Small-bowel capsule endoscopy: A ten-point contemporary review

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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 obscure gastrointestinal bleeding, known and/or suspected Crohn's disease and possible small-bowel neoplasia. A 2-L polyethylene glycol-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 non-steroidal anti-inflammatory drugs, to evaluate the type and extent of mucosal damage and, more importantly from a clinical point of view, in patients with known or suspected 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, QuickView and Fujinon Intelligent Chromo Endoscopy are some of the software tools that have been checked in various clinical studies to date.

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tion 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], Professor Swain presented the world’s first wireless capsule endoscope.

Indeed, the brainchild of Iddan[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 contemporary 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 source of further reading and reference.

WHICH ARE THE DIFFERENCES AMONG THE CURRENT COMMERCIALY AVAILABLE CAPSULES?

Since 2001, the year of approval by the Food and Drug Administration of the first video capsule with the proprietary, yet slightly unfortunate, brand name mouth-to-anus (M-A®; 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)[6,7]. 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 (Table 2)[8-11].

DO HIGH-GRAGE EVIDENCE SUPPORT THE USE OF CE 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: Obscure gastrointestinal bleeding (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, small-bowel polyposis syndromes and clinical suspicion of small-bowel neoplasia[15,16]. Therefore, we decided to summarise (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 small-bowel 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[13,30].

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[22,30]. 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].
Table 1  Available types of small-bowel capsule endoscopes and operating characteristics

| Capsule device | Company | Country | Field of view (°) | Lens | Image sensor | Optical enhancements | Reviewing software | FDA approval | Weight (g) | Battery life (h) | Frames per second (fps) | Dimensions (mm) | FDA review software | Operating characteristics |
|----------------|---------|---------|------------------|------|--------------|---------------------|-------------------|--------------|-----------|-----------------|-------------------------|--------------------------|-------------------------|-----------------------------|
| PillCam® SB2 | Given Imaging, Yokneam, Israel | 150 | Multi-element | CMOS | CMOS, CMOS | Radiofrequency | 密封7 | Yes | 3.45 | 11 × 26 | 3.45 | 9–11.5 | No | 核心8 |
| MiniCam® V2 | IntroMedic Co., Seoul, Korea | 170 | N/A | CMOS | CMOS | Radiofrequency | 密封V2 | Yes | 3.2 | 11 × 24 | 10 | 12 | No | 密封V2 |
| EndoCapsule | EndoCapsule Co., Tokyo, Japan | 146 | N/A | CMOS | CMOS | Radiofrequency | 密封V2 | Yes | 3 | 11 × 26 | 12 | 10 | Yes | 密封V2 |
| MiroCam® v2 | MiroView Co., Ltd., Korea | 140 | N/A | CMOS | CMOS | Radiofrequency | 密封v2 | Yes | 3 | 11 × 26 | 12 | 10 | Yes | 密封v2 |
| CapsoCam® SV1 | ALICE, A Large Ion Collider Experiment, United States | 360 | N/A | N/A | N/A | Radiofrequency | 密封v2 | No | 16 | 11 × 31 | 6 | 13 × 31 | No | 密封v2 |
| PillCam® SB2 (L) captures 2 fps - PillCam® SB2 (H) captures 4 fps - PillCam® SB2 (S) captures 8 fps - PillCam® SB2 battery life > 11.5 h - PillCam® SB2 battery life > 8 h. LED: Light-emitting diode; N/A: Not available; CMOS: Complementary metal-oxide-semiconductor; CCD: Charge-coupled device; EP: Electric field propagation; EPROM: Erasable programmable read-only memory; USB: Universal Serial Bus; FDA: Food and Drug Administration; FICE: Fujinon Intelligent Chromo Endoscopy; ALICE: A Large Ion Collider Experiment.

**IS THERE A ROLE FOR FAECAL TESTING (CALPROTECTIN) AS “SELECTION TOOL” FOR CAPSULE ENDOSCOPY**

Due to its high DY and its negative predictive value (NPV), CE has shown considerable cost-effectiveness. However, CE still remains less widely available and likely more expensive, when compared to other diagnostic modalities for the small-bowel. 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% 𝑖𝑛 [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. 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 non-steroidal anti-inflammatory drugs, to evaluate the type and extent of mucosal damage (Table 4) and, more importantly from a clinical point of view, in patients with known or suspected CD for assessment of inflammation activity (Table 4). In these patients, although there is no clear agreement on a cut-off level, FC seems to be a cost-effective “screening test”, able to identify those with higher possibility to present small-bowel lesions.

**HAS CE THE SAME DIAGNOSTIC CAPABILITY ALONG THE SMALL BOWEL?**

There are several papers, mostly case presentations and/or case series, reporting patients in whom CE failed to identify small-bowel lesions which were subsequently diagnosed by other modalities. Such missed lesions (including neoplastic pathology) were occasionally large and often located in the proximal small-bowel. Although there is still a lot of debate about the reasons of poor SBCE performance, it is worth remembering that for any non-steerable capsule progress is more rapid in the proximal than in lower segments of the small-bowel; 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. Hence, this evidence base provides an indirect confirmation of the limitations of SBCE in evaluating the proximal small-bowel.

Interestingly, even in earlier studies 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.
Table 2  Head-to-head trials of small-bowel capsule endoscopy systems

| Ref. | Country | Centre Objective(s) | Study type | Design | Outcome(s) |
|------|---------|----------------------|------------|--------|------------|
| [6]  | Germany | Single centre evaluation of technical live performance and DY comparison of EndoCapsule SB (Olympus America, Allentown, PA) vs PillCam SB (Given Imaging, Yoqneam, Israel) and MiroCam (IntroMedic Co. Ltd., Seoul, South Korea); | Prospective | Head-to-head comparison of 2 capsule systems | • CR: PillCam SB 33/40 (82%); EndoCapsule 40/40 (100%); MiroCam 25/30 (83.3%); CR=NS; PillCam SB vs EndoCapsule; EndoCapsule vs MiroCam; EndoCapsule vs PillCam SB. CR=NS; PillCam SB vs MiroCam; MiroCam vs EndoCapsule; MiroCam vs PillCam SB. CR NS. | • CR: PillCam SB 33/40 (82%); EndoCapsule 40/40 (100%); MiroCam 25/30 (83.3%); CR=NS; PillCam SB vs EndoCapsule; EndoCapsule vs MiroCam; EndoCapsule vs PillCam SB. CR=NS; PillCam SB vs MiroCam; MiroCam vs EndoCapsule; MiroCam vs PillCam SB. CR NS. |
| [7]  | USA     | Single centre evaluation of technical live performance and DY comparison of PillCam SB vs EndoCapsule and MiroCam | Prospective | Head-to-head comparison of 2 capsule systems | • CR: PillCam SB vs EndoCapsule and MiroCam; CR=NS. | • CR: PillCam SB vs EndoCapsule and MiroCam; CR=NS. |
| [8]  | USA     | Single centre evaluation of technical live performance and DY comparison of PillCam SB vs EndoCapsule and MiroCam | Prospective | Head-to-head comparison of 2 capsule systems | • CR: PillCam SB vs EndoCapsule and MiroCam; CR=NS. | • CR: PillCam SB vs EndoCapsule and MiroCam; CR=NS. |

DY: Diagnostic yield; CE: Capsule endoscopy; OGB: Obscure gastrointestinal bleeding; pts: Patients; CR: Completion rate; NS: Not significant (statistically); SB: Small-bowel; SBTT: Small-bowel transit time.
Most common indications: OGIB (60%); investigation of clinical symptoms (0.6%); definite suspected CD (0.4%);

Pooled DRs for overall, OGIB, CD, neoplasia: 59.4%, 60.5%, 55.3%, 55.9%, respectively;

Commonest cause for OGIB: angiodysplasia (50%);

Pooled CRs (overall): 83.5%, breakdown: 83.6% (OGIB), 84.8% (clinical symptoms); 84.2% (CD);

Pooled CRs (overall): 14.5%, breakdown: 12% (OGIB), 26% (clinical symptoms); 21% (CD);

Hence, most common indication for SBCE vs OGIB, with high DR and low RR.

A relatively high RR is associated with definite/suspected CD and neoplasms

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

| Ref. | Title | Search (start-end date) | Type | Subject | Data extractors | Titles entered meta-analysis | Individuals included | Outcome/conclusion |
|------|-------|------------------------|------|---------|----------------|-----------------------------|---------------------|-------------------|
| Liao et al | Indications, detection, completion, and retention rates of SBCE: A systematic review | 2000-June 2009 | Systematic review of evidence base | Indications, DR, CR and RR of SBCE | 227 | 227 | 227.53 | Pts; 22840 CE |
| Marmo et al | Meta-analysis: Capsule enteroscopy in diagnosis of small bowel diseases | 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 (290 OGIB and 237 CD) |
| Triester et al | A meta-analysis of the yield of CE compared to other diagnostic modalities in patients with OGIB | N/A-April 2005 | Meta-analysis of diagnostic test accuracy | IY (yield of CE-yield of comparative modality) and 95%CI of CE over comparative modalities | 2 | 80 | 14 | 396 CE-PF | 88 CE-SBBaR |
| Leighton et al | Capsule enteroscopy: A meta-analysis for use with OGIB and CD | N/A-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 | 517 pts |
| Leighton et al | Capsule enteroscopy: A meta-analysis for use with OGIB and CD | N/A-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 | 517 pts |
| Triester et al | A meta-analysis of the yield of CE compared to other diagnostic modalities in patients with non-stricturing SB Crohn’s disease | N/A-Aug 2005 | Meta-analysis of diagnostic test accuracy | IY (yield of CE-yield of comparative modality) and 95%CI of CE over comparative modalities | 2 | 82 | 9 | 250 pts |

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A relatively high RR is associated with definite/suspected CD and neoplasms

For OGIB, 37% (95%CI: 29.6-44.1) for Crohn's disease 45% (95%CI: 30.9-58.0);

For clinically significant findings DY was 42% (CE) vs 36% (SBBaR) IY = 36%

For OGIB, 37% (95%CI: 29.6-44.1) for Crohn's disease 45% (95%CI: 30.9-58.0);

For CE over PE/SB radiography to diagnose 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, C + IL, CT enterography, PE for diagnosing non-stricturing SBCD;

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 alternative methods;

Sub-analysis (pts with suspected CD): no difference in DY CE vs SBBaR (n = 88), IL (n = 48), CT enterography (n = 10), PE (n = 100);
| Reference | Methodology | Study Parameters | Key Findings |
|-----------|-------------|-----------------|--------------|
| Pasha et al. | Meta-analysis | 12 eligible studies (6 prospective/6 retrospective), including 16 sets of data; | - Significant difference in SBVQ 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); | - There was no statistically significant difference regarding CR rate. Purgatives did not affect VCE GTT or VCE SBTT. |
| Chen et al. | Meta-analysis | 8 studies (n = 277 pts) prospectively compared the yield of CE and DBE were included; | - No difference between the yield of CE and DBE (70/277 vs 156/277, OR 1.21, 95%CI: 0.64-2.29); | - No major complications reported; |
| Rokkas et al. | Meta-analysis | For suspected CD, several comparisons met statistical significance; Yields in this subgroup were: CE vs GTT: 71% (IYW = 3%, 95%CI: 58%-74%), CE vs SBTT: 63% (IYW = 6%, 95%CI: 50%-76%), CE vs SBCE: 71% (IYW = 7%, 95%CI: 61%-80%); | - No significant difference regarding CR rate. Purgatives did not affect VCE GTT or VCE SBTT. |
| Dionisio et al. | Meta-analysis | For suspected CD, several comparisons met statistical significance; Yields in this subgroup were: CE vs GTT: 71% (IYW = 3%, 95%CI: 58%-74%), CE vs SBTT: 63% (IYW = 6%, 95%CI: 50%-76%), CE vs SBCE: 71% (IYW = 7%, 95%CI: 61%-80%); | - No significant difference regarding CR rate. Purgatives did not affect VCE GTT or VCE SBTT. |
| Wu et al. | Meta-analysis | Adequate or excellent SB mucosa visualization in pts receiving Simethicone for GI endoscopic visibility; | - Adequate or excellent SB mucosa visualization in pts receiving Simethicone vs those who did not (66.1% vs 37.2%); | - No significant difference regarding CR rate. Purgatives did not affect VCE GTT or VCE SBTT. |
| Rokkas et al. | Meta-analysis | For suspected CD, several comparisons met statistical significance; Yields in this subgroup were: CE vs GTT: 71% (IYW = 3%, 95%CI: 58%-74%), CE vs SBTT: 63% (IYW = 6%, 95%CI: 50%-76%), CE vs SBCE: 71% (IYW = 7%, 95%CI: 61%-80%); | - No significant difference regarding CR rate. Purgatives did not affect VCE GTT or VCE SBTT. |
CE has a significantly higher DY in patients with suspected and established SBCE-CD: A meta-analysis

Dominio et al.[29] 2010 - May 2009

- Meta-analysis of diagnostic test accuracy
- DY of CE vs. modalities in patients with suspected/established CD
- Pooled SBCE-DY in IDA: 47% (95%CI: 42%-52%), with significant heterogeneity among included studies

Wu et al.[2] 2009 - Nov 2009

- Systematic review and meta-analysis of RCTs of Simethicone for GI endoscopic visibility

- Systematic review of RCTs
- Simethicone and CE
- Pooled DY for CE: 62% (95%CI: 47.3%-76.1%)

- Use of CE in diagnosis and management of pediatric patients, based on meta-analysis

Cohen et al.[26] 2010 - Jan 2001

- Systematic review of evidence base
- Systematic compilation of data on indications and outcomes of CE in pediatric patients
- Pooled OR = 2.84 (95%CI: 1.74-4.65, P = 0.00); no significant heterogeneity (P = 0.28);
- Sensitivity analyses stratified by factors such as bowel preparation (purging vs. fasting): Significant results for bowel preparation + fasting (OR = 4.43, 95%CI: 1.82-10.76, P = 0.00) with P = 0.78, I^2 = 38.9%.

- DBE and CE for OGIB: An updated meta-analysis

Teshima et al.[30] 2010 - June 2001

- Meta-analysis of diagnostic test accuracy
- OGB/B vs. CE or DBE
- Pooled DY for CE: 62% (95%CI: 47.3%-76.1%)
- Pooled DBE-DY 56% (95%CI: 48.9%-62.1%); OR for CE vs. DBE 1.39 (95%CI: 0.88-2.20; P = 0.16).

- Meta-analysis: efficacy of SB preparation for SBCE

Behery et al.[31] 2010 - Jan 2001

- Meta-analysis of RCTs
- Purgative use vs. fasting alone for SBCE
- Pooled DY for CE: 62% (95%CI: 47.3%-76.1%)
- Pooled DBE-DY 56% (95%CI: 48.9%-62.1%); OR for CE vs. DBE 1.39 (95%CI: 0.88-2.20; P = 0.16).

- The role of video CE in the diagnosis of coeliac disease: A meta-analysis

Rokkas et al.[32] 2011 - N/A

- Meta-analysis of diagnostic test accuracy
- Coeliacac CE
- 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

- Diagnostic yield of SBCE in patients with IDA: A systematic review

Koulaouzidis et al.[33] 2011 - Jan 2001

- Systematic review of evidence base
- IDA and CE
- Pooled SBCE-DY in IDA: 47% (95%CI: 42%-52%), with significant heterogeneity among included studies (I^2 = 78.8%, P < 0.0001).
- Pooled SBCE-DY (subgroup 1: 4 studies focused solely on IDA pts): 66% (95%CI: 61.0%-72.3%, I^2 = 44.3%)
- Pooled SBCE-DY (subgroup 2: 20 studies not focusing only on IDA pts): 44% (95%CI: 39.4%-48%, I^2 = 64.9%);
- SBCE in subgroup 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; OGB/B: Observe gastrointestinal bleeding; DY: Diagnostic Yield; pts: Patients; IY: Incremental yield; GTT: Gastric transit time; SBTT: Small bowel transit time; SBCE: Small-bowel capsule endoscopy; OR: Odds ratio; RR: Relative risk; C + IL: Colonoscopy with ileoscopy; PE: Push enteroscopy; SBCD: Small bowel Crohn’s disease; CT: Computed tomography; IDA: Iron deficiency anemia; FEM: Fixed effect model.

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

| Ref. | Country | Centre | Study Design       | Participants | FC | CE | Objective(s) | Outcome(s) |
|------|---------|--------|--------------------|--------------|----|----|--------------|------------|
| Goldstein et al<sup>40</sup> | United States | Multi-centre | Prospective study, double-blind, placebo controlled | 334 healthy subjects | N/A | M2A®; Given® Imaging, Yokenearn, 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<sup>43</sup> | United Kingdom | Multi-centre | Prospective study, double-blind, placebo controlled | 139 healthy subjects | Phical Calprotectin Test Kit NovaTec Immunodiagnostics, GmbH Dietzenbac, Germany | M2A®; Given® Imaging, Yokenearn, 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 (P=0.019; vs naproxen, P < 0.001) |
| Smecuol et al<sup>43</sup> | Spain, Argentina, Multi-centre | Prospective study, non-blinded study | 20 healthy subjects | Calprest<sup>®</sup> Eurohospital Spa, Trieste, Italy | M2A®; Given® Imaging, Yokenearn, 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 (6.05 μg/g; range 1.9-79.2 μg/g) increased significantly after ASA use |
| Werlin et al<sup>43</sup> | United States, Israel | Multi-centre | Prospective study, N/A | 42 pts with CP<sup>®</sup> (aged 10-36 yr); 29 had pancreatic insufficiency | Calprest<sup>®</sup> Eurohospital Spa, Trieste, Italy | PillCam<sup>®</sup>SB; Given® Imaging, Yokenearn, 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, 235 μg/g (normal < 50) |
| Koulaouzidis et al<sup>43</sup> | United Kingdom | Single centre | Retrospective Chart study | 70 pts with suspected CD and 10-36 yr; ≥ 92% bi-directional endoscopy | CALPRO NovaTec Immunodiagnostics GmbH, Dietzenbac, Germany | PillCam<sup>®</sup>SB; Given® Imaging, Yokenearn, Israel | Value of FC as selection tool for further investigation of the SB with SBCE, in a cohort of pts with suspected CD | ▶Short-term administration of low-dose ASA associated with higher SBCE (65%); confirmed CD in 50%; ▶Measurement of FC prior SBCE: useful tool to select patients for referral. If FC < 100 μg/g SBCE is not indicated (NPV 1.0) |
| Jensen et al<sup>43</sup> | Denmark | Single centre | Prospective, blinded study | 83 pts from GI OPD clinics with suspected CD | Calprotectin ELISA, BÜHLMANN Laboratories AG, Basel, Switzerland | PillCam<sup>®</sup>SB; Given® Imaging, Yokenearn, 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 890 μg/g vs 830 mg/kg, respectively (P = 1.0); ▶FC cut-off ≤ 50 μg/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 t/o CD and select patients for endoscopy |
Koulouzidis A et al. Tabulated review on capsule endoscopy

Koulouzidis et al. United Kingdom Single retrospective review 49 pts known or suspected CD CALPRO NovaTec Immuno-diagnostics GmbH, Dietzenbach, Germany PillerCam®; Given® Imaging, Yokneam, Israel; MiroCam®; IntroMedic Co., Seoul, South 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 < 100 μg/g ▶ CECDAI levels of 3.8 and 5.8 correspond to 1.5 thresholds of 135 and 790, respectively

Sipponen et al. Finland Single prospective study 84 pts known or suspected CD Calpresp® Eurosperital SpA, Trieste, Italy PillerCam®; Given® Imaging, Yokneam, Israel; MiroCam®; IntroMedic Co., Seoul, South 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 ischamic stricture ▶ Median FC/S100A12: 22 μg/g (range: 2-342 μg/g) / 0.08 μg/g (range: 0.003-1.215 μg/g) ▶ 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 (0.087 μg/g, range: 0.008-0.896 μg/g): no difference between the groups (P = 0.166) ▶ Sens, Spec, PPV, NPV in detecting SB inflammation; FC (cut-off 50 μg/g): 59%, 71%, 42%, 83%; S100A12 (cut-off 0.06 μg/g): 59%, 66%, 38%, 82%, respectively

| Ref. | CE | Type of CE model; Company | AoV seen, n (%) | Reviewers speed (fps) | Frames AoV visible | Comments |
|------|----|--------------------------|-----------------|----------------------|-------------------|----------|
| Wijeratne et al. | 138 | NS | 9 (6.0) | 1 | NS | NS | 4 FAP patients (AoV not seen) |
| Kong et al. | 110 | M2A®; Given® Imaging Ltd. | 48 (43.6) | 2 | 15 | 3.5 ± 2.5 |
| Clarke et al. | 125 | M2A®; Given® Imaging Ltd. | 13 (10.4) | 5 | NS | |
| Iaquinto et al. | 23 | PillerCam®; Given® Imaging Ltd. | 0 (0.0) | 2 | NS | NS | |
| Metzger et al. | 20 | PillerCam®; Given® Imaging Ltd. | 1 (5.0) | NS | NS | |
| | | PillerCam®; Given® Imaging Ltd. | 5 (25.0) | NS | NS | |
| Katsinelos et al. | 14 | NS | 0 (0.0) | 1 | NS | N/A | FAP patients (11/23 had duodenal polypy) |
| Nakamura et al. | 96 | PILCam®; Given® Imaging Ltd. | 18 (18.0) | 2 | 10 | NS |
| Karagianni et al. | 10 | PILCam®; Colon; Given® Imaging Ltd. | 6 (6.0) | NS | NS | Two-headed PILCam® |
| Lee et al. | 30 | PILCam®; Given® Imaging Ltd. | 13 (43.3) | NS | NS | |
| | | PILCam®; Given® Imaging Ltd. | 15 (50.0) | NS | NS | |
| | | PILCam®; Given® Imaging Ltd. | 0 (0.0) | 2 | NS | N/A |
| Selby et al. | 50 | PILCam®; Given® Imaging Ltd. | 9 (18.0) | 2 | NS | |
| | | PILCam®; Given® Imaging Ltd. | 0 (0.0) | 2 | NS | N/A | Two-headed PILCam® |
| | | PILCam®; Given® Imaging Ltd. | 1 (0.0) | 2 | NS | N/A | |
| | | PILCam®; Given® Imaging Ltd. | 4 (36.4) | 1 | NS | Two-headed PILCam® |
| | | PILCam®; Given® Imaging Ltd. | 1 (14.3) | 1 | 9 | |
| | | PILCam®; Given® Imaging Ltd. | 13 (43.3) | 6 | 7 | 3.1 ± 1.1 |
| | | PILCam®; Given® Imaging Ltd. | 6 (20.0) | 6 | 9 | |
| | | PILCam®; Given® Imaging Ltd. | 28 (10.7) | 1 | 6 | 36.35 ± 72.34 |
| Koulaouzidis et al. | 148 | PILCam®; Given® Imaging Ltd. | 13 (8.9) | 1 | 6 | 42.46 ± 69.3 |
| | | MiroCam®; IntroMedic Ltd. | 18 (8.6) | 1 | 6 | 87.20 ± 248.4 |
| Friedrich et al. | 25 | CapsCam®SV1; Capsovision Ltd. | 22 (71) | 3 | NS | 3.1 ± 1.8 |

1Published only as abstracts; 2mean ± SD. CE: Capsule endoscopy; NS: Not stated; N/A: Not available or not applicable; AoV: Ampulla of Vater; fps: Frames per second; FAP: Familial adenomatous polyposis syndrome.

CAPSULE ENDOSCOPE ASPIRATION; HOW COMMON IS THIS?

Capsule enteroscopy is generally considered safe, having an overall complication rate of about 1%-3%. Indeed, 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. 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

Unoubtedly, the most feared complication of CE is...
potential hurdles for the method, were shown to be very infrequent and/or without clinically relevant consequences[67-71]. Conversely, capsule aspiration - an unexpected complication - has been reported with increasing frequency (Table 6)[72-98]. Overall, this is probably related to the increase in the mean age of patients undergoing CE. In fact, capsule aspiration occurs in 1 out of 800-1000 procedures[88] mostly in elderly male patients with comorbidities 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[99].

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 average lasts about 2-5 h[99]. 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[99]. Therefore, focused and unidivided 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[96-102], it can be used only as supportive tool[102].

Given®Imaging Ltd. has also introduced another software tool, which aims specifically at shortening the CE reading time, the QuickView. 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 QuickView 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[104-112]. Olympus has similar software function (express mode) and are we aware of a single relevant study with very similar results[113].

In the last few years, Given®Imaging Ltd., through a collaboration with Fujinon Inc., Japan introduced the electronic chromo-endoscopy (Fujinon Intelligent Chromo Endoscopy, FICE) 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)[114-120]. Although this seems to facilitate the detectability of small-bowel findings, it is still under question whether it proves to be clinically significant[121]. Similar function from Olympus Inc., shows promising results[122].

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=s+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[124,131,141,177].
### Table 6  Case reports of aspiration of capsule endoscopes

| Case | Comorbidities | Swallowing difficulties | Final diagnosis | No. of attempts to swallow CE/ingestion | Aspiration time/where in bronchial tree seen | Company |
|------|---------------|-------------------------|----------------|----------------------------------------|------------------------------------------|---------|
| Schneider<br>et al[72] | 50 s/bifurcation of the trachea | No Hx of dysphagia, coughing | Spontaneous resolution | 2 min/trachea-bronchi | NS | M2A® | Given Imaging Ltd. |
| Sin<br>et al[73] | No Hx of dysphagia, coughing | Last attempt recurrent coughing | Spontaneous resolution | 2 min/trachea-bronchi | NS | M2A® | Given Imaging Ltd. |
| Tabib<br>et al[74] | No Hx of dysphagia | Coughing, difficulty swallowing, gagging | Spontaneous resolution | 1/coughed several times | NS | M2A® | Given Imaging Ltd. |
| Rondinotti<br>et al[75] | No Hx of dysphagia | Coughing, difficulty swallowing | Spontaneous resolution | 2 weeks/trachea-bronchi | NS | M2A® | Given Imaging Ltd. |
| Tabib<br>et al[76] | No Hx of dysphagia | Coughing, difficulty swallowing | Spontaneous resolution | 1/coughed several times | NS | M2A® | Given Imaging Ltd. |
| Supph<br>et al[77] | No Hx of dysphagia | Coughing, difficulty swallowing | Spontaneous resolution | 2 days/lobar bronchus | NS | M2A® | Given Imaging Ltd. |
| Koulaouzidis<br>et al[78] | No Hx of dysphagia | Coughing, difficulty swallowing | Spontaneous resolution | 1/coughed several times | NS | M2A® | Given Imaging Ltd. |
| Le<br>et al[79] | No Hx of dysphagia | Coughing, difficulty swallowing | Spontaneous resolution | 1/coughed several times | NS | M2A® | Given Imaging Ltd. |
| Broderskov<br>et al[80] | No Hx of dysphagia | Coughing, difficulty swallowing | Spontaneous resolution | 1/coughed several times | NS | M2A® | Given Imaging Ltd. |
| Choi<br>et al[81] | No Hx of dysphagia | Coughing, difficulty swallowing | Spontaneous resolution | 1/coughed several times | NS | M2A® | Given Imaging Ltd. |
| Depriest<br>et al[82] | No Hx of dysphagia | Coughing, difficulty swallowing | Spontaneous resolution | 1/coughed several times | NS | M2A® | Given Imaging Ltd. |
| Depriest<br>et al[83] | No Hx of dysphagia | Coughing, difficulty swallowing | Spontaneous resolution | 1/coughed several times | NS | M2A® | Given Imaging Ltd. |
| Choi<br>et al[84] | No Hx of dysphagia | Coughing, difficulty swallowing | Spontaneous resolution | 1/coughed several times | NS | M2A® | Given Imaging Ltd. |
| Depriest<br>et al[85] | No Hx of dysphagia | Coughing, difficulty swallowing | Spontaneous resolution | 1/coughed several times | NS | M2A® | Given Imaging Ltd. |
| Choi<br>et al[86] | No Hx of dysphagia | Coughing, difficulty swallowing | Spontaneous resolution | 1/coughed several times | NS | M2A® | Given Imaging Ltd. |
| Depriest<br>et al[87] | No Hx of dysphagia | Coughing, difficulty swallowing | Spontaneous resolution | 1/coughed several times | NS | M2A® | Given Imaging Ltd. |
| Choi<br>et al[88] | No Hx of dysphagia | Coughing, difficulty swallowing | Spontaneous resolution | 1/coughed several times | NS | M2A® | Given Imaging Ltd. |
| Depriest<br>et al[89] | No Hx of dysphagia | Coughing, difficulty swallowing | Spontaneous resolution | 1/coughed several times | NS | M2A® | Given Imaging Ltd. |
| Choi<br>et al[90] | No Hx of dysphagia | Coughing, difficulty swallowing | Spontaneous resolution | 1/coughed several times | NS | M2A® | Given Imaging Ltd. |
| Depriest<br>et al[91] | No Hx of dysphagia | Coughing, difficulty swallowing | Spontaneous resolution | 1/coughed several times | NS | M2A® | Given Imaging Ltd. |
| Choi<br>et al[92] | No Hx of dysphagia | Coughing, difficulty swallowing | Spontaneous resolution | 1/coughed several times | NS | M2A® | Given Imaging Ltd. |
Kurtz et al. 73/male Renal cell cancer,  
MV (bovine), hyperlipidaemia, melena NS No Hx of dysphagia Sips of water, 1st attempt, 2 min later non-productive cough (20s) Level of carina; then right main stem bronchus Bronchoscopy-retrieval basket (multiple spontaneous ejections from trachea prior bronchscopy) NS

Lucendo et al. 80/male Advanced PD, DM, walking + speech difficulties PillCam®SB; Given Imaging Ltd. No Hx of dysphagia Several attempts/persistent coughing and some dyspnoea 20s/tracheobronchial tree Spontaneous resolution Oesophageal ulcer + ideal ulcer

Pezzoli et al. 82/male Unexplained anaemia, HTN NS No Hx of dysphagia NS/asymptomatic (minimal cough) 3d/in the right bronchus Spontaneous resolution NS

Parker et al. 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. 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

Poudel et al. 80/male NS COPD, GORD NS No Hx of dysphagia NS/NS brief coughing NS/left main bronchus Bronchoscopy-snare + Roth net Endoscopic placement with AdvanCE® device

Girdhar et al. 81/male COPD, GORD NS No Hx of dysphagia NS/NS NS/right main bronchus Rigid bronchoscopy-crocodile grasping forceps + stiff-wire basket with a pin-vise handle Endoscopic placement with AdvanCE® device

Gourou et al. 83/male NS COPD, GORD NS No Hx of dysphagia NS/NS NS/right main bronchus Rigid bronchoscopy-crocodile grasping forceps + stiff-wire basket with a pin-vise handle Endoscopic placement with AdvanCE® device

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. | United States Single centre | Accuracy of SBI to number of blood transfusions | Retrospective | ▶Gold standard for 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. | United States Single centre | Assess accuracy of SBI | Retrospective | ▶Gold standard for lesions detected by experienced CE reviewer; ▶Significant lesions considered AVMs, ulcers, erosions, active bleeding; ▶Reviewing speed: 35fps | M2A; Given Imaging Ltd. | ▶Gold standard: 109 lesions; ▶SBI: 31 potential areas of blood correctly identified lesions: 26; ▶Overall: SBI (sens, PPV, accuracy): 25.7%, 90%, 34.8%, respectively; ▶For actively bleeding SBI lesions only: SBI (sens, PPV, accuracy): 81.2%, 81.3%, 83.3%, respectively | SBI has good Sens and PPV for actively bleeding SB lesions |
For suspected CD: SBI (Sens, NPV): 64%, 80.4%, respectively; SBI has low Sens.

Assess Sens/Spec of SBI (in OGIB).

Gold standard for lesions detected by experienced CE reviewers: SBI tags marked by another investigator; SBI tags calculated both per lesion and per patient by two reviewers, SBI tags marked by another investigator; reviewing speed: NS.

For OGIB: SBI Sens 58.3%; for anaemia: SBI Sens 41.3%; for active intestinal bleeding: 58.3%, 70%, respectively; for actively bleeding lesions: SBI Sens, Spec, PPV, NPV: 58.3%, 75.5%, 75%, 87.2%, respectively.

Overall Sens: 28%; Spec of SBI: 80.4%, 95 patients; 209 red findings; reviewing speed: 8-15 fps.

Concordance: same time code in frames selected by the reader and those tagged by SBI; review time: NS.

Complete review of the recordings is still necessary.

Lagrange et al.®

Park et al.®

D'Halluin et al.®

Signorielli et al.®

France

Spain

Italy

United States

Korea

Assess Sens/Spec of SBI (in QOB).

M2A;

Imaging Ltd.

SBI has low Sens/Spec in per-lesion and per-patient SBI evaluation.

SBI-based detection and capsule passage velocity in the models.

Red spots detection rate differs significantly per background colour of SB model, background velocity in the models and capsule passage velocity (0.5, 1, 2 cm/s).

SBI red spots detection rate decreases at rapid CE passage (1-2 cm/s) (P = 0.042) and increases at low CE velocity (0.5 cm/s) (P = 0.001).

Red spots detection rate no different according to velocity for light brown (P = 0.643) or dark brown (P = 0.396) background.

Red spots detection rate decreases at rapid CE passage (1-2 cm/s) (P = 0.042) and increases at low CE velocity (0.5 cm/s) (P = 0.001).

Red spots detection rate no different according to velocity for light brown (P = 0.643) or dark brown (P = 0.396) background.

SBI performance characteristics: Sensitivity of SBI (Sen): 64%, 80.4%, respectively; SBI Sens higher for identification of blood (61%) than for nonbleeding red spots, e.g., AVMs (26%).

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Red spots detection rate no different according to velocity for light brown (P = 0.643) or dark brown (P = 0.396) background.
Table 8  Studies looking at the clinical validity of QuickView, feature of capsule endoscopy reading software, in small-bowel capsule endoscopy

| Ref.          | Country       | Centre                  | Study type      | Objective(s)                                                                 | Design                  | Images                                                                 | FICE | CE     | Cases                                                                 | QuickView               | Lesions missed |
|---------------|---------------|-------------------------|-----------------|-------------------------------------------------------------------------------|-------------------------|----------------------------------------------------------------------|------|--------|-----------------------------------------------------------------------|-------------------------|----------------|
| Imagawa et al. | Japan         | Single centre           | Retrospective   | Assess whether visualization of SB lesions improves with FICE                 | ▶ 5 experienced readers compared CE-WL images to their FICE counterparts | FICE 1,2,3 Given Imaging Ltd. | PillCam®SB1;       |                   | ▶ Angiectasias (n = 23); ▶ Erosion/ulcers (n = 47); ▶ Tumour (n = 75) | ▶ FICE 1: AVMs: improvement in 87% (20/25) cases; erosion/ ulceration: improvement 33.3% (26/78) cases; tumour images: improvement 25.3% (19/75) cases; ▶ FICE 2: AVMs: improvement in 87% (20/25) cases; erosion/ ulceration: improvement in 25.3% (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) | 92.3 (QVWL P1 + P2) 96 (QVWL P1 + P2)         | NS  |
|               |               |                         |                 |                                                                               |                         |                                                                       | 50   | pts    |                                                                       |                         | 12             |

Table 9  Studies looking at the clinical validity of Fujinon® intelligent chromoendoscopy 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     | Cases                                                                 | QuickView               | Lesions missed |
|---------------|---------------|-------------------------|-----------------|-------------------------------------------------------------------------------|-------------------------|----------------------------------------------------------------------|------|--------|-----------------------------------------------------------------------|-------------------------|----------------|
| Imagawa et al. | 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 | FICE 1,2,3 Given Imaging Ltd. | PillCam®SB1;       |                   | ▶ Angiectasias detection: CE-WL: 17 AVMs; CE-FICE 1: 48 AVMs; CE-FICE 2: 45 AVMs; CE-FICE 3: 24 AVMs; significant CE-FICE 1 and 2 (P = 0.0003 and P < 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 ± 6.9 min; CE-FICE 1: 36 ± 6.4 min; CE-FICE 2: 38 ± 5.8 min; CE-FICE 3: 35 ± 6.7 min) |                         | 12             |
|               |               |                         |                 |                                                                               |                         |                                                                       | 50   | pts    |                                                                       |                         | 12             |
### Gupta et al. [8]
Belgium | Single centre | Retrospective | 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

- Assess potential benefit of FICE for SB lesion detection in patients with OGIB
- FICE 1,2,3

### Krystallis et al. [9,10]
United Kingdom | Single centre | Retrospective | 2 experienced physicians reviewed CE-WL images to FICE/Blue mode counterparts
---|---|---|---
| | | | 20 patients with OGIB

- Assess reproducibility and diagnostic accuracy of CE-FICE
- CE videos analysed by 2 GI

### Duque et al. [11]
Portugal | Single centre | Prospective | 4 physicians reviewed 150 FICE images
---|---|---|---
| | | | 20 patients with OGIB

- Assess FICE and Blue mode visualisation of SB lesions in CE
- FICE 1,2,3

### Nakamura et al. [12]
Japan | Single centre | Prospective | One experienced physician analysed CE videos in QuickView mode; Mean reading time, sensitivity and specificity for angiodysplasia detection were evaluated including SBI
---|---|---|---
| | | | 50 pts with angiodysplasia

- Assess preview of angiodysplasia by CE-FICE preview (compared to CE-WL)
- FICE 1,2,3

### Sakai et al. [13]
Japan | Single centre | Prospective | 4 gastroenterology trainees interpreted 12 CE videos with WL and FICE 1,2,3
---|---|---|---
| | | | 60 AVMs

- Assess whether CE-FICE improves detectability of SB lesions by CE trainees and if it contributes to reducing the bile-pigment effect
- 82 erosions/ulcers

### Summary

- 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
- 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
- Concordance between the 4 gastroenterologists: 0.650;
- CE-WL identified 75 findings and the CE-FICE 95
- 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:
- 60 angiodysplasia; 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-FICE, 38 by CE-FICE2, 31 by CE-FICE3;
- CE-FICE 1 and 2 significantly improved detectability of angiodysplasia ($P = 0.0017$ and $P = 0.041$, respectively) and erosions/ ulcers ($P = 0.0012$ and $P = 0.0094$, respectively);
- Detectability of SB lesions by CE-FICE1 was not affected ($P = 0.59$) by the presence of bile-pigments;
- Detectability of SB lesions by CE-WL ($P = 0.020$) and CE-FICE2 ($P = 0.0023$) was reduced by the presence of bile-pigments;
- In poor bowel visibility conditions, CE-FICE yielded a high rate of false-positive findings

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**FICE**: Fujinon Intelligent chromoendoscopy enhancement; **CE**: Capsule endoscopy; **SB**: Small bowel; **WL**: White light; **OGIB**: Obscure gastrointestinal bleeding; **SBI**: Suspected Blood Indicator; **AVM**: arterio-venous malformation; **κ**: 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 |
|------------|--------------------------------------------------------------------------|-----------|------------------|---------------------|-------------------------|
| Johannessen et al[79] | IDEAS: A miniature lab-in-a-pill multi-Sens or microsystem               | Prototype | No                | Yes                 | Yes                     |
| Karagözler et al[90] | Miniature endoscopy capsule robot using biomimetic micro-patterned adhesives | Prototype | Yes               | No                  | No                      |
| Quirini et al[94] | An approach to capsule endoscopy with active motion                        | Prototype | Yes               | No                  | No                      |
| Valdastri et al[123] | Wireless therapeutic endoscopic capsule: in vivo experiment                  | Prototype | No                | Yes                 | Yes                     |
| Glass et al[124] | A legged anchoring mechanism for capsule endoscopes using micro-patterned adhesives | Prototype | Yes               | No                  | No                      |
| Valdastri et al[125] | An endoscopic capsule robot: a meso-scale engineering case study          | Concept   | Yes               | No                  | No                      |
| Tortora et al[128] | Propeller-based wireless device for active capsule endoscopy in the gastric district | Prototype | Yes               | No                  | No                      |
| Valdastri et al[130] | A magnetic internal mechanism for precise orientation of the camera in wireless endoluminal applications | Prototype | No                | Yes                 | Yes                     |
| 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                  | No                      |
| Gao et al[134] | Design and fabrication of a magnetic propulsion system for self-propelled capsule endoscopy | 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 tract       | Concept   | Yes               | No                  | No                      |
| Filip et al[138] | Electronic stool (e-Stool): A novel self-stabilizing video capsule endoscope for reliable non-invasive colon imaging | Prototype | No                | Yes                 | No                      |
| Yim et al[139] | Design and rolling locomotion of a magnetically actuated soft capsule endoscope | Prototype | No                | Yes                 | No                      |
| Kong et al[140] | A robotic biopsy device for capsule endoscopy                               | Prototype | No                | Yes                 | No                      |
| Woods et al[141] | Wireless capsule endoscope for targeted drug delivery: Mechanics and design considerations | Prototype | No                | Yes                 | Yes                     |

Certain issues (i.e., best small-bowel preparation for CE[143,144]), 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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