions by CE trainees and if it contributes to reducing the bile-pigment effect  ►evaluate whether poor bowel preparing affects the accuracy of lesion recognition by FICE | ►4 gastroenterology trainees interpreted 12 CE videos with WL and FICE 1,2,3  ►Lesion detection rate under each of the three FICE settings was compared with that by conventional CE-WL | ►60 AVMs  ►82 erosions/ulcers | FICE 1,2,3 | PillCam®SB2;  Given®Imaging Ltd | ►60 angioectasias; CE trainees identified:  26 by CE-WL, 40 by CE-FICE1, 38 by CE-FICE2, 31 by CE-FICE3  ►82 erosions/ulcerations, CE trainees identified:  38 by CE-WL, 62 by CE-FICE1, 60 CE- FICE2, 20 by CE-FICE3  ►CE-FICE 1 and 2 significantly improved detectability of angioectasias (p 0.0017 and p=0.014, respectively) and erosions/ulcers (p=0.0012 and p=0.0094, respectively)  ►Detectability of SB lesions by CE-WL (p=0.020) and CE-FICE2 (p=0.0023) was reduced by the presence of bile-pigments  ►Detectability of SB lesions by CE-FICE1 was not affected (p=0.59) by the presence of bile-pigments  ►In poor bowel visibility conditions, CE-FICE yielded a high rate of false-positive findings |

FICE: Fujinon® Intelligent Chromo endoscopy Enhancement; CE: Capsule Endoscopy; SB: Small Bowel; WL: White Light; OGIB: Obscure Gastrointestinal Bleeding; SBI: Suspected Blood Indicator; AVM: arterio-venous malformation; K: inter-observer agreement; LICS: Lesions of indeterminate Clinical significance; Sens: Sensitivity; Spec: Specificity.

**Table 10 Experimental and models in development for capsule-endoscopy the future?**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | | **Project** | **Status** | **Active Actuation** | **Magnetic Propulsion** | | **Therapeutic Capabilities** | | |
| Tang *et al* [124] | | IDEAS: a miniature lab-in-a-pill multi-sensor microsystem | Prototype | No | Yes | | Yes | | |
| Karagozler *et al*[125] | | Miniature endoscopy capsule robot using biomimetic micro-patterned adhesives | Prototype | Yes | No | | No | | |
| Quirini *et al*[126] | | An approach to capsular endoscopy with active motion | Prototype | Yes | No | | No | | |
| Valdastri *et al*[127] | Wireless therapeutic endoscopic capsule: in vivo experiment | | Prototype | No | | Yes | | Yes |
| Glass *et al*[128] | | A legged anchoring mechanism for capsule endoscopes using micro-patterned adhesives | Prototype | Yes | No | | No | | |
| Valdastri *et al*[129] | | An endoscopic capsule robot: a meso-scale engineering case study | Concept | Yes | No | | No | | |
| Tortora *et al*[130] | | Propeller-based wireless device for active capsular endoscopy in the gastric district | Prototype | Yes | No | | No | | |
| Valdastri *et al*131] | | A magnetic internal mechanism for precise orientation of the camera in wireless endoluminal applications | Prototype | No | Yes | | No | | |
| Ciuti *et al*[132] | | Robotic magnetic steering and locomotion of capsule endoscope for diagnostic and surgical endoluminal procedures | Prototype | No | Yes | | Yes | | |
| Bourbakis *et al*[133] | | Design of new-generation robotic capsules for therapeutic and diagnostic endoscopy | Concept | Yes | No | | Yes | | |
| Gao *et al*[134] | | Design and fabrication of a magnetic propulsion system for self-propelled capsule endoscope | Concept | No | Yes | | No | | |
| Simi *et al*[135] | | Design, fabrication, and testing of a capsule with hybrid locomotion for gastrointestinal tract exploration | Concept | No | Yes | | No | | |
| Morita *et al*[136] | | A further step beyond wireless capsule endoscopy | Concept | No | Yes | | No | | |
| Yang *et al*[137] | | Autonomous locomotion of capsule endoscope in gastrointestinal | Concept | Yes | No | | No | | |
| Filip *et al*[138] | | Electronic Stool (e-Stool): A Novel Self-Stabilizing Video Capsule Endoscope for Reliable Non-Invasive Colonic Imaging | Prototype | Yes | No | | No | | |
| Yim and Sitti[139] | | Design and rolling locomotion of a magnetically actuated soft capsule endoscope | Prototype | Yes | No | | No | | |
| Kong *et al*[140] | | A Robotic Biopsy Device for Capsule Endoscopy | Prototype | Yes | No | | Yes | | |
| Woods *et al*[141] | | Wireless Capsule Endoscope for Targeted Drug Delivery: Mechanics and Design Considerations | Prototype | Yes | No | | Yes | | |