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Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2022

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MAIN RECOMMENDATIONS

MR1 ESGE recommends small-bowel capsule endoscopy as the first-line examination, before consideration of other endoscopic and radiological diagnostic tests for suspected small-bowel bleeding, given the excellent safety profile of capsule endoscopy, its patient tolerability, and its potential to visualize the entire small-bowel mucosa.
Strong recommendation, moderate quality evidence.

MR2 ESGE recommends small-bowel capsule endoscopy in patients with overt suspected small-bowel bleeding as soon as possible after the bleeding episode, ideally within 48 hours, to maximize the diagnostic and subsequent therapeutic yield.
Strong recommendation, high quality evidence.

MR3 ESGE does not recommend routine second-look endoscopy prior to small-bowel capsule endoscopy in patients with suspected small-bowel bleeding or iron-deficiency anemia.
Strong recommendation, low quality evidence.

MR4 ESGE recommends conservative management in those patients with suspected small-bowel bleeding and high quality negative small-bowel capsule endoscopy.
Strong recommendation, moderate quality evidence.

MR5 ESGE recommends device-assisted enteroscopy to confirm and possibly treat lesions identified by small-bowel capsule endoscopy.
Strong recommendation, high quality evidence.

MR6 ESGE recommends the performance of small-bowel capsule endoscopy as a first-line examination in patients with iron-deficiency anemia when small bowel evaluation is indicated.
Strong recommendation, high quality evidence.

MR7 ESGE recommends small-bowel capsule endoscopy in patients with suspected Crohn's disease and negative ileo-colonoscopy findings as the initial diagnostic modality for investigating the small bowel, in the absence of obstructive symptoms or known bowel stenosis.
Strong recommendation, high quality evidence.

MR8 ESGE recommends, in patients with unremarkable or nondiagnostic findings from dedicated small-bowel cross-sectional imaging, small-bowel capsule endoscopy as a subsequent investigation if deemed likely to influence patient management.
Strong recommendation, low quality evidence.

MR9 ESGE recommends, in patients with established Crohn's disease, the use of a patency capsule before small-bowel capsule endoscopy to decrease the capsule retention rate.
Strong recommendation, moderate quality evidence.

MR10 ESGE recommends device-assisted enteroscopy (DAE) as an alternative to surgery for foreign bodies retained in the small bowel requiring retrieval in patients without acute intestinal obstruction.
Strong recommendation, moderate quality evidence.

MR11 ESGE recommends DAE-endoscopic retrograde cholangiopancreatography (DAE-ERCP) as a first-line endoscopic approach to treat pancreaticobiliary diseases in patients with surgically altered anatomy (except for Billroth II patients).
Strong recommendation, moderate quality evidence.

ABBREVIATIONS

AI	artificial intelligence
BSG	British Society of Gastroenterology
CD	Crohn's disease
CECDAI	Capsule Endoscopy Crohn's Disease Activity Index
CI	confidence interval
CRP	C-reactive protein
CTE	computed tomography enterography
DAE	device-assisted enteroscopy
DBE	double-balloon enteroscopy
DPEJ	direct percutaneous endoscopic jejunostomy
EATL	enteropathy-associated T-cell lymphoma
EmA	antiendomysial antibody
ERCP	endoscopic retrograde cholangio-pancreatography
ESGE	European Society of Gastrointestinal Endoscopy
ESPGHAN	European Society for Paediatric Gastro-enterology, Hepatology and Nutrition
ESR	erythrocyte sedimentation rate
EUS	endoscopic ultrasound
FOBT	fecal occult blood testing
GI	gastrointestinal
GIST	gastrointestinal stromal tumor
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	hazard ratio
IBD-U	inflammatory bowel disease, unclassified type
ICCE	International Conference on Capsule Endoscopy
IDA	iron-deficiency anemia
IRT	iron replacement trial
MCV	mean corpuscular volume
MRE	magnetic resonance enterography
MRI	magnetic resonance imaging
NEN	neuroendocrine neoplasm
NPV	negative predictive value
NSAID	nonsteroidal anti-inflammatory drug
OGIB	obscure gastrointestinal bleeding
OR	odds ratio
PE	push-enteroscopy
PEJ	percutaneous endoscopic jejunostomy
PJS	Peutz–Jeghers syndrome
PPI	proton pump inhibitor
PPV	positive predictive value
RCD	refractory celiac disease
RCT	randomized controlled trial
RFIT	radiofrequency identification tag
RYGB	Roux-en-Y gastric bypass
SB	small-bowel
SBCE	small-bowel capsule endoscopy
SBE	single-balloon enteroscopy
SBT	small-bowel tumor
SEMS	self-expanding metal stent
SSBB	suspected small-bowel bleeding
tTG	antitransglutaminase antibody
UC	ulcerative colitis

SCOPE AND PURPOSE

This Guideline is an official statement from the European Society of Gastrointestinal Endoscopy (ESGE). It is an update of the previously published 2015 ESGE Clinical Guideline addressing the role of small-bowel capsule endoscopy (SBCE) and device-assisted enteroscopy (DAE) for diagnosing and treating small-bowel disorders.

Introduction

The introduction of small-bowel capsule endoscopy (SBCE) and device-assisted endoscopy (DAE) over 20 years ago marked the beginning of a new era for investigating the small intestine. There is now more solid scientific evidence on established indications, and more data on new applications of enteroscopy are available. The aim of this Guideline, commissioned by the European Society of Gastrointestinal Endoscopy (ESGE) as an update of the previous 2015 Guideline [1], is to provide guidance for the clinical application of enteroscopy techniques in the management of adult patients with small-bowel (SB) disorders.

Methods

ESGE commissioned this clinical Guideline (ESGE Guideline Committee Chair, K.T.) and appointed a guideline leader (M.P.) who formed a coordinating team (M.P., E.R., P.C.V.). The guideline leader established six task forces, each with its leader (C.S., E.D., M.K., D.S.S., T.M., X.D.). Key questions were prepared by the coordinating team according to the PICO (patients, interventions, controls, outcomes) format and divided among the six task forces (see **Table 1 s**, Key Questions, available online-only in Supplementary Material). Given that this is an update of the 2015 ESGE Clinical Guideline [1], each task force performed a structured, systematic search, using keywords, for available literature (English-language articles) from December 2014 to November 30 2021 in Ovid MEDLINE, EMBASE, Google Scholar, and the Cochrane Database of Systematic Reviews; the literature search was then updated up to April 1 2022, to look for recently released papers. A dedicated manual search was also performed in the same timeframe by checking references of relevant papers. The hierarchy of studies included in this evidence-based guideline was, in decreasing order of evidence level: published systematic reviews/meta-analyses, randomized controlled trials (RCTs), prospective and retrospective observational studies, and case series.

Evidence on each key question was summarized in tables (**Table 2 s**, Evidence tables), using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, wherever applicable [2]. The evidence grading depends on the balance between any health intervention's benefits and their risk or burden. Further details on ESGE guideline development are available elsewhere [3].

The literature search results and answers to PICO questions were presented to all guideline group members during an online meeting on October 8 2021. Subsequently, drafts for each topic were prepared by each task force leader and distributed between the task force members for revision and discussion. In June 2022, a draft prepared by the coordinating team, including all the statements, was sent to all guideline group members. All the statements were discussed and modified in real time, if necessary, during an online meeting on June 24 2022. After the agreement of all members was obtained, the manuscript was reviewed by two independent external reviewers. The manuscript was then sent to the 51 ESGE member societies and to individual members for further comments. The final revised manuscript, having been agreed upon by all authors, was submitted for publication to the journal *Endoscopy*.

This ESGE Guideline was issued in 2022 and will be considered for update in 2027. Any interim updates will be noted on the ESGE website: http://www.esge.com/esge-guidelines.html.

Evidence statements and Recommendations

Evidence statements and Recommendations are grouped according to the different task force topics: suspected small-bowel bleeding (SSBB) and iron-deficiency anemia (IDA) (task force 1), Crohn's disease (CD) (task force 2), small-bowel tumors (SBTs) and inherited polyposis syndromes (task force 3), celiac disease (task force 4), other indications (task force 5), and innovations (task force 6). Each statement is followed by the assessment of the strength of evidence, based on GRADE. ▶ **Table 1** summarizes all recommendations in this updated Guideline.

Suspected small-bowel bleeding

RECOMMENDATION

ESGE recommends small-bowel capsule endoscopy as the first-line examination, before consideration of other endoscopic and radiological diagnostic tests, for suspected small-bowel bleeding, given the excellent safety profile of capsule endoscopy, its patient tolerability, and its potential to visualize the entire small-bowel mucosa.

Strong recommendation, moderate quality evidence.

Small-bowel (SB) bleeding is defined as bleeding in the gastrointestinal (GI) tract between the ampulla of Vater and the ileocecal valve. SB bleeding is suspected when a patient presents with GI bleeding but has negative upper and lower endoscopy findings; it can present as overt or occult bleeding. The term "obscure gastrointestinal bleeding" (OGIB) should be reserved for patients not found to have a source of bleeding even after the performance of SB evaluation [4].

The diagnostic yield of small-bowel capsule endoscopy (SBCE) in patients with suspected small-bowel bleeding (SSBB) ranges from 55 % to 62 % [5–7]. Compared with alternative modalities, SBCE has been consistently shown in prospective studies to be significantly superior to push-enteroscopy [8], computed tomography enterography (CTE) [9], CT angiography and standard angiography [10], and intraoperative enteroscopy [11], and to be as good as DAE [6] in evaluating and finding the lesion(s) causing the bleeding in patients with SSBB.

Careful patient selection may improve the diagnostic yield of SBCE in patients with SSBB. Diagnostic yield is greatest if the interval between SBCE and the last bleeding episode is as short as possible [12] (see following statements and supporting evidence). Other characteristics associated with an increased yield include a history of an overt bleed, use of antithrombotic agents, inpatient status, male sex, older age, and liver and renal comorbidities [13, 14]. From a technical point of view, a careful and focused review, performed by adequately trained readers, using the latest available technological advances (e. g., chromoendoscopy [15], and artificial intelligence [AI]) might contribute to further increasing the diagnostic yield of capsule endoscopy.

In patients with SSBB, SBCE showed an excellent safety profile. The rates of capsule retention range from 1.2 % [5] to 2.1 % [16]. Thus, routine cross-sectional imaging or the use of a patency capsule is not essential before SBCE in these patients.

It is known that cross-sectional techniques may be helpful in SSBB [4]. This updated Guideline can report only a few further studies that have been published on this subject. A meta-analysis, with 9 mainly high quality studies (396 patients), evaluated the diagnostic accuracy of CTE on SSBB detection [17]. The pooled sensitivity and specificity of CTE were 0.724 (95 % CI 0.651–0.789) and 0.752 (95 %CI 0.691–0.807), respectively. The area under the curve (AUC) was 0.7916 (95 %CI 0.723–0.860). A small retrospective cohort study [18] showed that when CTE and SBCE were used in combination within 30 days, the sensitivity was significantly higher at 30/31 (96.8 %) than that of SBCE alone at 24/31 (77.4 %; $P = 0.0412$).

Although CTE showed only moderate accuracy in the diagnosis of SSBB, it must also be remembered that SBCE can miss solitary protruding lesions in the proximal small bowel, such as small-bowel tumors (SBTs) [19]. CTE may thus be reasonably used as a complementary diagnostic method to SBCE, especially when an SBT is suspected.

DAE is both diagnostic and therapeutic but compared with SBCE, it has a lower rate of complete examination of the small bowel and is more invasive. In addition, the diagnostic yield of double-balloon enteroscopy (DBE) improves from 56 % (95 %CI 48.9 %–62.1 %) to 75 % (95 %CI 60.1 %–90.0 %) if DBE is preceded by a positive SBCE (odds ratio [OR] for positive DBE 1.79, 95 %CI 1.09 %–2.96 %; $P = 0.02$) [6]. Although the clinical presentation may indicate the preferential endoscopic insertion route for DAE, SBCE is also an effective tool for guiding the selection of the correct DAE approach (oral vs. anal) [20].

▶ **Table 1** Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders. Summary of all ESGE Guideline 2015 and ESGE Guideline 2022 recommendations. Changes from the 2015 Guideline (new or modified recommendations) are shown in bold.

ESGE Guideline 2015	ESGE Guideline 2022 (in bold if modified)
Suspected small-bowel bleeding	
1. ESGE recommends small-bowel video capsule endoscopy as the first-line investigation in patients with obscure gastrointestinal bleeding (strong recommendation, moderate quality evidence).	**1. ESGE recommends small-bowel capsule endoscopy as the first-line examination, before consideration of other endoscopic and radiological diagnostic tests for suspected small-bowel bleeding, given the excellent safety profile of capsule endoscopy, its patient tolerability, and its potential to visualize the entire small-bowel mucosa.** **Strong recommendation, moderate quality evidence.**
2. ESGE recommends against push-enteroscopy as the first-line investigation in patients with obscure gastrointestinal bleeding, because of its lower diagnostic yield compared with small-bowel capsule endoscopy (strong recommendation, moderate quality evidence).	
3. ESGE recommends performance of small-bowel capsule endoscopy as the first-line examination, before consideration of small bowel radiographic studies or mesenteric angiography, when small-bowel evaluation is indicated for obscure gastrointestinal bleeding (strong recommendation, high quality evidence). Computed tomography enterography/enteroclysis may be a complementary examination to capsule endoscopy in selected patients (weak recommendation, low quality evidence).	
4. Because of capsule endoscopy's excellent safety profile, patient tolerability, and potential for complete enteroscopy, ESGE recommends performance of small-bowel capsule endoscopy as the first-line examination, before consideration of device-assisted enteroscopy, when small-bowel evaluation is indicated for obscure gastrointestinal bleeding (strong recommendation, moderate quality evidence).	
5. In patients with overt obscure gastrointestinal bleeding ESGE recommends performing small-bowel capsule endoscopy as soon as possible after the bleeding episode, optimally within 14 days, in order to maximize the diagnostic yield (strong recommendation, moderate quality evidence).	**2. ESGE recommends small-bowel capsule endoscopy in patients with overt suspected small-bowel bleeding as soon as possible after the bleeding episode, ideally within 48 hours, to maximize the diagnostic and subsequent therapeutic yield.** **Strong recommendation, high quality evidence.**
6. ESGE suggests that emergency small-bowel capsule endoscopy should be considered in patients with ongoing overt obscure gastrointestinal bleeding (weak recommendation, moderate quality evidence). In such patients, ESGE suggests that device-assisted enteroscopy should also be considered as a possible first-line test, given that it allows diagnosis and treatment in the same procedure (weak recommendation, low quality evidence).	**3. ESGE suggests that device-assisted enteroscopy be considered as an alternative first-line test in selected cases, given that it allows diagnosis and treatment in the same procedure, depending on the clinical scenario and local availability.** **Weak recommendation, low quality evidence.** **4. ESGE recommends, in patients with overt suspected small-bowel bleeding, device-assisted enteroscopy to be performed optimally within 48–72 hours after the bleeding episode.** **Strong recommendation, high quality evidence.**
7. Given the spectrum of findings usually identified in patients with obscure gastrointestinal bleeding, when small-bowel capsule endoscopy is unavailable or contraindicated, ESGE suggests consideration of device-assisted enteroscopy as the first diagnostic test in these patients (weak recommendation, low quality evidence). ESGE suggests that device-assisted enteroscopy performed with diagnostic intent should be done as soon as possible after the bleeding episode (weak recommendation, low quality evidence).	**5. ESGE suggests consideration of device-assisted enteroscopy and/or dedicated small-bowel cross-sectional imaging as the first diagnostic test in patients with suspected small-bowel bleeding, depending on availability, expertise, and clinical suspicion, when small-bowel capsule endoscopy is unavailable or contraindicated.** **Weak recommendation, low quality evidence.**
8. ESGE does not recommend the routine performance of second-look endoscopy prior to small-bowel capsule endoscopy; however whether to perform second-look endoscopy before capsule endoscopy in patients with obscure gastrointestinal bleeding or iron-deficiency anaemia should be decided on a case-by-case basis (strong recommendation, low quality evidence).	6. ESGE does not recommend routine second-look endoscopy prior to small-bowel capsule endoscopy in patients with suspected small-bowel bleeding or iron-deficiency anaemia. Strong recommendation, low quality evidence.
9. ESGE recommends conservative management in those patients with obscure gastrointestinal bleeding (OGIB) and a negative small-bowel video capsule endoscopy (VCE) who do not have ongoing bleeding shown by overt bleeding or continued need for blood transfusions, since their prognosis is excellent and the risk of re-bleeding is low (strong recommendation, moderate qualityevidence).	7. ESGE recommends conservative management in those patients with suspected small-bowel bleeding and high quality negative small-bowel capsule endoscopy. Strong recommendation, moderate quality evidence.

▶ **Table 1** (Continuation)

ESGE Guideline 2015	ESGE Guideline 2022 (in bold if modified)
10. ESGE recommends further investigation using repeat VCE, device-assisted enteroscopy, or computed tomography-enterography/enteroclysis for patients with OGIB and a negative VCE who have ongoing bleeding shown by overt bleeding or continued need for blood transfusions (strong recommendation, moderate quality evidence).	8. ESGE recommends further investigation using repeat small-bowel capsule endoscopy, device-assisted enteroscopy, or dedicated small-bowel cross-sectional imaging for patients with suspected small-bowel bleeding and high quality negative small-bowel capsule endoscopy who have ongoing overt bleeding or continued need for blood transfusions. Strong recommendation, moderate quality evidence.
11. In patients with positive findings at small-bowel capsule endoscopy, ESGE recommends device-assisted enteroscopy to confirm and possibly treat lesions identified by capsule endoscopy (strong recommendation, high quality evidence).	9. ESGE recommends device-assisted enteroscopy to confirm and possibly treat lesions identified by small-bowel capsule endoscopy. Strong recommendation, high quality evidence.
Iron-deficiency anaemia	
12. In patients with iron-deficiency anaemia, ESGE recommends that prior to small-bowel capsule endoscopy, all the following are undertaken: acquisition of a complete medical history (including medication use, comorbidities, and gynaecological history in premenopausal females), oesophagogastroduodenoscopy with duodenal and gastric biopsies, and ileocolonoscopy (strong recommendation, low quality evidence).	10. ESGE recommends that in patients with iron-deficiency anaemia, the following are undertaken prior to small bowel evaluation: acquisition of a complete medical history, esophagogastroduodenoscopy with duodenal and gastric biopsies, and ileocolonoscopy. Strong recommendation, low quality evidence.
13. In patients with iron-deficiency anaemia, ESGE recommends performance of small-bowel capsule endoscopy as a first-line examination, before consideration of other diagnostic modalities, when upper and lower gastrointestinal endoscopies are inconclusive and small-bowel evaluation is indicated (strong recommendation, moderate quality evidence).	11. ESGE recommends the performance of small-bowel capsule endoscopy as a first-line examination in patients with iron-deficiency anaemia when small bowel evaluation is indicated. Strong recommendation, high quality evidence.
Suspected Crohn's disease	
14. ESGE recommends ileocolonoscopy as the first endoscopic examination for investigating patients with suspected Crohn's disease (strong recommendation, high quality evidence).	12. ESGE recommends ileocolonoscopy as the first endoscopic examination for investigating patients with suspected Crohn's disease. Strong recommendation, high quality evidence.
15. In patients with suspected Crohn's disease and negative ileocolonoscopy findings, ESGE recommends small-bowel capsule endoscopy as the initial diagnostic modality for investigating the small bowel, in the absence of obstructive symptoms or known stenosis (strong recommendation, moderate quality evidence).	13. ESGE recommends small-bowel capsule endoscopy in patients with suspected Crohn's disease and negative ileocolonoscopy findings as the initial diagnostic modality for investigating the small bowel, in the absence of obstructive symptoms or known bowel stenosis. Strong recommendation, high quality evidence.
16. ESGE does not recommend routine small-bowel imaging or the use of the PillCam patency capsule prior to capsule endoscopy in these patients (strong recommendation, low quality evidence).	14. ESGE does not recommend routine cross-sectional small-bowel imaging or the use of a patency capsule prior to capsule endoscopy to prevent the retention of the device in patients with suspected Crohn's disease. Strong recommendation, high quality evidence.
17. In the presence of obstructive symptoms or known stenosis, ESGE recommends that dedicated small-bowel cross-sectional imaging modalities such as magnetic resonance enterography/enteroclysis or computed tomography enterography/enteroclysis should be used first (strong recommendation, lowquality evidence).	15. ESGE recommends that dedicated small-bowel cross-sectional imaging modalities be used first in patients with suspected Crohn's disease and obstructive symptoms or known bowel stenosis. Strong recommendation, moderate quality evidence.
	16. ESGE recommends the use of a patency capsule prior to small-bowel capsule endoscopy in patients with suspected Crohn's disease and obstructive symptoms. Strong recommendation, low quality evidence.
18. In the setting of suspected Crohn's disease, ESGE recommends careful patient selection (using the clinical history and serological/faecal inflammatory markers) prior to small-bowel capsule endoscopy, in order to improve the diagnostic accuracy of capsule endoscopy for lesions consistent with active small-bowel Crohn's disease (strong recommendation, low quality evidence).	17. ESGE recommends careful patient selection (using clinical history and serological/fecal inflammatory markers) prior to small-bowel capsule endoscopy to improve the diagnostic accuracy for lesions consistent with active small-bowel Crohn's disease. Strong recommendation, moderate quality evidence.

▶ **Table 1** (Continuation)

ESGE Guideline 2015	ESGE Guideline 2022 (in bold if modified)
19. ESGE recommends discontinuation of nonsteroidal anti-inflammatory drugs (NSAIDs) for at least 1 month before capsule endoscopy since these drugs may induce small-bowel mucosal lesions indistinguishable from those caused by Crohn's disease (strong recommendation, low quality evidence).	**18. ESGE recommends discontinuation of both selective and non-selective nonsteroidal anti-inflammatory drugs, including short-term use, as well as of low dose and/or enteric-coated aspirin (if the patient's condition allows), for at least 4 weeks before capsule endoscopy since these drugs may induce small-bowel mucosal lesions that are indistinguishable from those caused by Crohn's disease.** **Strong recommendation, low quality evidence.**
20. ESGE recommends device-assisted enteroscopy with small-bowel biopsy in patients with noncontributory ileocolonoscopy and with suspicion of Crohn's disease on small-bowel cross-sectional imaging modalities or small-bowel capsule endoscopy. Device-assisted enteroscopy with small-bowel biopsy is more likely to provide definitive evidence of Crohn's disease than cross-sectional imaging, although the latter offers a useful less invasive alternative that better defines transmural complication (strong recommendation, high quality evidence).	19. ESGE recommends device-assisted enteroscopy with small-bowel biopsies in patients with noncontributory ileocolonoscopy and suspected Crohn's disease on small-bowel cross-sectional imaging modalities or small-bowel capsule endoscopy. Strong recommendation, high quality evidence.
Established Crohn's disease	
21. In patients with established Crohn's disease, based on ileocolonoscopy findings, ESGE recommends dedicated cross-sectional imaging for small-bowel evaluation since this has the potential to assess extent and location of any Crohn's disease lesions, to identify strictures, and to assess for extraluminal disease (strong recommendation, low quality evidence).	20. ESGE recommends, in patients with established Crohn's disease based on ileocolonoscopy findings, dedicated cross-sectional imaging for small-bowel evaluation since this has the potential to assess the extent and location of any Crohn's disease lesions, to identify strictures, and to assess for extraluminal disease. Strong recommendation, high quality evidence.
22. In patients with unremarkable or nondiagnostic findings from such cross-sectional imaging of the small bowel, ESGE recommends small-bowel capsule endoscopy as a subsequent investigation, if deemed to influence patient management (strong recommendation, low quality evidence).	21. ESGE recommends, in patients with unremarkable or nondiagnostic findings from dedicated small-bowel cross-sectional imaging, small-bowel capsule endoscopy as a subsequent investigation if deemed likely to influence patient management. Strong recommendation, low quality evidence.
Not addressed in the 2015 Guideline	**22. ESGE suggests that small-bowel capsule endoscopy may be useful for assessment of Crohn's disease extent and for monitoring and guiding the "treat-to-target" strategy.** **Weak recommendation, low quality evidence.**
23. ESGE suggests the use of activity scores (such as the Lewis score and the Capsule Endoscopy Crohn's Disease Activity Index) to facilitate prospective small-bowel capsule endoscopy follow-up of patients for longitudinal assessment of the course of small-bowel Crohn's disease and its response to medical therapy (using mucosal healing as an end point) (weak recommendation, low quality evidence).	**23. ESGE recommends the use of activity scores (such as the Lewis score and the Capsule Endoscopy Crohn's Disease Activity Index [CEDCAI]) to facilitate prospective small-bowel capsule endoscopy follow-up of patients for longitudinal assessment of small-bowel Crohn's disease and its response to medical therapy (using mucosal healing as an endpoint).** **Strong recommendation, low quality evidence.**
24. When capsule endoscopy is indicated, ESGE recommends use of the PillCam patency capsule to confirm functional patency of the small bowel (strong recommendation, low quality evidence).	24. ESGE recommends, in patients with established Crohn's disease, the use of a patency capsule before small-bowel capsule endoscopy to decrease the capsule retention rate. Strong recommendation, moderate quality evidence.
25. ESGE recommends initial conservative treatment in the case of capsule retention. ESGE recommends device-assisted enteroscopy if medical therapy has not led to promote spontaneous passage (strong recommendation, low quality evidence).	25. ESGE recommends initial conservative treatment in the case of capsule retention. Strong recommendation, high quality evidence. 26. ESGE recommends device-assisted enteroscopy if medical therapy has not achieved spontaneous capsule passage. Strong recommendation, high quality evidence.
26. ESGE recommends device-assisted enteroscopy if small-bowel endotherapy is indicated (including dilation of Crohn's disease small-bowel strictures, retrieval of foreign bodies, and treatment of small-bowel bleeding) (strong recommendation, low quality evidence).	27. ESGE recommends device-assisted enteroscopy if small-bowel endotherapy is indicated (including dilation of Crohn's disease small-bowel strictures, retrieval of a retained capsule, and/or treatment of small-bowel bleeding). Strong recommendation, high quality evidence.
27. ESGE recognises small-bowel capsule endoscopy/device-assisted enteroscopy and magnetic resonance or computed tomography enterography/enteroclysis as complementary strategies (weak recommendation, low quality evidence). Cost-effectiveness data regarding optimal investigation strategies for diagnosis of small-bowel Crohn's disease are lacking.	*See statements 13,15,19,20,21,27*

▶ **Table 1** (Continuation)

ESGE Guideline 2015	ESGE Guideline 2022 (in bold if modified)
Familial adenomatous polyposis	
28. ESGE recommends that surveillance of the proximal small bowel in familial adenomatous polyposis is best performed using conventional forward-viewing and side-viewing endoscopes (strong recommendation, moderate quality evidence).	28. ESGE recommends surveillance of the proximal small bowel in familial adenomatous polyposis using conventional forward-viewing and side-viewing endoscopes. Strong recommendation, moderate quality evidence.
	29. ESGE does not recommend small-bowel capsule endoscopy for surveillance of the proximal small bowel in familial adenomatous polyposis. **Strong recommendation, moderate quality evidence.**
29. When small-bowel investigation is clinically indicated in familial adenomatous polyposis, ESGE suggests that small-bowel capsule endoscopy and/or cross-sectional imaging techniques may be considered for identifying polyps in the rest of the small bowel, but the clinical relevance of such findings remains to be demonstrated (weak recommendation, moderate quality evidence).	30. ESGE suggests that small-bowel capsule endoscopy and/or cross-sectional imaging techniques may be considered when investigation of the mid-distal small-bowel is clinically indicated in familial adenomatous polyposis. Weak recommendation, moderate quality evidence.
Peutz–Jeghers syndrome	
30. ESGE recommends small-bowel surveillance in patients with Peutz–Jeghers syndrome. Small-bowel capsule endoscopy and/or magnetic resonance enterography/enteroclysis appear adequate methods for this purpose, depending on local availability and expertise, or patient preference (strong recommendation, moderate quality evidence)	31. ESGE recommends, for small bowel surveillance in patients with Peutz–Jeghers syndrome, small-bowel capsule endoscopy and/or magnetic resonance enterography, depending on local availability and expertise and/or patient preference. Strong recommendation, moderate quality evidence.
31. ESGE recommends device-assisted enteroscopy with timely polypectomy when large polyps (> 10–15 mm) are discovered by radiological examination or small-bowel capsule endoscopy in patients with Peutz–Jeghers syndrome (strong recommendation, moderate quality evidence).	**32. ESGE recommends device-assisted enteroscopy with polypectomy when large polyps (> 15 mm) or symptomatic polyps are discovered by radiological examination or small-bowel capsule endoscopy in patients with Peutz–Jeghers syndrome.** **Strong recommendation, moderate quality evidence.**
Juvenile polyposis	
Not addressed in the 2015 Guideline	**33. ESGE recommends that routine evaluation of the small bowel in juvenile polyposis patients should be limited to the duodenum and based on flexible forward-viewing endoscopy.** **Strong recommendation, low quality evidence.**
Small-bowel tumors	
32. ESGE recommends early use of small-bowel video capsule endoscopy in the search for a small-bowel tumour when obscure gastrointestinal bleeding and iron-deficiency anaemia are not explained otherwise (strong recommendation, moderate quality evidence).	**34. ESGE recommends the use of small-bowel capsule endoscopy in patients where there is an increased risk of a small-bowel tumor.** **Strong recommendation, moderate quality evidence.**
33. In the setting of suspicion of a small-bowel tumour, ESGE does not recommend specific investigations before small-bowel capsule endoscopy in patients without evidence for stenosis or previous small-bowel resection (strong recommendation, low quality evidence).	35. ESGE does not recommend, in the setting of suspected small-bowel tumor, specific investigations before small-bowel capsule endoscopy unless patients are considered to be at risk of capsule retention. Strong recommendation, low quality evidence.
34. ESGE recommends consideration of device-assisted enteroscopy in preference to small-bowel capsule endoscopy if imaging tests have already shown suspicion of small-bowel tumour (strong recommendation, low quality evidence).	36. ESGE recommends consideration of device-assisted enteroscopy in preference to small-bowel capsule endoscopy if imaging tests have already demonstrated suspected small-bowel tumor. Strong recommendation, low quality evidence.
35. ESGE recommends cross-sectional imaging to ascertain operability when there is a small-bowel capsule endoscopy finding of small-bowel tumour with a high diagnostic certainty. When there is uncertain diagnosis of small-bowel tumour at capsule endoscopy, biopsy sampling by device-assisted enteroscopy is required (strong recommendation, low quality evidence).	37. ESGE recommends cross-sectional imaging for staging and ascertaining operability when there is a small-bowel capsule endoscopy finding of a small-bowel tumor with high diagnostic certainty. Strong recommendation, low quality evidence. 38. ESGE recommends, when there is an uncertain diagnosis of small-bowel tumor at capsule endoscopy, biopsy sampling and tattooing of its location by device-assisted enteroscopy. Strong recommendation, low quality evidence.

▶ **Table 1** (Continuation)

ESGE Guideline 2015	ESGE Guideline 2022 (in bold if modified)
36. When a submucosal mass is detected by small-bowel capsule endoscopy, ESGE recommends confirmation of the diagnosis by device-assisted enteroscopy (strong recommendation, low quality evidence).	**39. ESGE recommends, when a subepithelial mass is detected by small-bowel capsule endoscopy, confirmation of the diagnosis by device-assisted enteroscopy and/or cross-sectional imaging, depending on local availability and expertise. Strong recommendation, low quality evidence.**
37. When capsule endoscopy shows high suspicion of submucosal mass and there is a negative but incomplete device-assisted enteroscopy, ESGE suggests cross-sectional imaging tests to confirm the diagnosis (weak recommendation, low quality evidence).	
38. ESGE recommends against small-bowel capsule endoscopy in the follow-up of treated small-bowel tumours because of lack of data (strong recommendation, low quality evidence).	40. ESGE does not recommend small-bowel capsule endoscopy in the follow-up of treated small-bowel tumors because of lack of data. Strong recommendation, low quality evidence.
Not addressed in the 2015 Guideline	**41. ESGE suggests considering enteroscopic placement of self-expanding metal stents in the palliation of malignant small-bowel strictures as an alternative option to surgery. Weak recommendation, low quality evidence.**
Celiac disease	
39. ESGE strongly recommends against the use of small-bowel capsule endoscopy for suspected coeliac disease but suggests that capsule endoscopy could be used in patients unwilling or unable to undergo conventional endoscopy (strong recommendation, low quality evidence).	**42. ESGE does not recommend small-bowel capsule endoscopy to diagnose celiac disease. Strong recommendation, low quality evidence.**
40. ESGE recommends that there is no role for small-bowel capsule endoscopy in assessing the extent of disease or response to a gluten- free diet (strong recommendation, low quality evidence).	
41. ESGE suggests the use of small-bowel capsule endoscopy in cases of equivocal diagnosis of coeliac disease (weak recommendation, low quality evidence).	**43. ESGE recommends using small-bowel capsule endoscopy in cases of equivocal diagnosis of celiac disease since it is essential for final diagnosis and therapy. Strong recommendation, low quality evidence.**
42. ESGE recommends initial assessment by small-bowel capsule endoscopy followed by device-assisted enteroscopy in nonresponsive or refractory coeliac disease (strong recommendation, low quality evidence).	44. ESGE recommends in nonresponsive or refractory celiac disease, small-bowel capsule endoscopy followed by device-assisted enteroscopy for diagnosis and disease monitoring. Strong recommendation, high quality evidence.
Chronic abdominal pain	
Not addressed in the 2015 Guideline	**45. ESGE does not recommend small-bowel capsule endoscopy as the first-line investigation for patients with isolated chronic abdominal pain. Strong recommendation, low quality evidence.**
Foreign-body retrieval	
Not addressed in the 2015 Guideline	**46. ESGE recommends device-assisted enteroscopy as an alternative to surgery for foreign bodies retained in the small bowel requiring retrieval in patients without acute intestinal obstruction. Strong recommendation, moderate quality evidence.**
DAE-assisted percutaneous endoscopic jejunostomy (PEJ) for enteral feeding	
Not addressed in the 2015 Guideline	**47. ESGE suggests that in patients requiring jejunostomy for enteral feeding, DAE-assisted percutaneous endoscopic jejunostomy (PEJ) is a possible alternative to surgical jejunostomy. Weak recommendation, moderate quality evidence.**
DAE-ERCP in patients with altered anatomy	
Not addressed in the 2015 Guideline	**48. ESGE recommends DAE-ERCP as a first-line endoscopic approach to treat pancreaticobiliary diseases in patients with surgically altered anatomy (except for Billroth II patients). Strong recommendation, moderate quality evidence.**

DAE, device-assisted enteroscopy; ERCP, endoscopic retrograde cholangiopancreatography; ESGE, European Society of Gastrointestinal Endoscopy; PEJ, percutaneous endoscopic jejunostomy

As already stated in previous guidelines [1] and on the basis of all the above scientific evidence, SBCE can be recommended as the first-line investigation in patients with SSBB. This agrees with the recommendations of other scientific societies [4, 21, 22].

▶ **Fig. 1** presents recommended approaches for diagnosis and treatment of SSBB.

RECOMMENDATION

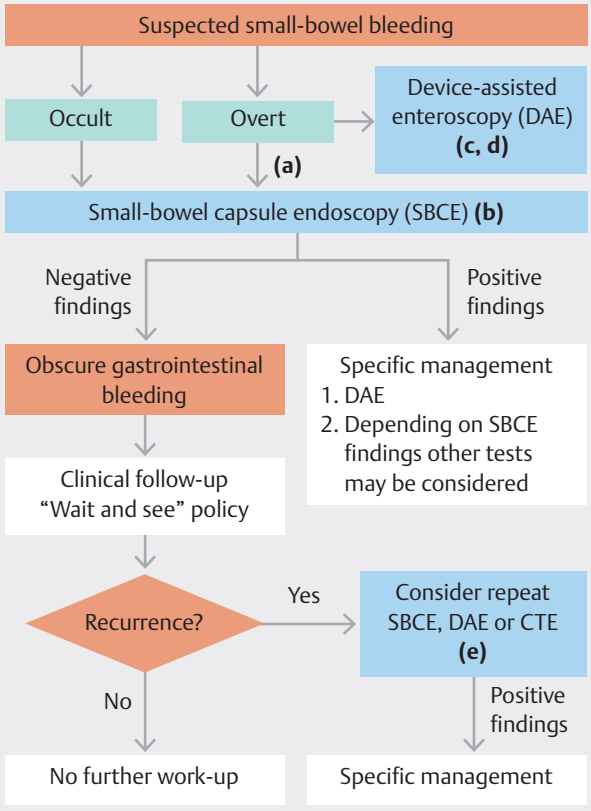
ESGE recommends small-bowel capsule endoscopy in patients with overt suspected small-bowel bleeding as soon as possible after the bleeding episode, ideally within 48 hours, to maximize the diagnostic and subsequent therapeutic yield.

Strong recommendation, high quality evidence.

Despite the unquestionable role of early SB evaluation in patients with SSBB, especially in cases of overt bleeding, the optimal timing is still debated. The 14-day timeframe, suggested in the previous ESGE guideline [1], is somewhat arbitrary and quite broad.

Since the publication of the initial guideline [1], six retrospective studies and two meta-analyses have been published to compare the diagnostic and therapeutic yield of SB endoscopic procedures in the setting of overt SB bleeding according to the timing of SB evaluation (performed with either SBCE or DAE).

Zhao et al. [23] carried out a propensity score-matching study on 997 patients, that supported previous ESGE statements; they found that early SBCE (within 14 days from last bleeding event) was associated with a significantly higher rate of diagnosis (56.4% vs. 45.5%, $P=0.001$), with ORs of 0.648 (95%CI 0.496–0.847, $P=0.001$) and 0.666 (95%CI 0.496–0.894, $P=0.007$) at univariate and multivariate analysis, respectively. In this study, the incidence of rebleeding within 1 year following treatment was significantly lower (24.7% vs. 36.7%, $P=0.041$) for patients who underwent early SBCE. Chao et al. [24] reported a detection rate for the source of bleeding ranging from 70% to 77.6% if SBCE was performed in the first 3 days from the first bleeding episode in patients (n=60) with overt bleeding. In contrast, the detection rate decreased to 36.4% if SBCE was performed after the 4th day. Using a 48-hour cut-off, Kim et al. [25] found that among 94 patients, the 30 who underwent SBCE within 2 days from the last bleeding had a greater diagnostic yield (66.7% vs. 40.6%, $P=0.019$), a greater subsequent therapeutic yield (24.7% vs. 9.4%, ($P=0.028$) and a shorter hospital stay (5 days, 95%CI 4.8–7.7 vs. 7 days, 95%CI 6.9–10.1, $P=0.039$)0. A shorter hospital stay, as well as a decrease in resource utilization in the index hospitalization, was also demonstrated by Wood et al. [26] in inpatients receiving an early SBCE. Iio et al. [27] found a lesion detection rate of 80% (12/15) in patients with ongoing overt bleeding who underwent early SBCE (15/127) compared to 47% (53/112) in the "late" group ($P=0.0174$). These data were consistent with the results of Song et al. [28], who showed that early deployment of SBCE results in a significantly higher diagnostic yield (OR for relevant lesion detection was 4.99 for <24-h group vs. 8-day group). On the other hand, in the study of Gomes et al. [29] (n=115), where the timing of SBCE was further divided (≤48 h, 48h–14 d, ≥14 d), the overall diagnostic yield was high (about 80%) and similar among the three groups irrespective of SBCE timing ($P=0.39$). However, the three timing-based subgroups were small (about 30 patients in each) and when SBCE was performed within 48 hours, a trend toward an increased diagnostic yield was observed ($P=0.06$). In addition, the early group showed the highest therapeutic yield (66.7% vs. 40% vs. 31.7%, $P=0.005$) and the lowest rebleeding rate (15.4% vs.



▶ **Fig. 1** Recommended approaches for diagnosis and treatment of suspected small-bowel bleeding (SSBB). **a** In patients with overt SSBB, small-bowel capsule endoscopy (SBCE) should be performed as soon as possible after the bleeding episode, ideally within 48 hours. **b** When SBCE is contraindicated or unavailable, device-assisted enteroscopy (DAE) and/or dedicated small-bowel (SB) cross-sectional imaging may be considered for SB evaluation, depending on availability, expertise, and clinical suspicion. **c** DAE can also be considered as alternative first-line examination in selected cases, depending on the clinical scenario and local availability, and should be performed optimally within 48–72 hours after the bleeding episode. **d** In patients with significant active bleeding and unsuitable for flexible endoscopy, computed tomography (CT) angiography or angiography may be considered. **e** Upper and/or lower gastrointestinal endoscopy may also be considered on a case-by-case basis to identify lesions overlooked at baseline endoscopy. CTE, computed tomography enterography.

34.3 % vs. 46.3 %, $P = 0.007$), with a longer time to rebleed when compared with the > 48-h groups ($P = 0.03$).

Recently, a meta-analysis from Uchida et al. [30], by pooling 19 previous studies (9 prospective, 9 retrospectives, 1 unspecified), confirmed that performing SBCE within 2 days leads to high diagnostic and therapeutic yields (55.9 % and 65.2 %, respectively). However, the metaregression was based on subgroups with small sample size and heterogeneous data [30]. The largest meta-analysis available so far, involving 39 studies, confirmed higher pooled diagnostic yields for SBCE performed in the first 24, 48, and 72 hours, being 83.4 % (95 %CI 76.30 %–90.46 %), 81.3 % (95 %CI 75.20 %–87.43 %) and 63.6 % (95 %CI 45.59 %–81.51 %), respectively. The pooled therapeutic yields for the same timings were 57.56 % (95 %CI 36.95 %–78.16 %), 59.09 % (95 %CI 43.66 %–74.52 %) and 18.90 % (95 %CI 11.26 %–26.54 %), respectively [31].

RECOMMENDATION

ESGE suggests that device-assisted enteroscopy be considered as an alternative first-line test in selected cases, given that it allows diagnosis and treatment in the same procedure, depending on the clinical scenario and local availability.

Weak recommendation, low quality evidence.

RECOMMENDATION

ESGE recommends, in patients with overt suspected small-bowel bleeding, device-assisted enteroscopy to be performed optimally within 48–72 hours after the bleeding episode.

Strong recommendation, high quality evidence.

Two previously mentioned studies [30, 31] not only evaluated the diagnostic yield of SBCE but also dealt with the performance of DAE in the same setting. According to Estevinho et al. [31], the pooled diagnostic and therapeutic yields of early DAE were superior to those of SBCE by 7.97 and 20.89 percentage points, respectively ($P < 0.05$). However, it is not possible to exclude that the DAE results may be influenced both by a selection bias, related to patient features (e. g., patients undergoing direct DAE are likely to have more severe bleeding), and by a detection bias, since several patients may have received another diagnostic test, with a positive result, before DAE. In addition, urgent DAE may raise significant organizational issues; it is not readily available in most centers and requires trained personnel.

Therefore, even in overt SSBB, a sequential approach with a diagnostic examination (e. g., SBCE, CT angiography etc.) followed by a potentially therapeutic one (e. g., DAE) should be preferred. Performance of DAE in the first 72 hours is most often dependent on performance of SBCE in the first 48 hours [31]. A recent retrospective study with a large sample size of patients undergoing both SBCE and DBE [32] also confirmed that a short interval between the two procedures maximizes the effectiveness of the diagnostic/therapeutic process. Although the agreement between SBCE and DBE was generally rated as suboptimal ($k = 0.059$), it markedly improved ($k = 0.323$) when the procedures were performed within 1–5 days of each other. As demonstrated for SBCE, in the overt SB bleeding setting, recent data confirm the importance of keeping the interval between DAE and the bleeding episode as short as possible. In fact, in the pooled analysis of double-arm studies [31], the odds for a positive diagnosis (OR 3.99; $P < 0.01$; $I^2 = 45\,\%$) and subsequent therapeutic intervention (OR 3.86; $P < 0.01$; $I^2 = 67\,\%$) were significantly superior in the early group, for either DAE or SBCE.

RECOMMENDATION

ESGE suggests consideration of device-assisted enteroscopy and/or dedicated small-bowel cross-sectional imaging as the first diagnostic test in patients with suspected small-bowel bleeding, depending on availability, expertise, and clinical suspicion, when small-bowel capsule endoscopy is unavailable or contraindicated.

Weak recommendation, low quality evidence.

SBCE has a very limited number of absolute contraindications [33], such as GI obstruction. However, SBCE may also be unavailable, especially in emergency settings, although lately, there is a trend of increasing use outside the endoscopy suite [34]. Overall, there is not enough evidence-based data to recommend a single specific examination as first-line when SBCE is unavailable. A meta-analysis [9] of a total of 18 studies (n = 660 patients) reported the pooled diagnostic yield of CTE in evaluating SSBB as 40 % (95 %CI 33 %–49 %). Seven studies (n = 279) compared the yield of CTE with SBCE. The yields for CTE and SBCE for all findings were 34 % and 53 %, respectively (incremental yield −19 %, 95 %CI −34 % to −4 %). Therefore, CTE has been described as an effective modality to show the precise location of bleeding and guide subsequent enteroscopy management, especially in patients with bleeding from tumors and overt bleeding [9]. In an emergency setting, DAE has been described as effective as suggested by a recent systematic review and meta-analysis [31], including retrospective studies in which this procedure was performed as first-line for selected patients.

RECOMMENDATION

ESGE does not recommend routine second-look endoscopy prior to small-bowel capsule endoscopy in patients with suspected small-bowel bleeding or iron-deficiency anemia.

Strong recommendation, low quality evidence.

Good quality upper and lower GI endoscopy is crucial in the investigation of SSBB. Evidence and recent guidelines propose an acceptable minimal examination time to ensure good quality examination and meeting minimum standards [35, 36]. In patients where bidirectional endoscopy has been negative, with the persistence of symptoms or suspicion of SB bleeding, SBCE is the preferred next diagnostic test. Several studies had investigated routine second-look endoscopy before capsule endoscopy and highlighted this as not being cost-effective, as stated in the 2015 Guideline [1]. Since the publication of the latter, eight further studies have been published on this subject. A study by Innocenti et al. [37] showed non-SB lesions detected in 30 % of cases, of which 43 % were bleeding. The study was retrospective and without randomization. Similarly, another retrospective study by Clere-Jehl et al. [38] studied 69 endoscopy-negative patients >65 years, with persistent IDA. Further investigations were performed in 45 patients; 64 % of the second-look GI endoscopies led to significant changes in treatment compared with 25 % for the capsule endoscopies. Conventional diagnoses of IDA were ultimately established for 19 (27 %) patients and included 3 cancer patients suggesting second-look endoscopy is favored for persistent IDA. On the other hand, a prospective study by Riccioni et al. [39] showed that at SBCE, findings in the upper GI tract were found in 21 % and the colon in 6.4 %. Subsequent studies by Akin et al. [40], Hoedemaker et al. [41], and Juanmartiñena Fernández et al. [42–44] (this last group published three separate studies about esophageal, gastroduodenal, and colonic findings on SBCE), all retrospective in nature, conclude that clinicians should carefully review not just SB images but also those of the esophagus, stomach, and colon.

There have been no further cost-effectiveness studies.

Overall, the current literature is inadequate to support routine repetition of standard endoscopy, and this should be reserved on a case-by-case basis. However it highlights the importance of a good standard of baseline endoscopy performance.

RECOMMENDATION

ESGE recommends conservative management in those patients with suspected small-bowel bleeding and high quality negative small-bowel capsule endoscopy.

Strong recommendation, moderate quality evidence.

RECOMMENDATION

ESGE recommends further investigation using repeat small-bowel capsule endoscopy, device-assisted enteroscopy, or dedicated small-bowel cross-sectional imaging for patients with suspected small-bowel bleeding and high quality negative small-bowel capsule endoscopy who have ongoing overt bleeding or continued need for blood transfusions.

Strong recommendation, moderate quality evidence.

Analogously to upper and lower GI endoscopy, for SBCE to be considered a reliable diagnostic tool on which subsequent follow-up is based, it must be rated a high quality examination, according to ESGE quality standards [45], and evaluated by a dedicated and properly trained reader, according to ESGE curriculum criteria [46]. Even more than in upper and lower endoscopy, given the passive nature of capsule endoscopy (e. g., lavage and aspiration cannot be done), the characteristics of the luminal contents (e. g., presence of bubbles, fecal material, or turbid fluid) strongly impact the quality of the examination. Therefore, adequate SB visualization is a crucial element in ensuring a reliable assessment of the small intestine. Although the current ESGE technical guidelines specifically address this issue [47], the evidence is rapidly evolving [48] and remains somewhat controversial [49].

A systematic review and meta-analysis [50], including 26 mostly high quality studies with 3657 individuals, showed that a negative SBCE implies adequate assurance of a subsequently low risk of rebleeding. The pooled rate of rebleeding after negative SBCE was 0.19 (95 %CI 0.14–0.25; $P<0.0001$). The pooled OR of rebleeding was 0.59 (95 %CI 0.37–0.95; $P<0.001$), and moreover, the effect was more pronounced in studies with a short follow-up (OR 0.47, 95 %CI 0.24–0.94; $P<0.001$). On top of that, prospective studies showed a lower OR of rebleeding at 0.24 (95 %CI 0.08–0.73; $P=0.01$). Lastly, there was no statistically significant difference in rebleeding after SBCE for occult and overt OGIB. Therefore, patients with negative SBCE after an episode of SSBB can be safely managed with watchful waiting, at least in the short term [51, 52].

However, in the long-term, recurrence of bleeding is not uncommon [53–55], and further investigations could be required. In these cases, repeating the diagnostic workup by SBCE appears to have more diagnostic value than DAE; a small study from Japan showed that the rate of positive findings in the repeat SBCE group was significantly higher than in the DBE group [56]. A closer follow-up has been proposed in patients with a higher red blood cell transfusion requirement previous to an SBCE and overt bleeding [55, 57, 58] or severe anemia [59], as they are associated with higher rebleeding rates. Recently, de Sousa Magalhães et al. developed and validated a score (RHEMITT) that accurately predicts the individual risk of SB rebleeding after initial SBCE [60, 61].

RECOMMENDATION

ESGE recommends device-assisted enteroscopy to confirm and possibly treat lesions identified by small-bowel capsule endoscopy.

Strong recommendation, high quality evidence.

It is known that the diagnostic yield of DBE significantly improves if DBE is preceded by a positive SBCE [6] and a recent meta-analysis reported that this sequential approach increased the diagnostic yield for vascular lesions by 7 % [62]. Moreover, in patients with negative SBCE, a subsequent DBE can identify the source of the bleeding in about one third [6, 56]. In addition

to its therapeutic possibilities, DBE has been reported to help clarify the origin of bleeding when SBCE shows only blood in the lumen or doubtful findings [63]. The correct management of patients with SSBB involves using both techniques.

Although several studies have assessed the diagnostic and therapeutic yield of SBCE and DAE in SB bleeding, the emphasis should be on meaningful results when we consider outcomes in clinical practice. In this clinical setting, a positive patient outcome should be either bleeding cessation or anemia resolution. In addition, other important clinical outcomes for evaluation may include mortality and hemoglobin levels or the reduction in the numbers of endoscopic procedures, hospitalizations, and blood transfusions.

In this regard, both the older literature [1] and the more recent studies evaluating the impact of SB endoscopy on the clinical outcomes of patients with SB bleeding have produced conflicting results [32, 64–68]. This is probably because considerable heterogeneity exists across studies in the definition, relevance, and clinical management of vascular lesions and follow-up periods. Furthermore, the studies differ in the severity of the bleeding of the enrolled patients, and, above all, a standardized intervention protocol for the identified bleeding lesions had not always been established a priori. Though a recent meta-analysis [31] assessing the impact of early SB endoscopy in patients with overt SSBB showed a lower recurrent bleeding rate (OR 0.40; $P < 0.01$; $I^2 = 0\%$) when SBCE/DAE was performed very close to the bleeding episode, further high quality research, including randomized trials, is needed to clarify the open questions and clinical management regarding SB bleeding.

Iron-deficiency anemia

RECOMMENDATION

ESGE recommends that in patients with iron-deficiency anemia, the following are undertaken prior to small-bowel evaluation: acquisition of a complete medical history, esophagogastroduodenoscopy with duodenal and gastric biopsies, and ileocolonoscopy.

Strong recommendation, low quality evidence.

RECOMMENDATION

ESGE recommends the performance of small-bowel capsule endoscopy as a first-line examination in patients with iron-deficiency anemia when small bowel evaluation is indicated.

Strong recommendation, high quality evidence.

The evidence published since the previous ESGE guideline [1] and the most recent practice guideline on IDA [69] confirm that, before evaluation of the small-bowel, patients with IDA should undergo a thorough anamnestic evaluation and a multistep diagnostic–therapeutic workup that includes endoscopic evaluation of the upper and lower digestive tract.

Furthermore, the British Society of Gastroenterology (BSG) guideline for the management of IDA in adults [69] recommends that, before the SB evaluation is planned, an empirical iron replacement trial (IRT), should be performed with appropriate dosage and duration. According to the BSG guideline, endoscopic SB examination should be performed only if the target values are not reached in the initial IRT or if anemia recurs at the end of treatment. However, no clinical trials have compared the clinically relevant outcomes (e. g., diagnostic yield and possible diagnostic delay) in patients referred for SB study according to the IRT outcome. This policy may lead to different results in different subgroups of patients. Therefore, the available evidence appears insufficient to recommend using the IRT as a decision-making tool in deciding to perform an SB study.

Considering multiple clinical issues, a comprehensive overall assessment should always be performed when planning SBCE. Several studies pursued the aim of identifying such predictive factors for SB pathology. Male sex, older age, low mean corpuscular volume (MCV), low hemoglobin values, high transfusion requirement, use of nonsteroidal anti-inflammatory drugs (NSAIDs) in the last 2 weeks before SBCE, and antithrombotic therapy have been demonstrated to correlate with diagnostic yield in IDA patients [70–75]. Hypoalbuminemia has also been shown to increase the proportion of positive findings at SBCE in a subgroup of celiac disease patients presenting with persistent IDA despite a gluten-free diet (GFD) [76].

In recent years, new evidence has also emerged concerning the possible role of fecal occult blood testing (FOBT), either guaiac or immunochemical, as a filter test to select IDA patients for SBCE [77–79]. The meta-analysis by Yung et al. [80] found, for all positive FOBT, sensitivity 0.60 (95 %CI 0.50–0.69), specificity 0.72 (95 %CI 0.52–0.86), and diagnostic OR 3.96 (95 %CI 1.50–10.4) for SB findings. Corresponding values for fecal immunochemical testing alone were sensitivity 0.48 (95 %CI 0.36–0.61), specificity 0.60 (95 %CI 0.42–0.76), and diagnostic OR 1.41 (95 %CI 0.72–2.75). Nevertheless, there is still insufficient evidence to recommend FOBT in routine practice as a screening tool for deciding whether to perform SBCE in IDA patients. Larger studies may better clarify its usefulness and lead to future guidance changes.

In recent years, it has also been shown that, although there are some differences in terms of both diagnostic yield and the spectrum of findings between young and elderly patients, age is not a discriminating factor when SB studies are performed in patients with IDA and negative bidirectional endoscopy [74]. Interestingly, two studies [81, 82] focused on the subgroup of female IDA patients and showed a lower diagnostic yield in premenopausal women compared to post-menopausal women. Moreover, Silva et al. [82] found that in premenopausal women, only 1.8 % required therapeutic endoscopy, whereas in 17.3 % of post-menopausal women, SBCE findings led to additional endoscopic treatment. Furthermore, the rebleeding rate at 1, 3 and 5 years was 3.6 %, 10.2 %, and 10.2 % in premenopausal women and 22.0 %, 32.3 %, and 34.2 % in post-menopausal women. These figures might suggest a higher threshold for SBCE in pre-

menopausal women. However, this evidence is insufficient to make any firm recommendation.

According to previous ESGE guidelines [1], large studies have confirmed that SBCE is the test of choice for evaluating the small intestine in patients with IDA, both because of its high diagnostic yield and favorable safety profile [70, 71, 77, 83, 84]. In contrast, there is conflicting and inconclusive evidence about the role of second-look endoscopy before SBCE in IDA patients [37, 38, 73]. Therefore, repetition of upper and lower endoscopies should be decided on a case-by-case basis, considering the timing and quality of upper and lower endoscopy performed before SBCE.

Furthermore, recent data confirm that negative SBCE provides adequate evidence of a low risk of rebleeding. Such patients can therefore be safely managed with watchful waiting [50, 53, 85, 86]. Nevertheless, SB neoplasia and diverticula are mural-based lesions that can cause IDA but can be missed at SBCE, and for which CTE has been shown to have higher sensitivity [9, 17, 87]. Since the 2015 ESGE clinical guideline [1] there have been no recent large studies that have investigated the diagnostic yield of DAE exclusively in IDA patients. However, performance can be similar to that reported for patients in the SSBB setting.

Crohn's disease

Suspected Crohn's disease

RECOMMENDATION

ESGE recommends ileocolonoscopy as the first endoscopic examination for investigating patients with suspected Crohn's disease.

Strong recommendation, high quality evidence.

RECOMMENDATION

ESGE recommends small-bowel capsule endoscopy in patients with suspected Crohn's disease and negative ileocolonoscopy findings as the initial diagnostic modality for investigating the small bowel, in the absence of obstructive symptoms or known bowel stenosis.

Strong recommendation, high quality evidence.

RECOMMENDATION

ESGE does not recommend routine cross-sectional small-bowel imaging or the use of a patency capsule prior to capsule endoscopy to prevent the retention of the device in patients with suspected Crohn's disease.

Strong recommendation, high quality evidence.

Up to 83 % of patients with CD have SB involvement at diagnosis [88], and in approximately 90 % of patients with SB CD, the disease involves the terminal ileum [89]. Thus, ileocolonoscopy is considered to be the first-line investigation for CD and is sufficient to establish the diagnosis in most patients [90]. While the addition of capsule assessment may improve specificity, the discriminatory ability of SBCE was shown in a recent study not to be superior to ileocolonoscopy alone as an initial investigation for CD [91].

Skip lesions may result in a false-negative ileocolonoscopy [92], and SBCE should be considered when ileoscopy is not achieved or when proximal SB disease must be excluded.

For patients with suspected CD, two recent meta-analyses have confirmed SBCE has a diagnostic yield for SB disease similar to that of magnetic resonance enterography (MRE), CTE, and abdominal ultrasound, while confirming its superiority to both small-bowel follow-through and enteroclysis [93, 94]. Subgroup analysis of the 2017 meta-analysis of Koplov et al. [93] suggests that for patients with established disease, SBCE is more sensitive for proximal (jejunal) disease compared with MRE (OR 2.79, 95 %CI 1.2–6.48; $P = 0.02$). Similarly, Choi et al.'s meta-analysis [94] found that SBCE detected more ileal disease in patients with established CD than ileocolonoscopy (SBCE 60 % vs. ileocolonoscopy 48 %; weighted incremental yield [Iyw] 0.11, 95 %CI 0.00–0.22; $P = 0.004$). Two recent studies have confirmed a diagnostic advantage for SBCE in assessing SB disease in established CD, for the entire small bowel versus MRE [95], and for the proximal and mid-small bowel versus MRE and CTE [96]. These studies support SBCE as the appropriate next investigation in patients with suspected CD after failed ileocolonoscopy and as the most sensitive means of mapping SB disease in patients with established CD [95, 96].

SBCE should be seen as complementary to ileocolonoscopy in doubtful cases, to confirm the diagnosis and simultaneously determine disease location, extent, and activity. Even after positive ileocolonoscopy findings, SBCE can add important diagnostic information and support a CD diagnosis.

A retrospective observational study by Freitas et al. [97] investigated 102 patients found to have "isolated terminal ileitis" at ileocolonoscopy, endoscopic abnormalities proximal to the terminal ileum were found in 36.3 % of patients; one third (35/102) were finally diagnosed with CD. Similarly, isolated ileitis on SBCE can frequently herald an ultimate diagnosis of CD, even in patients with an initial negative ileocolonoscopy [98, 99].

The risk of capsule retention in patients with suspected CD, without obstructive symptoms or known stenosis, and no history of SB resection is low and similar to that of patients who are being investigated for SB bleeding [100]. A careful clinical history may be the most helpful way to determine the risk of capsule retention in this setting.

In 2017, Rezapour et al. [16] published a meta-analysis showing a slightly higher SBCE retention rate even in suspected CD than previously reported. Retention rates were 8.2 % (95 %CI 6.0 %–11.0 %) for established CD and 3.6 % (95 %CI 1.7 %–8.6 %) for suspected CD (studies of patients with strictures on CTE/MRE or patency capsule retention were excluded). However, there was significant heterogeneity among the studies ($I^2 = 69\%$).

A more recent meta-analysis by Pasha et al. [100] evaluated SBCE retention in patients with suspected and established CD. The retention rate in patients with established CD was 4.63 % (95 %CI 3.42 %–6.25 %; 32 studies) and in patients with suspected CD it was 2.35 % (95 %CI 1.31 %–4.19 %; 16 studies). Patients with established CD were 3.5 times more likely to experience retention than those with suspected CD (95 %CI 2.12–5.78; 16 studies).

Several additional observational studies have also reported a low risk of capsule retention in patients with suspected CD [91, 101–103]. These studies have also shown that the use of either cross-sectional imaging [101, 102] or patency capsule tests [102] in high risk patients with suspected CD (suspected stricture) can avoid capsule retention.

RECOMMENDATION

ESGE recommends that dedicated small-bowel cross-sectional imaging modalities be used first in patients with suspected Crohn's disease and obstructive symptoms or known bowel stenosis.

Strong recommendation, moderate quality evidence.

RECOMMENDATION

ESGE recommends the use of a patency capsule prior to small-bowel capsule endoscopy in patients with suspected Crohn's disease and obstructive symptoms.

Strong recommendation, low quality evidence.

If patients with suspected CD present with obstructive symptoms or known stenosis, dedicated SB cross-sectional imaging in the form of CTE or MRE (which may also provide an additional evaluation of mural and extramural disease) should be the investigation of choice.

Recent studies have shown a high incidence of SB strictures in patients with newly diagnosed CD, particularly in those with isolated SB rather than ileocolonic disease (OR 3.04, $P=0.02$ [104]; and 20.5 % vs. 9.4 %, $P=0.002$ [105]). The efficacy of MRE to detect SB stenosis has been confirmed in a meta-analysis [106] and a comparative observational study with enteroscopy [107], reporting sensitivities of 65 % and 61 % and specificities of 93 % and 93 %, respectively. Moreover, magnetic resonance imaging (MRI) combined with clinical assessment can accurately predict complications (fistulas in 98 % and intra-abdominal abscesses in 99 %) [108].

The retrospective study by Al-Bawardy et al. [109] revealed that patients with SBCE retention were more likely to have, as identified on pre-SBCE CTE, strictures (63 % vs. 23 %), partial SB obstruction (63 % vs. 38 %), or SB anastomosis (88 % vs. 23 %), as compared with patients who had passed the capsule. SBCE may still be applied in this setting if the use of a patency capsule confirms the functional patency of the small bowel. Dedicated SB cross-sectional imaging can overestimate or have low specificity and low positive predictive value (PPV) for the presence of stenosis [110, 111]. Therefore, use of a patency capsule is recommended even in cases of negative findings from cross-sectional modalities in those with suspected CD and obstructive symptoms. A study in 2016 by Rondonotti et al. [110] supports this assertion, with capsule retention occurring in their at-risk cohort with negative CTE findings prior to SBCE. Rozendorn et al. [111] evaluated the ability of MRE to predict retention; because of the low specificity (59 %) and low PPV (40 %) of MRE for prediction of retention, the authors also recommended patency capsule use prior to SBCE in at-risk patients, regardless of MRE findings.

The corollary is also true; in 2008, Herrerias et al. [112] evaluated 106 patients with stenosis seen on small-bowel follow-through or CT, who were subsequently also given a patency capsule. The patency capsule confirmed functional patency in 59 patients (56 %). These patients later underwent SBCE safely, with no cases of capsule retention. González-Suárez et al. reported similar overestimation of stenosis for MRE [95].

It is also important to note that a few case series have reported patency capsule retention in patients with suspected CD [113, 114]. In all patients with findings of wall thickening or stenosis, CT was performed before patency capsule use. Patency capsule retention may cause transient obstructive symptoms, which usually resolve spontaneously, albeit resultant SB perforation has been reported [114, 115].

RECOMMENDATION

ESGE recommends careful patient selection (using clinical history and serological/fecal inflammatory markers) prior to small-bowel capsule endoscopy to improve the diagnostic accuracy for lesions consistent with active small-bowel Crohn's disease.

Strong recommendation, moderate quality evidence.

SBCE is indicated for investigating patients with suspected CD, nondiagnostic terminal ileitis, or inflammatory bowel disease, type unclassified (IBD-U) [116]. Symptoms alone are a poor predictor of CD. The International Conference on Capsule Endoscopy (ICCE) [117] recommended a broader definition of suspected CD that includes inflammatory markers, abnormal imaging, and/or extraintestinal manifestations [118, 119]. It has also been demonstrated that ICCE criteria can be used as an effective selection tool for SBCE since patients with fewer than two ICCE criteria are not only unlikely to have inflammatory changes in the small bowel but also to be diagnosed with CD in the follow-up [118].

Recent meta-analyses have consistently demonstrated that fecal calprotectin has significant diagnostic accuracy for detecting SB CD [120–122]. The likelihood of a positive diagnosis is very low in patients with suspected CD with calprotectin <50 µg/g. A cutoff of 100 µg/g has demonstrated high sensitivity and specificity and appears to be the optimal cutoff value to be used as a screening tool for SB CD [118, 121]. Moreover, in a prospective validation study, a combined diagnostic strategy

based on clinical presentation with Red Flags index score ≥8 and/or fecal calprotectin >250 ng/g showed average values (ranges) of sensitivity 100 % (29 %–100 %), specificity 72 % (55%–85 %), PPV 21 % (5 %–51 %), and NPV 100 % (88–100 %) for the diagnosis of CD [123]. Evidence also shows that a combination of biomarkers can further enhance patient selection.

A diagnostic workflow is proposed for investigation of patients with suspected CD and nondiagnostic ileocolonoscopy (▶ **Fig. 2**).

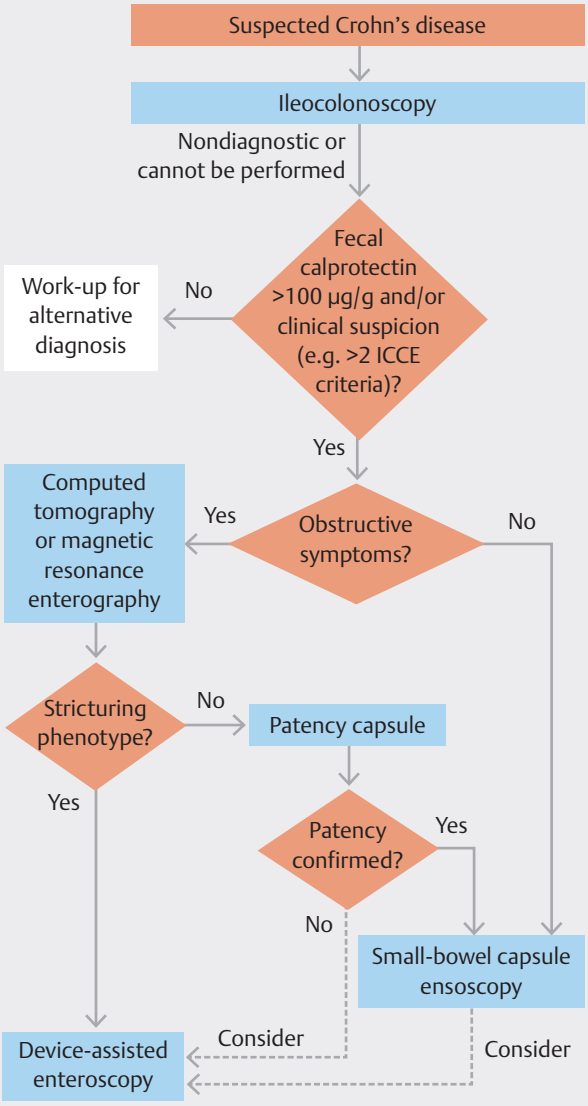
RECOMMENDATION

ESGE recommends discontinuation of both selective and nonselective nonsteroidal anti-inflammatory drugs, including short-term use, as well as of low dose and/or enteric-coated aspirin (if the patient's condition allows), for at least 4 weeks before capsule endoscopy since these drugs may induce small-bowel mucosal lesions that are indistinguishable from those caused by Crohn's disease.
Strong recommendation, low quality evidence.

NSAIDs, including enteric-coated or low-dose aspirin, are a common cause of SB erosions and ulcerations because of direct toxicity and systemic effects on prostaglandin metabolism. Cyclo-oxygenase 2 (COX 2)-selective agents have also been shown to cause comparable SB damage; therefore, the current ESGE recommendations apply to both selective and nonselective NSAIDs. Severe enteropathy, such as circumferential ulcers with stricturing (diaphragmatic disease), has been described in approximately 2 % of patients on long-term NSAID use [124]. Short-term use results in SB injury in most patients, manifesting as multiple petechiae or red spots, erythematous patches, loss of villi, erosions, and ulcers [125]. After only 2 weeks of treatment, up to 71 % of patients have some evidence of drug-induced SB lesions [124, 126, 127], and the reported prevalence in long-term low dose aspirin users is 88.5 %–100 % [128]. Characteristic features of NSAID-induced injury include: (i) multiple superficial lesions; (ii) similar distribution in the jejunum and ileum; (iii) lesions <1 cm; (iv) uncommon ileocecal valve involvement [129].

The use of proton pump inhibitors (PPIs), histamine H2-receptor antagonists, or enteric-coated aspirin formulations is associated with a higher risk for NSAID-induced enteropathy [130, 131]. Indeed, a prospective SBCE study found that PPI use (OR 2.04, 95 %CI 1.05–3.97) and use of enteric-coated aspirin (OR 4.05, 95 %CI 1.49–11.0) were the two most important risk factors for the presence of mucosal breaks [132]. Chronic acid suppression could lead to SB bacterial overgrowth, namely of enterobacteria which contribute to the development of NSAID-induced enteropathy, while enteric-coated aspirin formulations dissolve in the small bowel rather than the stomach or duodenum, resulting in localized direct toxicity.

No data are available regarding the interval required for spontaneous healing of NSAID/low dose aspirin and/or enteric-coated aspirin-induced SB mucosal lesions. However, in the setting of suspected CD, the current recommendation to suspend



▶ **Fig. 2** Algorithm for the investigation of patients with suspected Crohn's disease and nondiagnostic ileocolonoscopy. ICCE, International Conference on Capsule Endoscopy

NSAIDs for 4 weeks before SBCE to allow for complete mucosal healing remains generally recommended if the patient's clinical condition allows. If discontinuation is clinically contraindicated, interpretation of SBCE findings should consider that any lesion identified may have been caused by the ongoing use of these medications.

RECOMMENDATION

ESGE recommends device-assisted enteroscopy with small-bowel biopsies in patients with noncontributory ileocolonoscopy and suspected Crohn's disease on small-bowel cross-sectional imaging modalities or small-bowel capsule endoscopy.
Strong recommendation, high quality evidence.

As stated in the previous guideline [1], despite all the recent advances in endoscopic and dedicated SB cross-sectional imaging, CD may still pose a diagnostic challenge, mainly if it is confined to the small bowel [90, 133]. Furthermore, it may be challenging to differentiate inflammatory SB lesions with other etiologies, such as infection (e.g., mycobacterial disease), drugs (e.g., NSAIDs and olmesartan), and malignancy (e.g., lymphoma), from similar lesions caused by CD. In such circumstances, direct endoscopic evaluation and biopsy of lesions at DAE is helpful in ruling out other causes and/or providing corroborative evidence of a diagnosis of SB CD [1,47]. Since 2015 [1], there has been further support for the usefulness of DAE in this context [134,135]. A retrospective series by Tun et al. (n = 100) [134], evaluated the role of DBE in the setting of suspected CD, where a definitive diagnosis through other modalities remained elusive. In this cohort, histopathology of biopsies taken at DBE was helpful to support a diagnosis of CD in 23 %. In another similar retrospective series by Holleran et al., which included 13 adult patients, single-balloon enteroscopy (SBE) contributed to the diagnosis of CD in 39 % [135].

Established Crohn's disease

RECOMMENDATION

ESGE recommends, in patients with established Crohn's disease based on ileocolonoscopy findings, dedicated cross-sectional imaging for small-bowel evaluation since this has the potential to assess the extent and location of any Crohn's disease lesions, to identify strictures, and to assess for extraluminal disease.

Strong recommendation, high quality evidence.

RECOMMENDATION

ESGE recommends, in patients with unremarkable or nondiagnostic findings from dedicated small-bowel cross-sectional imaging, small-bowel capsule endoscopy as a subsequent investigation if deemed likely to influence patient management.

Strong recommendation, low quality evidence.

RECOMMENDATION

ESGE suggests that small-bowel capsule endoscopy may be useful for assessment of Crohn's disease extent and for monitoring and guiding the "treat-to-target" strategy.

Weak recommendation, low quality evidence.

The present ESGE guideline confirms that, in the setting of established CD, when SB evaluation is indicated, SB cross-sectional imaging with CTE or MRE generally takes precedence over SBCE since these modalities can assess the transmural and extraluminal nature of the disease and its anatomical distribution [1,136]. However, as discussed previously, there is growing evidence from published meta-analyses and observational studies to show that SBCE is more sensitive than cross-sectional imaging for mucosal disease throughout the small bowel in patients with established as well as suspected CD [93–96]. SBCE has been shown to be a complementary test, increasing the identification of more diffuse SB disease even in patients with a positive ileocolonoscopy.

Recent studies have evaluated the potential benefit of a panenteric capsule endoscopy for further evaluation of patients with CD. A study by Bruining et al. [137] compared panenteric capsule endoscopy with MRE and ileocolonoscopy. The overall sensitivities for active enteric inflammation (panenteric capsule endoscopy vs. MRE and/or ileocolonoscopy) were 94 % vs. 100 % ($P = 0.125$) and the specificities were 74 % vs. 22 %, respectively ($P = 0.001$). The sensitivity of panenteric capsule endoscopy was superior to that of MRE within the proximal small bowel (97 % vs. 71 %, $P = 0.021$), and similar to that of MRE and/or ileocolonoscopy within the terminal ileum and colon ($P = 0.500$–0.625). The study by Tai et al. [102] showed that the use of panenteric capsule endoscopy resulted in management change in 46.5 % of cases. Overall, the presence of active inflammatory findings resulted in a change in medical management in 64.6 % of patients with established CD. Proximal SB findings led to an upstaging of disease in 19.7 % and predicted escalation of therapy (OR 40.3). Similarly, in a prospective comparative study of panenteric capsule endoscopy and ileocolonoscopy by Leighton et al. [138] in patients with active CD, panenteric capsule endoscopy was shown to have a higher lesion detection rate in all SB segments including the terminal ileum.

Despite recommendation by new guidelines that all patients newly diagnosed with CD undergo SB assessment by ultrasound, MRE, and/or SBCE [90], it is still not clear whether these techniques are alternative or complementary. Evidence is scarce, but Greener et al. [139] compared the changes in disease extent and localization after performing MRE, SBCE, and both modalities. The investigators demonstrated that previously unrecognized disease locations were detected with SBCE and MRE in 51 % and 25 %, respectively ($P < 0.01$) and by both modalities combined in 44 patients (55 %). Using both modalities together may alter the original Montreal classification in 64 % of patients [139].

For patients with established CD, the use of SBCE and panenteric capsule endoscopy may lead to changes in management in 50 %–60 % of patients [102,140], as they allow assessment of mucosal healing [141]. Indeed, in a meta-analysis by Niv [142], mucosal healing detection by capsule was shown to be a good predictor of long-term clinical remission.

Although the Lewis score and the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) have shown good correlation with each other [142,143], there seems to be poor correlation between capsule activity index scores and clinical and laboratory parameters. The study by Kopylov et al. [144] emphasizes that SBCE may detect mucosal inflammation even in patients in clinical and biomarker remission. Furthermore, a Lewis score of ≥ 270 has been identified as a predictor of

disease-related hospitalization [145], and a baseline Lewis score of ≥350 predicts long-term disease flare-ups [146].

The 2015 ESGE guideline recommended using SBCE to assess postoperative recurrence if colonoscopy is contraindicated or unsuccessful [1]. Since then, however, new evidence and a meta-analysis have emerged. Recent studies are consistently showing that in this setting, SBCE has a higher sensitivity for lesion detection, when compared with MRE and ultrasound [147, 148], even before symptoms appear [149], and may effectively drive further patient management [147, 149].

Conversely, since the 2015 guideline [1], only scant data regarding the role of SBCE in IBD-U have been published. Monteiro et al. [116] published a multicenter retrospective study of 36 patients with IBD-U, and analyzed inflammatory activity with SBCE using the Lewis score. In this study, 25 % of patients were then diagnosed with CD (Lewis score ≥ 135), 44 % of patients with ulcerative colitis (UC), and 27 % continued to have a diagnosis of IBD-U, supporting the potential role of SBCE in reclassifying some cases of IBD-U.

RECOMMENDATION

ESGE recommends the use of activity scores (such as the Lewis score and the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI)) to facilitate prospective small-bowel capsule endoscopy follow-up of patients for longitudinal assessment of small-bowel Crohn's disease and its response to medical therapy (using mucosal healing as an endpoint).

Strong recommendation, low quality evidence.

The invention of capsule endoscopy introduced the need for quantitative metrics to assess mucosal inflammation. Furthermore, as treatment targets focus on mucosal healing, this has become even more essential. Several quantitative inflammatory scores for capsule endoscopy have been developed over the years [1, 141–143]. Regarding SBCE reporting, along with the Lewis score and CECDAI, a new activity index, the Eliakim score combining evaluation of SB and colonic findings, has been proposed. When panenteric capsule endoscopy is used to allow for an integrated assessment of the small bowel and the colon, the Eliakim score has shown a good correlation with the Lewis score [150].

RECOMMENDATION

ESGE recommends, in patients with established Crohn's disease, the use of a patency capsule before small-bowel capsule endoscopy to decrease the capsule retention rate.

Strong recommendation, moderate quality evidence.

The patency capsule is a noninvasive and safe device developed to confirm functional patency of the intestinal lumen in patients with suspected stenosis, to avoid SB capsule endoscope retention. If the patency capsule is egested intact, retention of an actual capsule is unlikely. When the patency capsule is not egested within 30 hours, cross-sectional imaging is favored over abdominal radiography to confirm its exact location [151]. Silva et al. [152] observed that using the radiofrequency identification tag scanner, part of the patency capsule equipment, is also not helpful and may be avoided.

Given the higher risk of capsule retention in established CD, several strategies have been evaluated to identify patients with reduced functional patency. Nemeth et al. [153] evaluated capsule retention in two groups of patients who underwent a previous patency test: (i) a preselected group of patients with obstructive symptoms or previous abdominal surgery; and (ii) a group with nonselective patency capsule administration. No difference in capsule retention rates was observed (1.3 % vs. 1.6 %, $P = 0.9$). However, capsule endoscopy after a positive patency test was associated with a high retention risk (11.1 %).

A large (n = 3117) multicenter, prospective, observational study by Rondonotti et al. [110] evaluated capsule retention rates in low risk and high risk patients. Patients were considered high risk (n = 175) if they met one of the following criteria: recurrent abdominal pain, previous SB surgery, chronic NSAID use, SB stenosis detected in imaging techniques, prior abdominal radiation therapy, or refractory celiac disease. Of these 175 high risk patients, 24 underwent CTE or MRE before SBCE and the remaining 151 were given a patency capsule instead. In high risk patients, the subsequent capsule retention rate was 0.7 % (1/151) for the patency capsule subgroup and 8.3 % (2/24) for the cross-sectional imaging subgroup. The authors concluded that in high risk patients, a patency capsule is still required, regardless of radiological findings. Dedicated SB cross-sectional imaging, although helpful, can underestimate or overestimate the presence/degree of any stricturing.

RECOMMENDATION

ESGE recommends initial conservative treatment in the case of capsule retention.

Strong recommendation, high quality evidence.

RECOMMENDATION

ESGE recommends device-assisted enteroscopy if medical therapy has not achieved spontaneous capsule passage.

Strong recommendation, high quality evidence.

Capsule retention is the main adverse event of SBCE. As stated in the previous guideline [1], the recommendation is that asymptomatic patients should be managed conservatively/medically in the first instance, with DAE retrieval reserved for cases of persistent retention. Large series published since 2015 [1] have confirmed the validity of this recommended strategy. A multicenter retrospective study by Fernández-Urién

et al. (n = 5428; different indications for SBCE) [154] showed an overall retention rate of 1.8%; >50% of retained capsules passed with conservative management (37% spontaneously; 20% with concomitant medical therapy). Nemeth et al., 2 years later also demonstrated a favorable outcome with this strategy: medical management resulted in the passage of 24% of retained capsules, while endoscopic retrieval was required in 44% [155]. This recommendation was also supported by the findings of another large retrospective series (n = 5348; all indications) [156] and a retrospective study focused on patients with established CD, which also reported a high rate (70.5%) of passage of retained capsules with conservative measures [157].

The evidence to support specific medical management regimens remains scant, albeit most series reported on the use of glucocorticoids for capsule retention in the context of CD [154, 155, 157], with immunomodulators also used as an alternative [157]. Published egestion rates with medical management range from 10% to 70% [155–157], being higher in patients with established CD. In a multivariate analysis published by Lee et al. [158], the presence of abdominal symptoms after capsule retention was an independent predictive factor for a surgical outcome (OR 18.56, 95%CI 1.87–183.82; $P = 0.013$).

Endoscopic retrieval has been a safe alternative in asymptomatic patients or in those with slight symptoms. Recently, a systematic review of 12 studies (n = 150) regarding the use of DBE for retrieval of retained capsules [159], demonstrated a pooled retrieval success rate of 86.5% (95%CI 75.6%–95.1%). Factors associated with higher success were the antegrade approach (74.7% vs. 26.3%; $P < 0.001$) and the presence of malignant strictures (100.0% vs. 78.3%; $P = 0.043$) [159].

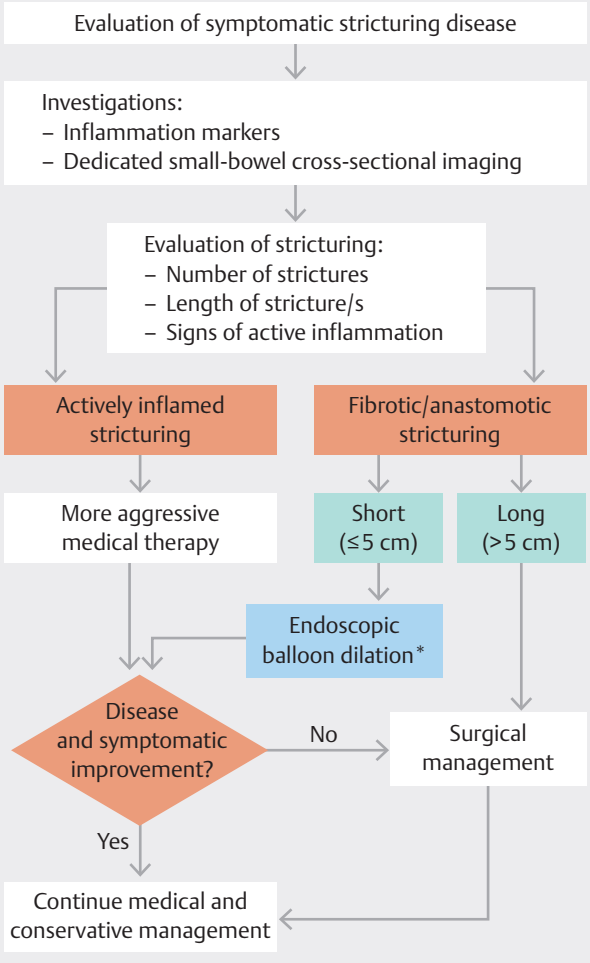
RECOMMENDATION

ESGE recommends device-assisted enteroscopy if small-bowel endotherapy is indicated (including dilation of Crohn's disease small-bowel strictures, retrieval of a retained capsule, and/or treatment of small-bowel bleeding).

Strong recommendation, high quality evidence.

Since the publication of the 2015 ESGE guideline [1] the evidence favoring the effectiveness and safety of DAE-facilitated endoscopic balloon dilation (EBD) of CD SB strictures has strengthened. This is best summarized in a recent meta-analysis by Bettenworth et al. [160], which evaluated 18 studies including a total of 463 patients and 1189 endoscopic balloon dilations. The pooled per-study analysis demonstrated that the technical success of endoscopic balloon dilation was 95% (95% CI 86.7%–98.1%; 13/18 studies), with clinical efficacy in 82.3% of patients (95%CI 68.1%–91%; 9/18 studies) in the short term. The major complication rate (including bleeding, perforation, and emergency surgery) was 5.3% (95%CI 3.5%–8.1%; 14/18 studies). Longer-term outcomes (as reflected by 20.5 months of follow-up) showed that symptomatic recurrence had occurred in 48.3% of patients (95%CI 33.2%–63.7%; 11/18 studies). Nonetheless, this was managed by repeat endoscopic balloon dilation in 38.8% of patients (95%CI 27%–52%); 16/18 studies); recourse to surgery was required in 27.4% (95%CI 21.9%–33.8%; 15/18 studies). This meta-analysis [160] further interrogated detailed data from four of the included high volume centers (218 patients; 384 dilations) to identify potential risk factors associated with outcomes. On per-patient-based multivariable analysis, active SB disease was associated with reduced short-term clinical efficacy (OR 0.32, 95%CI 0.14–0.73; $P = 0.007$). Furthermore, concomitant active disease of the small and/or large bowel increased the risk for surgery (hazard ratio [HR] 1.85, 95%CI 1.09–3.13; $P = 0.02$; and HR 1.77, 95%CI 1.34–2.34; $P < 0.001$]. Conversely, ongoing anti-TNF-alpha treatment at the time of dilation correlated with reduced re-intervention (HR 0.78, 95%CI 0.63–0.96; $P = 0.019$).

Based on the current evidence, an algorithm for the endoscopic management of SB strictures is suggested in ▶ **Fig. 3** [161, 162].



▶ **Fig. 3** Algorithm for the endoscopic management of benign small-bowel strictures (modified from [161, 162] with permission). * Consider surgery as a possible alternative to endoscopic balloon dilation, depending on location/presence of prestenotic dilatation/angulation and local set-up.

Inherited polyposis syndromes

Familial adenomatous polyposis

RECOMMENDATION
ESGE recommends surveillance of the proximal small bowel in familial adenomatous polyposis, using conventional forward-viewing and side-viewing endoscopes.
Strong recommendation, moderate quality evidence.

RECOMMENDATION
ESGE does not recommend small-bowel capsule endoscopy for surveillance of the proximal small bowel in familial adenomatous polyposis.
Strong recommendation, moderate quality evidence.

RECOMMENDATION
ESGE suggests that small-bowel capsule endoscopy and/or cross-sectional imaging techniques may be considered when investigation of the mid–distal small bowel is clinically indicated in familial adenomatous polyposis.
Weak recommendation, moderate quality evidence.

The recent literature does not suggest an increased risk of distal (namely, beyond the proximal jejunum that is accessible at standard upper endoscopy) SB cancer in familial adenomatous polyposis [163–165]. This is concordant with the ESGE 2019 [166] and the ASGE 2020 [167] recommendations. Since SBCE may miss polyps in the proximal small bowel, it does not appear suitable for surveillance at this level [168]. If SBCE is justified in selected patients (anemia, major duodenojejunal burden of adenomas), prior patency examination or abdominal imaging is suggested in some studies [165, 167]. In a therapeutic context, the ASGE recommendations consider the use of DAE, bearing in mind that that neither SBCE nor DAE studies report the presence of advanced adenomas deeper than the proximal jejunum [163, 165, 167].

In conclusion, endoscopy using a long axial endoscope and a lateral-viewing endoscope remains the gold standard of SB examination in familial adenomatous polyposis patients in 2022.

RECOMMENDATION
ESGE recommends, for small-bowel surveillance in patients with Peutz–Jeghers syndrome, small-bowel capsule endoscopy and/or magnetic resonance enterography, depending on local availability and expertise and/or patient preference.
Strong recommendation, moderate quality evidence.

Peutz–Jeghers syndrome

Most polyps are localized within the small bowel in patients with Peutz–Jeghers syndrome (PJS). Patients have a significant risk of non-neoplastic complications (intussusception, bleeding, anemia) as well as an increased risk of malignancies (intestinal and extraintestinal) [169]. SB surveillance in PJS aims to prevent polyp-related complications (by reduction of the polyp burden) and to detect early premalignant or malignant changes with advancing patient age.

Guidelines from ESGE and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommend starting SB surveillance no later than 8 years of age (and earlier in patients with symptoms or complications) [166, 170]. Based on the number and size of SB polyps, a 1–3-yearly surveillance interval is recommended [166]. Cancer risk is significantly increased in PJS [171]. However, the potential for malignant transformation of the SB hamartomas remains unknown.

SB surveillance should be a part of the complex multiorgan screening program for patients with PJS [169]. SBCE is superior at detecting SB polyps in comparison with small-bowel follow-through and standard CT scans [168, 172]. The direct comparison of MRE and SBCE shows at least equivalent sensitivity of both methods in detection of SB hamartomas; there is some risk of missing clinically relevant polyps with both techniques [173, 174]. Some data suggest better localization of polyps and more accurate size estimation with MRE [173, 174], but SBCE superiority for detection of small polyps (< 15 mm) [174]. A meta-analysis of 15 comparative studies (821 patients) of DAE and SBCE confirmed high concordance (93 %) in the identification of SB polyps and tumors [172]. In a retrospective multicenter study, 25 patients underwent SBCE followed by DBE when treatment was indicated. Authors found a strong agreement for polyp location and size but not for the number of polyps; DAE was more accurate for the latter [175]. Two small studies reported high concordance of MRE with DBE, laparoscopic enteroscopy, or surgery (93 %). They also showed comparable diagnostic yields from MRE and DBE for SB polyps > 15 mm [176, 177].

In summary, MRE, SBCE, and DAE are complementary methods with similar diagnostic yields and a similar risk of missed lesions. The limited data do not allow preference for any one of the methods. Thus, both noninvasive techniques (SBCE or MRE) can be recommended for SB surveillance in patients with PJS, based on local availability and experience.

A patient history of SB resection (and therefore a risk of intra-abdominal adhesions) may mean a higher risk of SBCE retention, especially in patients with obstructive symptoms [178]. The routine use of the patency capsule [179] is not recommended in PJS and should be considered only on a case-by-case basis.

RECOMMENDATION

ESGE recommends device-assisted enteroscopy with polypectomy when large polyps (>15 mm) or symptomatic polyps are discovered by radiological examination or small-bowel capsule endoscopy in patients with Peutz–Jeghers syndrome.

Strong recommendation, moderate quality evidence.

An SB polyps size >15 mm is the most important risk factor for SB intussusception, which can lead to intestinal obstruction and acute abdomen [180, 181]. On the other hand, in children (because of the smaller intestinal diameter), even polyps smaller than 15 mm may represent a risk, and polyps may result in other complications such as chronic bleeding with IDA [181]. Consequently, large (>15 mm), symptomatic, or rapidly growing polyps should be promptly removed.

Both in adults and children, DAE is clinically useful for diagnosis and relatively safe for therapy of SB polyps [180, 182–184]. In a study of 50 enteroscopies using the antegrade (84 %) and retrograde (16 %) approach, the therapeutic interventions resulted in complete clearance of polyps >10 mm in 76 % of patients [184]. However, considering the safety profile of DAE polypectomy (complication rate in PJS patients: 4 %–6 % [183–185]), enteroscopy should be used only as a targeted approach after previous noninvasive SB examination (using SBCE or MRE).

Motorized spiral enteroscopy has only recently been used in patients with PJS [186]. The published data on this technique are promising but insufficient for a final recommendation for patients with PJS.

Various technical improvements, including underwater resection [187] and ischemic polypectomy using polyp strangulation with endoclips and/or detachable snare (possibly also with an underwater approach), have been reported [188, 189]. They could represent a safer and faster alternative to conventional polypectomy; however, their benefits need future verification. In some clinical situations (high polyp burden and incomplete polyp clearance during previous DAE), the direct indication for the next DAE (without repeated SBCE or MRE) can be considered in an individualized time frame. A gradual decline in polyp size, numbers, and complication rate can be expected in the course of surveillance and repeated DAE polypectomies [182, 185, 190, 191].

When a polyp is too large for safe removal with DAE or cannot be reached using this modality (because of adhesions), intraoperative enteroscopy as a complementary technique could be considered for SB evaluation and polypectomy [183, 184]. Combined treatment of SB hamartomas with device-assisted and intraoperative enteroscopy significantly increases clearance success by 16 % [184]. This approach may reduce the need for future surgery and SB resection in PJS patients.

Juvenile polyposis

RECOMMENDATION

ESGE recommends that routine evaluation of the small bowel in juvenile polyposis patients should be limited to the duodenum and based on flexible forward-viewing endoscopy.

Strong recommendation, low quality evidence.

Involvement of the small bowel in juvenile polyposis seems infrequent and mainly limited to the duodenum in patients harboring a SMAD4 mutation [192, 193]. No case of SB cancer has been reported at this time in the well-characterized juvenile polyposis family. The ESGE 2019 consensus and the recent pediatric consensus on genetic syndromes do not recommend using SBCE or DAE in juvenile polyposis syndrome [166, 194].

In conclusion, there is no evidence of the usefulness of capsule endoscopy and no published case of histologically proven juvenile polyposis in the distal small bowel in these patients. According to ESGE and ESPGHAN recommendations, duodenoscopy appears sufficient, specifically in SMAD4 mutation carriers, because of the frequency of duodenal polyps.

Small-bowel tumors

RECOMMENDATION

ESGE recommends the use of small-bowel capsule endoscopy in patients where there is an increased risk of a small-bowel tumor.

Strong recommendation, moderate quality evidence.

Most SBTs are detected during work-up for SSBB or unexplained IDA but are the cause in only about 3.5 %–5 % of these patients, making these symptoms weak predictors. Some subsets of patients have an increased risk of SBT, such as those with liver metastases of previously undiagnosed primary neuroendocrine tumor, stage IV malignant melanoma, or stage III malignant melanoma with positive FOBT, or with nonresponsive/complicated celiac disease (see **Celiac disease** section) [19]. In contrast, recent data do not suggest a significant yield for SBT or polyps in patients with sporadic duodenal adenomas [195], long-standing SB CD [196], or asymptomatic Lynch syndrome [197, 198]. The risk for underlying SBT does not seem to be higher in patients with recurring or ongoing bleeding than in patients with the first bleeding episode [199].

Because of the rarity of SBTs, prospective studies are lacking, and data are primarily retrospective from SSBB and IDA studies. In this setting, SBCE has exhibited good diagnostic performance for identifying SBTs [74, 200]. Although Johnston et al. have reported more frequent detection of SB malignancy at SBCE in younger patients (<55 years) [201], most studies did

not reveal any significant differences in the incidence of SBTs depending on the age of the patients, albeit there were variations in the definition of the younger versus older age groups [202–204]. The diagnostic yields of double-balloon enteroscopy for SBTs in the SSBB setting were also similar between patients <65 years old and elderly patients (>65 years), except for cases of incomplete SB obstruction where a higher rate of adenocarcinoma was identified in the elderly group (19.4% vs. 7.1%, $P=0.038$) [205].

In an RCT in the setting of SSBB, SBCE had a higher diagnostic yield for SBTs and polyps than push enteroscopy [206]. Compared to DAE in SSBB, SBCE had detection rates similar to single-balloon enteroscopy for SBTs [207, 208]. Also double-balloon enteroscopy and SBCE had comparable diagnostic yields for SBTs [209, 210], even in a context of SB re-examination, where double-balloon enteroscopy was compared to repeat SBCE for SSBB [56]. Nevertheless, the concordance between SBCE and single-balloon enteroscopy was not significant regarding SB masses [211], and the agreement between SBCE and double-balloon enteroscopy was lower for SBTs than for other SB pathology in the setting of SSBB [212, 213]. Suspected SB neoplasia was related to increased diagnostic and therapeutic yield for both single- and double-balloon enteroscopy. Although previous SB investigations, including SBCE and/or imaging studies, improved the diagnostic yield of enteroscopy, this was not statistically significant [214].

On the other hand, the risk of false-negative SBCE results has been documented for SBTs, especially for lesions located in the proximal SB [168] or subepithelial tumors with minimal endoluminal components, such as GI stromal tumors (GISTs) [215] and neuroendocrine neoplasms (NENs) [216]. Therefore, in the case of a negative SBCE, albeit with a strong suspicion of an SBT, further dedicated SB cross-sectional imaging should be performed for confirmation.

Regarding imaging studies, CTE was accurate in raising the suspicion of SBTs [18], primarily when performed for SSBB [217]. CT angiography had a higher diagnostic yield for bleeding SBTs than for SB bleeding of nontumoral origin [218]. In a retrospective comparison of CTE and MRE, all cases of SBTs were accurately diagnosed by both modalities [219]. Conversely, in a prospective study comparing SBCE and CTE in the context of SSBB, the sensitivity of SBCE for SBTs was 66.67% compared to 100% for CTE [87]. In a retrospective study comparing double-balloon enteroscopy with SBCE and imaging modalities (CTE and MRE) for detecting SBTs, double-balloon enteroscopy was superior to all methods in terms of sensitivity, specificity, accuracy, and negative predictive value (NPV). Only CTE exhibited slightly higher PPV than double-balloon enteroscopy (93.5% vs. 90.0%) with comparable specificity, whereas MRE was outperformed in every aspect [220]. In another retrospective study comparing SBCE, double-balloon enteroscopy, and CTE for SSBB, all three approaches were comparable, complementing each other in detecting SBTs [221]. Thus, a combination of SBCE, dedicated cross-sectional SB imaging (e.g., CTE) and DAE may be required in the setting of suspected SBT since all three modalities are complementary to each other and provide supplementary information to establish the diagnosis of an SBT.

RECOMMENDATION

ESGE does not recommend, in the setting of suspected small-bowel tumor, specific investigations before small-bowel capsule endoscopy unless patients are considered to be at risk of capsule retention.

Strong recommendation, low quality evidence.

RECOMMENDATION

ESGE recommends consideration of device-assisted enteroscopy in preference to small-bowel capsule endoscopy if imaging tests have already demonstrated suspected small-bowel tumor.

Strong recommendation, low quality evidence.

The ESGE Technical Review on SBCE and DAE recommends that no specific investigations be routinely performed on every patient referred for SBCE unless they are considered at risk for capsule retention. Careful assessment of symptoms such as abdominal pain/distension, nausea/vomiting, a history of previous SB resection, abdominal/pelvic radiation, or chronic use of NSAIDs may be used to distinguish patients at a higher risk of capsule retention [47]. Ultrasound could be a noninvasive initial diagnostic option in these patients, as a sensitivity of >90% for SBTs >2 cm has been reported [222].

The capsule retention rate in the case of SBTs varies among studies [201, 203]; nevertheless, in a meta-analysis, the capsule retention rate was 2.1% for patients with SSBB, representing the most common indication for SB investigations in patients with SBTs [16]. In the setting of suspected SBT in imaging studies, DAE should be preferred over SBCE to avoid capsule retention and acquire biopsies for histological diagnosis [1]. Furthermore, in the case of capsule retention, surgery remains the mainstay of treatment when neoplastic disease is unequivocally suggested, allowing both capsule retrieval and tumor resection [47]. If the nature of the SB lesion cannot be determined with certainty, then DAE can be an alternative for capsule retrieval and tissue sampling and/or endoscopic resection if deemed feasible in the case of benign tumors [159, 223].

RECOMMENDATION

ESGE recommends cross-sectional imaging for staging and ascertaining operability when there is a small-bowel capsule endoscopy finding of a small-bowel tumor with high diagnostic certainty.

Strong recommendation, low quality evidence.

RECOMMENDATION
ESGE recommends, when there is an uncertain diagnosis of small-bowel tumor at capsule endoscopy, biopsy sampling and tattooing of its location by device-assisted enteroscopy.
Strong recommendation, low quality evidence.

RECOMMENDATION
ESGE recommends, when a subepithelial mass is detected by small-bowel capsule endoscopy, confirmation of the diagnosis by device-assisted enteroscopy and/or cross-sectional imaging, depending on local availability and expertise.
Strong recommendation, low quality evidence.

When SBCE findings strongly suggest an SBT (stenotic or protruding, ulcerated, bleeding mass lesion), direct surgical referral without preoperative histological diagnosis would be justifiable. In these cases, preoperative cross-sectional imaging is mandatory to provide further information on disease extent and resectability. If the underlying etiology of the tumor is uncertain (e. g., adenocarcinoma vs. lymphoma), tissue sampling through DAE is indicated to establish a histopathological diagnosis that may guide the course of subsequent management. When subepithelial protrusions or bulges of uncertain nature are identified on SBCE, further investigations (DAE or/and dedicated SB cross-sectional imaging) are warranted to avoid a false-positive diagnosis of subepithelial lesions such as GISTs or NENs. It should be noted that the prominent extraluminal component of GISTs may challenge endoscopic diagnosis, not only with SBCE but with DAE too. The effectiveness of histological confirmation by DAE in this setting has a wide range (46 %–88 %) [223–225]. Placement of a tattoo during DAE is mandatory to facilitate recognition of an SB mass lesion at subsequent (laparoscopic) surgery [1].

Regarding SB subepithelial lesions, CTE was shown to be superior to abdominopelvic CT for identifying SB GISTs [215] and SB NENs [226]. MRE has exhibited high degrees of sensitivity for the diagnosis of NENs >10 mm (94 %), but for lesions <10 mm, sensitivity was only 45 % [227]. In a retrospective study assessing imaging techniques and double-balloon enteroscopy for the management of SB NENs, double-balloon enteroscopy was significantly better at identifying the primary tumor than CT, MRI, or somatostatin receptor imaging, as well as for detection of multifocal lesions when compared to CT and somatostatin receptor imaging but not compared to MRI [228]. Double-balloon endoscopy also detected additional lesions in 62.2 % of patients who underwent an evaluation to exclude multifocal disease in the setting of SB NENs [216].

RECOMMENDATION
ESGE does not recommend small-bowel capsule endoscopy in the follow-up of treated small-bowel tumors, because of lack of data.
Strong recommendation, low quality evidence.

In patients with treated follicular lymphoma, Nakamura et al. found that SBCE detected lesions at a similar rate to double-balloon endoscopy; however, identifying residual lymphoma required biopsy, and the authors recommend DBE for follow-up [229]. Only 1 of 11 patients with an SBCE diagnosis of malignant SBT who underwent surgery had recurrent bleeding; in this patient, it was caused by metastasis of gastric and papillary cancer in familial adenomatous polyposis [230]. After complete resection of SB GIST in 32 patients, no intraluminal recurrence was seen during a median follow-up of 30 months (range 3–54 months) [225].

There are no studies that support regular follow-up of asymptomatic patients after resection of SBT in the absence of inherited polyposis syndromes.

Similarly, SBCE seems to have a very limited role in staging SBTs diagnosed with other techniques. SBCE and enteroscopy can help define the extent of GI non-Hodgkin's lymphoma, although they do not change the stage of follicular lymphoma [231]. Similarly, the number of detected NENs in the small bowel could be increased without demonstrating an impact of multifocality on outcomes [216].

RECOMMENDATION
ESGE suggests considering enteroscopic placement of self-expanding metal stents in the palliation of malignant small-bowel strictures as an alternative option to surgery.
Weak recommendation, low quality evidence.

A summary of published reports on self-expanding metal stents (SEMSs) placement by endoscopy (n = 69) in malignant SB strictures found the method to be safe and effective [232]. Recent small series confirmed this result. Clinical improvement was observed following SEMS placement but not with medical treatment [233]. DAE can also be applied for ink marking of malignant SB strictures for palliative surgery [234].

Celiac disease

RECOMMENDATION
ESGE does not recommend small-bowel capsule endoscopy to diagnose celiac disease.
Strong recommendation, low quality evidence.

In studies assessing the utility/efficacy of SBCE in diagnosing celiac disease (i. e., ability to detect histologically proven villous atrophy), the sensitivity, specificity, PPV, and NPV of SBCE were 70 %–100 %, 64 %–100 %, 96 %–100 % and 71 %–93 %, respectively [235–239]. All these studies consistently show that, in the presence of antiendomysial antibody (EmA) or significantly elevated antitransglutaminase antibody (tTG), the PPV and specificity for recognizing endoscopic markers of celiac disease are 100 %. However, the high pre-test probability of celiac disease in all of these studies may be a potential limitation leading to an overestimation of SBCE performance. A later meta-analysis confirms the previous findings [240], and an RCT has demonstrated that frontal and lateral view capsules are equivalent in detecting villous atrophy [241]. From a clinical point of view, new data suggest that when upper endoscopy is impossible, a diagnostic pathway similar to the pediatric sequence, based upon serology, could also be applied in adults [242], further limiting the potential use of SBCE in this setting.

Consequently, the actual scenario does not support the use of SBCE in this setting (basically, patients with positive serology necessitating a histological confirmation of the diagnosis) and probably, when necessary, the adoption of serological criteria could avoid any endoscopic procedure to diagnose celiac disease. Although currently unproven, the use of computerized image enhancement could modify this situation in future [243].

As with the previous ESGE guideline [1], there is no new evidence supporting the use of SBCE to routinely map the extent of disease. However, two recent studies from Chetcuti Zammit et al. [244, 245] reported that the extent of villous atrophy could be efficiently verified by SBCE and atrophy extent could correlate with clinical parameters in some specific subgroups of patients (e. g., those with nonresponsive celiac disease, or severe bone involvement). The first study analyzed SBCE in 300 celiac patients and demonstrated an acceptable agreement among readers to define the severity of celiac disease [244]; the second analyzed a cohort of 80 celiac patients and showed that, in individuals with a relevant percentage of small bowel involved by villous atrophy, bone mineral density decreased significantly [245]; furthermore, bone mineral density did not correlate with histological severity of atrophy, underlining the potential relevance of atrophy extent. In conclusion, more recent studies suggest that atrophy extent could be efficiently quantified using SBCE and that this finding could correlate with some clinical parameters. However, because of the absence of other than gluten-free diet therapies for celiac disease, this factor is merely descriptive, and SBCE cannot be routinely recommended for this purpose. Nevertheless, this scenario could rapidly change in the near future once pharmacological therapies for celiac disease become available.

RECOMMENDATION

ESGE recommends using small-bowel capsule endoscopy in cases of equivocal diagnosis of celiac disease since it is essential for final diagnosis and therapy.

Strong recommendation, low quality evidence.

Equivocal cases of celiac disease represent a clinical challenge and a clear indication for SBCE. Two subgroups of patients can fit within the “equivocal cases” definition: patients with positive celiac serology (i. e., positive IgA tTG and/or EmA) but normal duodenal histology, and patients with histologically detected villous atrophy but negative celiac serology [246]. In the first scenario, previous studies indicated that SBCE usually does not detect relevant findings that change the clinical management of the patients [238, 247, 248].

In the case of seronegative villous atrophy, the diagnostic yield of capsule endoscopy is higher with relevant findings at SBCE. In the study by Kurien et al. [248], based on SBCE appearances and other ancillary tests, several patients were diagnosed with celiac disease and further patients were diagnosed with SB Crohn’s disease as a cause of villous atrophy.

Two recent studies, single-center by Chetcuti-Zammit et al. [249] and multicenter by Luján-Sanchis et al. [250], demonstrated the central role of capsule endoscopy in equivocal cases. In the first study, 177 patients were enrolled; the overall diagnostic yield was 31.6 %. Furthermore, a positive correlation between mortality and atrophy extent was found in the 11 patients who died during the study follow-up. This finding underlines the prognostic role of SBCE in these cases and its relevance as a monitoring tool to assess therapeutic response. The multicenter second study evaluated 163 patients who underwent SBCE, with an overall diagnostic yield of 54 %; again, the diagnostic yield was higher in the case of seronegative villous atrophy (74 %) with relevant SBCE findings and diagnoses such as Crohn’s disease and lymphoproliferative disorders. Notably, in this previous study, SBCE revealed a significant management impact, with 71 % of patients changing therapy after undergoing SBCE.

RECOMMENDATION

ESGE recommends in nonresponsive or refractory celiac disease, small-bowel capsule endoscopy followed by device-assisted enteroscopy for diagnosis and disease monitoring.

Strong recommendation, high quality evidence.

Celiac disease frequently presents a benign course with an optimal prognosis; however, up to 20 % of patients show persistent or recurrent symptoms despite 6–12 months of following a strict gluten-free diet [246, 251]. This “nonresponsive” form of celiac disease requires a careful diagnostic work-up to detect the presence of preneoplastic and neoplastic complications, such as refractory celiac disease (RCD), ulcerative jejunoileitis, enteropathy-associated T-cell lymphoma (EATL), and SB adenocarcinoma. RCD is defined by malabsorption and villous atrophy despite a correct gluten-free diet; RCD can be further subtyped into RCD type 1 (RCD-1) and type 2 (RCD-2) depending on the presence of an aberrant T-cell type in the duodenal mucosa, detected using cytofluorimetry. RCD-2 is less frequent but characterized by a severe prognosis with mortality of up to 50 % in 5 years and a higher risk of neoplastic evolution [252].

For these reasons, nonresponsive celiac disease and RCD-1 and RCD-2 warrant surveillance of the small bowel and early detection of neoplastic complications.

Previously, two studies evaluating patients with nonresponsive disease identified a few severe complications with SBCE [248, 253]. Focusing on RCD, Barret et al. [254] used SBCE to investigate disease severity in 29 RCD patients; notably, after tissue sampling with DAE, they diagnosed 3 cases of EATL and 5 cases of ulcerative jejunoileitis requiring specific treatment in the RCD cohort. The sequential approach, SBCE followed by DAE in the case of suspect findings, appears justified by the potentially relevant diagnosis (EATL and ulcerative jejunoileitis) and the importance of the consequent therapies [255, 256].

More recently, different studies have investigated the clinical use of SBCE and DAE in this setting, including a large number of patients in single-center and multicenter patient cohorts [256–261]. Notably, all these studies confirmed a diagnostic yield of SBCE close to 50 %, with the detection of SBTs in 3 %–10 % of cases. SBCE represents the first-line investigation, while DAE is performed to obtain tissue samples that usually reveal an EATL or that can be used in cytofluorimetry to diagnose or monitor RCD.

Furthermore, two studies [257, 259] demonstrated that atrophy extent correlates with mortality more than histology does. In 40 % of cases, SBCE findings were beyond the Treitz ligament and thus not accessible at upper endoscopy, underlining the pivotal role of SBCE/DAE in RCD. These findings have been strengthened by a recently published meta-analysis [262] demonstrating a diagnostic yield for malignancies and ulcerative jejunoileitis of 13 % in the case of SBCE and 30 % for DAE. Given the scenario described above, in the case of nonresponsive celiac disease or RCD, upper endoscopy and SBCE are mandatory; the first to take biopsies to perform routine histology, the second to detect other lesions to be targeted by DAE [263].

Other indications

Chronic abdominal pain

RECOMMENDATION

ESGE does not recommend small-bowel capsule endoscopy as the first-line investigation for patients with isolated chronic abdominal pain.

Strong recommendation, low quality evidence.

Chronic abdominal pain is usually defined as a constant or recurrent pain that lasts 3 months or more. Chronic abdominal pain without pathological findings in upper endoscopy, colonoscopy and/or imaging techniques is a prevalent condition [264].

Interestingly, many case reports and case series have described diagnosis by SBCE of significant pathologies in patients with chronic abdominal pain (e. g., Meckel's diverticulum [265], eosinophilic enteritis [266], and SBTs [220]). However, the available evidence highlights that the probability of detecting significant findings at SBCE is very low (below 20 %) when isolated chronic abdominal pain is the indication for SBCE. At the same time, this rises significantly when associated with signs/symptoms or altered laboratory findings.

Shim et al. [267] retrospectively analyzed 110 patients with unexplained chronic abdominal pain: diagnostic yield was 17.3%, and in multivariate analysis weight loss was a significant risk factor for positive findings at SBCE (OR 18.6, 95 %CI 1.6–222.4; $P=0.02$). Katsinelos et al. [268] conducted an open-label prospective nonrandomized multicenter clinical trial. In this study, diagnostic yield was 44.4 %, and in multivariate regression analysis positive findings from SBCE were associated with elevated erythrocyte sedimentation rate (ESR) (OR 67.9, 95 %CI 9.3–310.6, $P<0.001$) and C-reactive protein (CRP) (OR 41.5, 95 %CI 6.2–213.4, $P<0.001$). Huang et al. [269] conducted a retrospective study which included 341 patients with chronic abdominal pain. In this study, the diagnostic yield was 28.15 %, and these features were positively associated with SBCE diagnosis: weight loss (OR 2.827, 95 %CI 1.938–4.926; $P=0.038$), hypoalbuminemia (OR 6.142, 95 %CI 4.129–8.274; $P=0.008$), elevated ESR (OR 4.025, 95 %CI 3.178–6.892; $P=0.016$), and increased CRP (OR 7.539, 95 %CI 5.365–11.723; $P=0.002$). More recently, Kim et al. [270] performed a meta-analysis showing that the presence of elevated CRP (OR 14.09, 95 %CI 2.81–70.60; $P=0.001$) and ESR (OR 14.45, 95 %CI 0.92–227.33; $P=0.06$) significantly increased the diagnostic yield of SBCE in patients with unexplained abdominal pain.

These data underscore how, on the one hand, the SB endoscopic evaluation plays a very limited role in cases of isolated abdominal pain and, on the other, how relevant it is in this subset of patients to plan a comprehensive diagnostic workup (including laboratory tests, imaging tests, and accurate collection of clinical history), since when abdominal pain is associated with other clinical features, SBCE may lead to establishing a definite diagnosis.

Foreign body retrieval

RECOMMENDATION

ESGE recommends device-assisted enteroscopy as an alternative to surgery for foreign bodies retained in the small bowel requiring retrieval in patients without acute intestinal obstruction.

Strong recommendation, moderate quality evidence.

SB foreign-body retention that needs intervention is a rare event. Most frequently the foreign bodies involved are endoscopy capsules or other medical devices (e. g., migrated plastic or metallic stents). Capsule retention is defined as a capsule remaining in the digestive tract for at least 2 weeks, and retention rates vary between 2.1 % and 8.2 % [16]. Previous abdominal surgery or SB disease (e. g., stricturing CD or SBT) may contribute to retention. A systematic review has shown that DAE is a

reliable alternative to surgery, with a retrieval rate of 74.7% when the capsule is retained in the jejunum and can be reached via the antegrade approach [158]. However, when the capsule is retained in the ileum, the retrograde approach often necessitates endoscopic balloon dilation of the stricture before the capsule can be reached and is, therefore, less effective, as illustrated by a retrieval rate of only 26.3%. The serious adverse event rate is low (1.3% SB perforation risk) and associated with balloon dilation or neoplasia. One multicenter study reported that symptoms were the only independent predictor of successful retrieval using DAE (OR 13.40, 95%CI 1.10–162.56; P = 0.042) [271]. In addition to retrieving the retained capsule, DAE can also facilitate the diagnosis and treatment of the underlying intestinal disease, by endoscopic biopsy, endoscopic balloon dilation, and preoperative tattooing. However, the indication for endoscopic or surgical intervention should be evaluated on a case-by-case basis and depends on local availability and expertise.

DAE-assisted percutaneous endoscopic jejunostomy (PEJ) for enteral feeding

RECOMMENDATION

ESGE suggests that in patients requiring jejunostomy for enteral feeding, DAE-assisted percutaneous endoscopic jejunostomy (PEJ) is a possible alternative to surgical jejunostomy.

Weak recommendation, moderate quality evidence.

Direct percutaneous endoscopic jejunostomy (DPEJ) is an accepted alternative to nasojejunal or surgical jejunal feeding in patients who require long-term post-pyloric feeding [272].

DPEJ using an enteroscope has a technical success rate of up to 90%. Technical failures are reported mostly because of limited enteroscope advancement in patients with a history of abdominal surgery and adhesions. DPEJ by DAE has a significant adverse event rate of 3.5% [273–276]; these include bleeding and SB perforation. DAE-assisted PEJ can represent an alternative to surgical jejunostomy according to local availability and expertise.

DAE-ERCP in patients with altered anatomy

RECOMMENDATION

ESGE recommends DAE-ERCP as a first-line endoscopic approach to treat pancreaticobiliary diseases in patients with surgically altered anatomy (except for Billroth II patients).

Strong recommendation, moderate quality evidence.

Since the advent of DAE, multiple retrospective studies have been published on DAE-endoscopic retrograde cholangiopancreatography (ERCP) in patients with surgically altered anatomy. Biliary indications are more frequent than pancreatic indications. The most frequently met surgical reconstructions are Billroth II partial gastrectomy, Roux-en-Y total gastrectomy, Roux-en-Y gastric bypass (RYGB), Whipple's pancreaticoduodenectomy (also with Roux-en-Y), and Roux-en-Y hepaticojejunostomy [277]. According to ESGE guidelines [278], use of a side-viewing duodenoscope is the first option for performing ERCP in Billroth II patients. However, DAE-ERCP is equally effective [279].

Several recent meta-analyses on using long and short DBE, SBE, and manual spiral enteroscopy for performing ERCP in patients with altered anatomy, are based on multiple retrospective case series [280–284] (see **Table 3 s**). They show that procedural success has seemed to increase over time, reaching >75% in the most recent meta-analysis, and even much higher success rates in individual retrospective series. DBE and SBE are equally effective. Short versions of both DBE and SBE have been developed, allowing the use of conventional ERCP accessories. Studies have shown equal procedural success when using short-type DAE, except in the cases of Roux-en-Y surgery without gastrectomy and long limb Roux-en-Y surgery such as RYGB, where the short-type DAE device may be too short to reach the biliopancreatic system [283, 285, 286]. Except for a single preliminary case report, there are currently no data available on the use of motorized spiral enteroscopy to perform ERCP in patients with surgically altered anatomy [287]. Overall, adverse events show low rates (up to 8% in meta-analysis reviews) and are mild with little indication for surgical intervention (mainly due to intestinal perforation), and mortality related to DAE-ERCP is close to 0%.

DAE-ERCP in patients with surgically altered anatomy can be considered a first-line technique to treat biliopancreatic pathology thanks to the good overall procedural success rate and the low adverse event rate. However, since the overall procedural success rate is good but not excellent, alternative, more invasive techniques have emerged, showing both higher technical success and adverse event rates. Thanks to the excluded stomach in RYGB, multiple alternative approaches currently exist, including laparoscopy-assisted ERCP, endoscopic ultrasound (EUS)-directed transgastric ERCP, EUS-guided intrahepatic puncture with antegrade clearance, and percutaneous transhepatic biliary drainage [288, 289]. Both laparoscopy-assisted ERCP and EUS-directed transgastric ERCP have high (>90%) procedural success rates but also higher adverse event rates (12%–24%) [290]. Also, in patients with Whipple's pancreaticoduodenectomy, transgastric EUS-guided drainage of the pancreatic duct is feasible with a good technical success rate of more than 70%, but with an adverse event rate of 20%–35% [291, 292]. ERCP in patients with surgically altered anatomy is challenging and should be referred to expert centers. The technique of choice depends on local availability and expertise, as previously suggested by ESGE [293].

Innovations

SBCE

Since their inception at the dawn of this millennium, SBCE and DAE have continually evolved. For the former, two main paths lead to further development. First, technological advances are expected to lead to paradigm shifts. Second, patient- and society-related outcomes may drastically change SBCE practice in the coming years.

The latest generation of commercially available SBCE devices and software currently provides high resolution images captured by powerful central processing units, an adaptive frame rate, post-processing chromoendoscopy options, long-life batteries (enabling gastroenteric or enterocolonic examinations) and expert systems (allowing faster reading) [294]. Implementation of AI in software is a significant step [295]. These solutions allow a drastic reduction (of around 90 %) in image selection and reading time, while maintaining very high sensitivity (above 98 %) for lesion detection [296, 297]. Further high level clinical assessment and discussions with scientific societies and regulatory authorities are required before AI can routinely be used in clinical practice. This allows the triage of normal videos and/or images within videos. Additionally, some AI software also enables characterization of abnormalities [297]. Researchers in AI are working to address the challenges of automated evaluation of anatomical landmarks, of completion, and of cleanliness [295]. In addition, progress in miniaturization and energy-saving may provide more room for batteries within the capsule and thereby longer battery life.

Consequently, it is expected that a genuinely "panenteric" (mouth-to-anus) capsule endoscope will be available in the near future [298]. In addition, magnetically guided capsule endoscopy has been developed and clinically assessed for examination of the stomach or combined stomach and small bowel [299, 300]. However, active capsules with embedded AI, microbiota or tissue sampling, or therapeutic options, are still in the early stages of development [300].

Furthermore, emerging healthcare and societal trends may profoundly modify how we practice SBCE. For example, some capsule endoscopy manufacturers have recently obtained approval from the US Food and Drug Administration for capsule home delivery, provided that a healthcare provider accompanies patients for the procedure [300]. As a result, patients' comfort and reporting times would be significantly improved. In addition, there is growing concern regarding the ecological impact of endoscopy. Capsule endoscopy is expected not to escape the debate around avoiding the yearly release of tens of thousands of batteries and electronic material into the environment [300]. Overall, such developments may widen the indications for capsule endoscopy and how we practice SBCE in the future.

DAE

Motorized spiral enteroscopy

A novel motorized spiral enteroscopy device (Olympus, Tokyo, Japan) has recently been introduced. The activation of an integrated electric motor permits the rotational movement of a spiral overtube, achieving advancement by pleating the SB. Since its introduction, several case reports have been published, showing the potential abilities of this new endoscopy device. The first prospective trial was conducted in 132 patients from two European tertiary referral centers. It showed diagnostic and therapeutic yields for antegrade explorations similar to those from previous studies with balloon enteroscopy. However, longer insertion length (mean 450 cm, range 0–600 cm) in a shorter procedural time (mean 25 min, range 3–122 min) was achieved [301]. Two other clinical studies from Europe and Asia reported similar results; moreover, total enteroscopy rates were 61 % and 70 % [302, 303]. Nonetheless, some issues regarding this technique are still unclear, such as the need for general anesthesia for antegrade procedures, the learning curve, and the target population. Furthermore, only minimal information exists on the impact of prior major abdominal surgery on the feasibility and the safety of motorized spiral enteroscopy [304, 305].

Water-aided enteroscopy

The water-exchange intubation technique has been proposed to achieve higher total enteroscopy rates. The method is the same as when applied for the exploration of the colon, with warm saline (37 °C) infused into the intestinal lumen to maintain the endoscopic view and mostly suctioned during the insertion phase. During the antegrade procedure, saline is infused once the ligament of Treitz is reached, while during the retrograde procedure, water exchange begins from insertion at the anus [306]. Of note, an adaptor connecting the water pump tube to the accessory channel of the enteroscope is needed.

The two studies available so far have produced conflicting results. One randomized, nonblinded, single-center study compared the total enteroscopy rates between patients undergoing water-exchange-assisted (n = 55) and CO2-insufflated (n = 55) SBE [306]. The total enteroscopy rate was significantly higher in the water-exchange group (58.2 % vs. 36.4 %), as well as the overall and antegrade approach insertion depths, the overall insertion time, and the insertion time for the oral route. Diagnostic yields and adverse event rates were similar between groups. In a prospective, comparative and observational study, 46 patients were randomly allocated to water exchange-assisted (n = 23 patients) and CO2-insufflated (n = 23 patients) DBE. The median insertion depth was greater in the CO2 group, at 260 cm vs. 160 cm ($P = 0.048$). Multiple logistic regression showed a statistically significant difference in the insertion depth using CO2 insufflation (OR 1.009, 95 %CI 1.001–1.017; $P = 0.034$). Adverse event rates were similar between groups [307]. Other larger RCTs comparing the water-exchange technique with CO2 are awaited.

Interventional enteroscopy

Snare and ischemic polypectomy, and conventional and underwater mucosectomy by DAE, have become the first-line treatments for SB polyps, especially in the setting of PJS. These techniques are efficient, safe and cost-effective. Complete resection rates are over 60 %, with infrequent adverse events (mostly in the form of immediate or delayed bleeding and pancreatitis) [183, 184]. The outcomes of DAE dilation of benign SB strictures are mentioned in a previous section.

Disclaimer

The legal disclaimer for ESGE Guidelines [3] applies to this Guideline.

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Competing interests

C. Carretero provides consultancy and receives speakers fees from Medtronic (ongoing). X. Dray is a founder of and shareholder in Augmented Endoscopy (May 2019 to present); he is a member of the International CApsule Endoscopy REsearch (iCARE) group (December 2021 to present); he holds four patents (shared with his institutions) related to artificial intelligence in endoscopy. E. J. Despott has received educational grants in support of conference organization, and honoraria, from Fujifilm, Pentax, and Olympus (2017–2021), and honoraria from Ambu (2021). L. Elli has held a lecture/consultancy role for Medtronic (2018-2020) and Capsocam (2016). L. Fuccio is a Co-Editor of *Endoscopy* journal. M. Keuchel has received speaker's fees and travel support from and provided consultancy to Medtronic, and received speaker's fees from Olympus (both from 2021 to present); his department has received study support from AnX Robotics (from 2021 to present). A. Koulaouzidis is a co-founder and shareholder of AJM MED-i-Caps (from 2017, ongoing) and iCERV (from 2022, ongoing), and has received consultancy fees from CHI and Jinshan Science & Technology and lecture honoraria from Medtronic (all from 2020, ongoing), travel assistance fees from Aquilant (2019), material support for clinical research from SynMed and Intromedic (2016–2020), and lecture honoraria and AB meeting fees from Dr Falk Pharma UK (2016–2020), and has participated in an advisory board for Ankon (2019); his department has received a grant from Medtronic (2016–2020); he is a founding and board member of iCARE; he or his department holds a patent related to this Guideline. D. McNamara received an iCloud Capsule Platform introductory fee waiver from Medtronic (2021–2022). T. Moreels received speaker's fees from Olympus (2019–2022). H. Neumann is a consultant to Fujifilm, Medtronic, and Jinsha (from 2020, ongoing); his department receives study support from Fujifilm (from 2020, ongoing). M. Pennazio received speaker's fees from Medtronic, Olympus, and Alfasigma (2015–2019). E. Perez-Cuadrado-Robles provided consultancy to Boston Scientific (2020–2021). E. Rondonotti has been an expert group member and speaker for Fujifilm (January 2021 to December 2021) and provided consultancy to Medtronic (2021); his department received a research grant from Fufifilm (January 2021 to December 2021). B. Rosa provided consultancy to Medtronic (2020–2021). C. Spada provided consultancy to Medtronic (2017–2022) and AnX Robotics (2020–2022). J. C. Saurin provided consultancy to Intromedic, Capsovision, Medtronic, and Povepharm (2021–2024), and teaching for Medtronic (2021–2024). I. Tacheci is Scientific Secretary to the Czech Society of Gastroenterology and responsible for dissemination of guidelines (2022). P. Cortegoso Valdivia, B. Gonzalez Suarez, L. Kunovsky, E. Perez-Cuadrado-Martinez, S. Piccirelli, D.S. Sanders, R. Sidhu, K. Triantafyllou, and E. Vlachou have no competing interests.

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Supplementary material

Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: ESGE Guideline (update 2022)

Coordinating Team: Pennazio **(Guideline Leader),** Rondonotti, Cortegoso-Valdivia

Online Table 1s. Key questions

Task force 1- Suspected small-bowel bleeding and iron-deficiency anaemia

Spada **(Leader)** Sidhu, Piccirelli, Perez-Cuadrado Robles, Koulaouzidis

KEY QUESTIONS TASK FORCE 1: Suspected small-bowel bleeding

Role of SBCE vs other investigations:

Questions:

1. Is there any new evidence to support/reject/change previous guideline recommendations? Recent evidence leads to increase/decrease the level of evidence and/or the strength of recommendation?

2. Is there any new evidence to support the use of push-enteroscopy, DAE, small-bowel radiographic examinations or mesenteric angiography or computed tomography instead of SBCE as a first-line test in patients with suspected small-bowel bleeding?

3. In this setting, is there any evidence to support the earlier use of SBCE (e.g., before colonoscopy) in the diagnostic work up of patients with ongoing/overt bleeding? If so, is this evidence strong enough to provide a statement?

Second-look endoscopy before SBCE:

Questions:

1. Is there any new evidence to support/reject/change previous guideline recommendations? Recent evidence leads to increase/decrease the level of evidence and/or the strength of recommendation?

2. Is there any evidence of clinical or temporal or patient-related or medication-related features that suggest repeating upper and/or lower endoscopy before SBCE?

Supplementary material

3. Is there any new evidence to support an iron trial in patients with iron-deficiency anaemia before planning SBCE? Is there any subset of patients in which this policy could be endorsed?

Timing of SBCE:

Questions:

1. Is there any new evidence to support/reject/change previous guideline recommendations? Recent evidence leads to increase/decrease the level of evidence and/or the strength of recommendation?

Emergency setting/ongoing overt suspected small-bowel bleeding:

Questions:

1. Is there any new evidence to support/reject/change previous guideline recommendations? Recent evidence leads to increase/decrease the level of evidence and/or the strength of recommendation?

2. Is there any evidence of clinical or temporal or patient-related features that suggest preferring other examinations (e.g., CT angiography, mesenteric angiography, DAE etc.) over SBCE?

3. In this setting, is there any evidence to support the earlier use of SBCE (e.g., before colonoscopy) in the diagnostic work up of patients with ongoing/overt bleeding? If so, is this evidence strong enough to provide a statement?

Alternative to SBCE (when unavailable/contraindicated):

Questions:

1. Is there any new evidence to support/reject/change previous guideline recommendations? Recent evidence leads to increase/decrease the level of evidence and/or the strength of recommendation?

2. Is there any evidence of clinical or temporal or patient-related features that suggest preferring one specific examination (e.g., mesenteric angiography, CT angiography, abdominal CT, CT enterography, DAE etc.) when SBCE is unavailable?

Negative SBCE:

Questions:

1. Is there any new evidence to support/reject/change previous guideline recommendations? Recent evidence leads to increase/decrease the level of evidence and/or the strength of recommendation?

2. In case of negative SBCE, is there any evidence to suggest the best follow-up schedule over time? If not please provide an expert-based proposal.

Supplementary material

3. When is clinically indicated to plan further diagnostic tests? Should the individual risk of small bowel rebleeding after initial SBCE be assessed with dedicated bleeding scores (such as PRSSB/ RHEMITT score, etc..)?

4. Is there any evidence to support the use of any particular of the diagnostic / operative tools in patients with negative SBCE and clinical signs of rebleeding?

Positive SBCE:

Questions:

1. Is there any new evidence to support/reject/change previous guideline recommendations? Recent evidence leads to increase/decrease the level of evidence and/or the strength of recommendation?

2. Is there evidence to support the use of any particular of the diagnostic/operative tools in this setting according to SBCE findings, patient-related issues, comorbidities, ongoing medications etc.?

KEY QUESTIONS TASK FORCE 1: Iron deficiency anemia

Questions:

1. Is there any new evidence to support/reject/change previous guideline recommendations? Recent evidence leads to increase/decrease the level of evidence and/or the strength of recommendation?

2. Which tests should be performed before planning SBCE in patients with iron-deficiency anaemia?

3. In patients with IDA, is an iron trial indicated before SBCE? Is there new evidence supporting an iron trial before planning SBCE? Is there any subset of patents in which this policy could be endorsed?

Task force 2 - Crohn's disease

Despott **(Leader)**, Rosa, McNamara, González-Suárez, Carretero, Kunovsky, Neumann

KEY QUESTIONS TASK FORCE 2: Crohn's disease

Suspected Crohn's disease:

Questions:

1. Is there any new evidence to support/reject/change previous guideline recommendations? Recent evidence leads to increase/decrease the level of evidence and/or the strength of recommendation?

Supplementary material

2. In the presence of obstructive symptoms or known stenosis, negative dedicated small-bowel cross-sectional imaging modalities (such as magnetic resonance enterography/enteroclysis or computed tomography enterography/enteroclysis) are reliable enough to exclude capsule retention or patency capsule is still required?

Suspected CD: selection criteria:

Questions:

1. Is there any new evidence to support/reject/change previous guideline recommendations? Recent evidence leads to increase/decrease the level of evidence and/or the strength of recommendation?

2. How can suspected CD (worth receiving SBCE) could be defined?

3. About serological and faecal inflammatory markers: is there any threshold for effective patient selection in the setting of suspected Crohn's disease?

4. About NSAIDs; should low-dose aspirin and enteric-coated aspirin be stopped for at least one month before SBCE in the setting of suspected CD?

Established CD (SBCE):

Questions:

1. Is there any new evidence to support/reject/change previous guideline recommendations? Recent evidence leads to increase/decrease the level of evidence and/or the strength of recommendation?

2. In the setting of established CD, are dedicated cross-sectional imaging techniques alternative or complementary to SBCE?

3. Is patency capsule always necessary before SBCE in patients with established Crohn's disease?

4. How patients with established Crohn's disease and SBCE retention might be managed? Is medical therapy recommended? If so, which one? What is the excretion rate after medical therapy? Is there any role for retrieval of SBCE by DAE?

5. Is there a role of SBCE to determine IBD-U or to detect postoperative recurrence?

6. In the setting of established Crohn's disease, is there a role of SBCE in mucosal surveillance over time or mucosal healing evaluation? In this setting are there relevant indexes/scores to be used for objectively reporting? If so, which one should be used?

Established CD (DAE):

Supplementary material

Questions:

1. Is there any new evidence to support/reject/change previous guideline recommendations? Recent evidence leads to increase/decrease the level of evidence and/or the strength of recommendation?

2. When DAE is indicated which is its optimal timing in CD?

1. What is the efficacy of small-bowel dilation by DAE in CD?

Task force 3 - Inherited polyposis syndromes and suspected small bowel tumours

Keuchel **(Leader)**, Saurin, Vlachou, Tacheci

KEY QUESTIONS TASK FORCE 3: Inherited polyposis syndromes and suspected small-bowel tumours

Inherited polyposis (FAP):

Questions:

1. Is there any new evidence to support/reject/change previous guideline recommendations? Recent evidence leads to increase/decrease the level of evidence and/or the strength of recommendation?

2. Is there any role for SBCE in all FAP patients or in a subgroup of them? If so, how SBCE compares with other diagnostic techniques (e.g., cross sectional small bowel techniques)? Which is the optimal timing of SBCE in FAP patients? When is DAE indicated?

Inherited polyposis (PJS):

Questions:

1. Is there any new evidence to support/reject/change previous guideline recommendations? Recent evidence leads to increase/decrease the level of evidence and/or the strength of recommendation?

2. Is there any role for SBCE in all PJS patients or in a subgroup of them? If so, how SBCE compares with other diagnostic/therapeutic techniques? Which is the optimal timing of SBCE in FAP patients? When is DAE indicated?

Suspected small bowel tumour:

Questions:

Supplementary material

1. Is there any new evidence to support/reject/change previous guideline recommendations? Recent evidence leads to increase/decrease the level of evidence and/or the strength of recommendation?

2. Please define what “suspected small-bowel tumour means” (e.g., positive cross sectional imaging techniques and/or specific symptoms etc.).

3. Is there a particular diagnostic approach depending on the setting of clinical suspicion of small-bowel tumour? (i.e only anaemia, *vs* radiological suspicion of SB neoplasia, *vs* suspected NET, *vs* Lynch syndrome,..)

4. What is the role of SBCE tumour scoring systems?

1. Is there any role for palliation of small bowel tumours by DAE?

Task force 4 **Coeliac disease**

Sanders **(Leader)**, Elli

KEY QUESTIONS TASK FORCE 4: Coeliac disease

Coeliac disease:

Questions:

1. Is there any new evidence to support/reject/change previous guideline recommendations? Recent evidence leads to increase/decrease the level of evidence and/or the strength of recommendation?

2. Please define what equivocal diagnosis (positive specific serology and negative histology or vice versa); please specify if there are differences in terms of effectiveness of SBCE in these two scenarios

3. What’s the role of SBCE in refractory coeliac disease? How SBCE compares to cross-sectional imaging techniques and DAE? Are these three examinations alternative or complementary? When SBCE is indicated which is its optimal timing in refractory coeliac disease? In the setting of refractory coeliac disease is patency capsule and/or dedicated small-bowel cross-sectional imaging techniques always recommended to rule out small-bowel stenoses? When is DAE indicated?

Task force 5 **Other indications**

Moreels **(Leader),** Perez-Cuadrado Martinez, Fuccio

Supplementary material

KEY QUESTIONS TASK FORCE 5: other indications

Abdominal pain (SBCE and DAE):

Questions:

1. Is there any role for SBCE in patients with isolated abdominal pain (i.e. without alarm symptoms or changes in lab tests)? If so, which is the optimal timing? If so, is any specific precaution required before SBCE?
2. Is there any role for DAE in patients with isolated abdominal pain (i.e. without alarm symptoms or changes in lab tests)? If so, which is the optimal timing? If so, is any specific precaution required before SBCE?
3. Is there any role for SBCE in patients with abdominal pain when this is associated with other sign or symptoms? If so, which is the optimal timing? If so, is any specific precaution required before SBCE?
4. Is there any role for DAE in patients with abdominal pain when this is associated with other sign or symptoms? If so, which is the optimal timing? If so, is any specific precaution required before DAE?

ERCP with DAE in surgical altered GI anatomy:

Questions:

1. Please define which patients are suitable to receive ERCP with DAE
2. How does DAE-ERCP compare with other procedures, such as EUS-guided or laparoscopic assisted, in this setting?
3. What are the enteroscopic, diagnostic and procedural success rates in patients receiving ERCP with DAE. What are the DAE-ERCP related complications (including the need for surgery) and what is their frequency? Is there any difference in these parameters according to patients features?

Foreign body retrieval (DAE):

Questions:

1. Is there any role for DAE in retrieving foreign bodies entrapped in the small bowel? If so, is any specific precaution required before DAE? Which is the success rate and the complication rate?

DAE assisted direct percutaneous endoscopic jejunostomy (DPEJ)

Questions:

1. Is there any role for DAE in performing DPEJ? If so, is any specific precaution required before DAE? Which is the success rate and the complication rate?

Supplementary material

Task force 6 **New technical novelties with potential impact on application of SBCE/DAE**

Dray **(Leader)**, González-Suárez, Koulaouzidis, Fuccio

KEY QUESTIONS TASK FORCE 6: New technical novelties with potential impact on application of SBCE/DAE

1. Focus on technical novelties with the potential to modify/change/ease the use of SBCE/DAE in clinical practice in the near future (e.g., for SBCE: magnetically driven capsule, use of colon capsule for panintestinal endoscopy, artificial intelligence. – for DAE: motorized spiral enteroscope).

Supplementary material

Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: ESGE Guideline update 2022

Online Table 2s. Evidence Tables

Task force 1- Suspected small-bowel bleeding and iron-deficiency anaemia
Spada **(Leader)**Sidhu, Piccirelli, Perez-Cuadrado Robles, Koulaouzidis

Author, year	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
Zhao et al 2021	Retrospective	997 patients with SSBB (943 pts overt bleeding, 225 pts with ongoing bleeding) Early group: CE within 14d Late group: CE after 14d (timingfrom the last bleeding event)	To compare among the two groups (before and after a PSM): -CE diagnostic rates -prevalence of post-CE rebleeding in patients with initial negative CE findings within 1 year	Early vs late group diagnostic rate: 56.4% vs 45.5%, P= 0.001 Rebleeding within 1 year in patients with negativeCE: 24.7% vs 36.7%, P=0.041 Univariate analysis: timing of CE and impact on positive diagnostic rates: OR 0.648,95% CI 0.496–0.847, P= 0.001	Retrospective despite the effort to perform PSM Limit for follow-up data	Early CE can improve the reliability of OGIB diagnosis while also reducing rates of post-CE rebleeding.
Rezapour et al 2017	Meta-analysis, (1995-2015)	25 studies including pts with GI bleeding, suspected and established IBD	evaluatethe VCE retention	focus on: evaluatingthe VCE retention in suspected IBD patients	<u>retention rate (sub-analysis 1):</u> established IBD (11 studies): 8.2% (95% CI, 6.0%-11.0%) suspected IBD (9 studies): 3.6% (95% CI, 1.7%-8.6%)	<u>retention rate (sub-analysis 2):</u> patients included after the completion of either a patency capsule or CTE/MRE and exclusion of those patients who were found to have retention with patency capsule or CTE/MRE:

Supplementary material

					note: Patients with strictures demonstrated on MRE and/or CTE or retention of the patency capsule were excluded from this sub- analysis	VCE retention rate decreased to 2.7% in IBD patients (95% CI, 1.1%-6.4%). suspected and established IBD counted together in this sub-analysis
Tziatzios et al. 2019	Meta analysis	14 studies; 1023 patients with obscure gastrointestinal bleeding(role of anthithrombotics – anticoagulants)	Evaluations of factors associatedwithpositive CE findings	antithrombotic treatment was associated with an increased prevalence of positive findings [OR 1.98 (95% CI 1.34-2.93); P = 0.0006]. This effect did not differ between antiplatelet and anticoagulant treatments [OR 2.22 (95% CI 1.28-3.84); P = 0.005 and 2.53 (95% CI 1.66-3.87); P < 0.0001, respectively].	Significant heteroge- neity was noted in all but one of the endpoints studied Meta-analysis of retrospec- tive cohort studies is prone to confounding and selection bias. Stratification by specific classes of medications was not possible since evidence on this topic was absent. Classification of positive VCE finding was heterogeneous across studies	Antithrombotic treatment is associated with more positive findings in small-bowel video capsule endoscopy in OGIB as well as higher odds of re-bleeding.
Chao et al 2021	Retrospective	60 patients with melena or hematochezia and negative bidirectional endoscopy	to evaluate, analyze, and determine the optimal time for performing CE in patients with occult	Detection rate Day 1: 77.8% Day 2: 73.3% Day 3: 70.0% ≥4 days: 36.4%	Retrospective Single center Small size	The most optimal time to perform CE is within three days after GI bleeding occurs.

Supplementary material

		Day 1: 9 pts Day 2: 30 pts Day 3: 10 pts ≥4 days: 11 pts (timing calculated from the first bleeding event)	GI bleeding by using for analytical models (CE at day1, day2, day3 and >day4	GI bleeding days (d) 1)Within 3d: male: 17 (68.0) Female: 32 (91.4) ≧4 days Male: 8 (32.0) Female 3 (9.4) X2 5.35 p=0.039		
Kim et al 2015	Retrospective	94 patients with overt OGIB < 48 h: 30 pts ≥ 48 h: 64 pts (timing calculated from the last bleeding)	To evaluate the DY and efficacy of VCE to assess overt OGIB with respect to the timing of application (48 h cut off)	DY < 48 h: 66.7% > 48 h 40.6% (P= 0.019) TY < 48h: 26.7% > 48h: 9.4% P=0.028 Mean lengths of hospital stay: < 48-h: 5d (95% CI,4.8–7.7) > 48-h: 7d (95 %CI, 6.9–10.1) (P= 0.039)	Retrospective	Performing VCE within 2 days from the last overt OGIB results in a higher diagnostic yield, higher therapeutic intervention rate, and shorter hospital stay. Therefore, VCE application with a 48-h cutoff could improve the outcome of patients with overt OGIB.
Iio et al 2019	Retrospective	146 patients with ongoing overt GI bleeding Patients with a bleeding source located outside the small bowel were excluded	To investigate the clinical utility of emergency CE for detecting the source of ongoing overt OGIB and compare CE with DBE findings.	LDR: ≤ 48 h: 80% ≥ 48 h: 47% (p = 0:0174). Diagnostic concordance rate between emergency CE and DBE: ≤ 48 h: 100%	Retrospective Single center Small size	Emergency CE represents a useful diagnostic modality in patients with ongoing overt OGIB, potentially improving detection rates and reducing rebleeding risk.

Supplementary material

		≤ 48 h: 15 pts ≥ 48 h: 112 pts (timing calculated from the first bleeding event)		≥ 48 h: 92.9% Rebleeding after endoscopic treatment: ≤ 48 h: 0% ≥ 48 h: 2%		
Gomes et al 2018	Retrospective	115 patients with overt-bleeding ≤ 48 h: 39 pts 48 h-14 d: 35 pts ≥ 14 d: 41 pts (timing from first/last bleeding not specified)	To evaluate, according to the timing of CE, of: DY and TY of CE Rebleeding rate time to rebleed	Overall: DY: 80% TY: 46.1% Rebleeding Rate: 32.2% Rebleeding at 1y: 17.8% ≤ 48 h: DY: 82.1% TY: 66.7% Rebleeding rate: 15.4% Rebleeding at 1y: 11.8% 48 h-14 d: DY: 85.7% TY: 40% Rebleeding rate: 34.3% Rebleeding at 1y: 20.1% ≥ 14 d: DY: 73.2% TY: 31.7% Rebleeding rate: 46.3% Rebleeding at 1y: 21.9% (DY P = 0.37) (TY P = 0.005) (RR P = 0.007) (TtR P = 0.03)	Retrospective Single-center Small sample size	Performing CE within 48 h from overt-OGIB is associated to a higher TY, a lower rebleeding rate and longer time to rebleed.

Supplementary material

Uchida et al 2020	SRMA	22 studies (1907 patients) -19 studies SBCE -4 studies BAE	to assess the pooled DYs and TYs of small bowel endoscopy and to investigate the relationship between the timing of small bowel endoscopy and the DYs and TYs of endoscopy in patients with overt SBB.	PooledDYs SBCE: 65.2% (95% CI 58.9–71.2%). (I2 = 81%, P< 0.000001). BAE: 74.0% (95% CI 62.3–84.3%). (I2 = 84.4%, P = 0.000244). PooledTYs SBCE: 55.9% (95% CI 44.3–67.1%) (I2 = 78.9%, P < 0.000076) BAE: 35.8% (95% CI 30.6–41.2%; I2 = 0%, P = 0.559437). Meta-regression subgroup analysis (6 groups based on endoscopy timing) DY of SBCE/BAE -ongoing: 0.858 (0.675-0.979)/NA -24h:0.533 (0.066-0.965)/0.88 (0.740-0.978) -48h:0.873 (0.53-1.00)/0.846 (0.515-1.000) -72h:0.663 (0.284-0.953)/0.849 (0.724-0.943) -14d:0.723 (0.417-0.954)/0.666(0.421-0.0841)	Heterogeneity of studies despite meta-regression Possible overestimation of BAE as it was performed after SBCE and findings were not blinded Small sample size for each subgroup analysis	SBCE and BAE are useful and accurate diagnostic tools in overt bleeding. The optimal timing of endoscopy (both CE and BAE) would be within 2 days

Supplementary material

				->14d:0.419 (0.141-0.727)/0.637(0.404-0.841)		
Estevinho et al 2022	SRMA	4825 patients (39 studies) Early CE: performed within 14 days Early DAE: performed within 72 hours	to compare DY and TY, detection of active bleeding and vascular lesions, recurrent bleeding, and mortality of "early" versus "nonearly" SBCE and DAE	Pooled data DY early SBCE: 80.35 (95% CI, 73.85-86.85; P < .01; I2 Z 93%) DY early DAE: 88.32 (95% CI, 84.73-91.91; P < .01; I2 Z 89%) TY SBCE 52.25% (37.65-66.85) I2 92%, P < .001 TY DAE: 73.14% (55.34-90.94) I2 96% P < .001 OR of early DAE vs SBCE: -active bleeding: OR 5.09; I2 = 53 OR for early studies vs non-erarly -positive diagnosis: OR 3.99; I2 = 45%) -therapeutic intervention: OR 3.86; I2 = 67%)(P < .01). -recurrent bleeding: OR .40; P < .01; I2 = 0%)	Different definition of early approach Number of studies limited in some subgroup analysis and Heterogeneous data	The role of small-bowel studies in the early evaluation of OGIB is unquestionable, impacting diagnosis, therapeutic intervention, and prognosis. Comparative studies are still needed to identify optimal timing.
Marya et al 2018	RCT	87 patients with new-onset NHGIB	To measure:	Localization rate Early arm: 64.3%	Single center	For patients admitted to the hospital for NHGIB, early CE is a

Supplementary material

		-Standard arm: 45pts (usual work up with CE after negative EGD and IC - early CE arm 42 pts (soon after admission. Further endoscopic examination based on findings/ gastroenterologist's discretion):	-localization rate (blood or lesion) during hospitalization -Therapeutic intervention -rebleeding rate within 30 days of discharge -all-cause mortality rate within 30 days of hospitalization	OR for colic lesion:4.09 (1.12–15.00) standard arm: 31.1% (P < .01) Diagnosis by the end of admission Early arm: 69% standard arm: 46.7% (P=0.035) OR 2.67 (1.04–6.86) Therapeutic intervention Early arm:26.2% standard arm: 28.9% (p=0.77) Rebleeding rate Early arm: 0% standard arm: 8.9% (p=0.11) All-cause mortality Early arm: 2.4% standard arm: 4.4% (p=1.1)	Observer bias (no blinded study personnel)	safe and effective alternative for the detection of the source of bleeding.
Yin et al 2020	Retrospective	265 patients with overt SSBB (pts who had prior positive findings on CE and radiographic imaging were excluded) Emergent DBE: < 3days of last bleeding onset Early DBE: 3-7days Late DBE: > 7 days	to investigate the role of diagnosis and therapy of emergent DBE in patients with overt SSBB.	DY Emergent:84.4% Early:65.1% (P<0.05) Late:59.8% TY Emergent:78.1% Early:58.2% Late:39.1% (P<0.05)	Retrospective Single center Relatively small sample size Follow-up not included	Emergent DBE had the highest yields for diagnosis and therapy. The study finding showed a pivotal role of emergent DBE in overt SSBB.

Supplementary material

Maeda et al 2015	Retrospective	89 patients with overt OGIB and negative bidirectional endoscopy. Only patients with findings suitable for treatment underwent DBE	to show the clinical outcome of the strategy of initial VCE, followed by DBE	Pts with CE findings: 58/89 Pts with findings suitable for DBE: 37/58 CE accuracy compared to DBE (%)(95 % CI) Sens: 100 (94.5–100) Spec: 85.4 (78.9–85.4) PPV: 88.9 (84.0–88.9) NPV: 100 (92.4–100) Accuracy: 93.3 (87.3–93.3)	Retrospective Single center	VCE as the initial examination can efficiently identify overt OGIB patients who require DBE. The strategy of initial VCE for overt OGIB appears to be reasonable.
Sung et al 2016	RCT	71 patients with UGIB (“coffee ground” vomiting or “tarry stool”) CE group:34 pts (3 excluded) (hospital admission based on CE findings) Standard (ST) group: 34 pts (monitoring and upper GI endoscopy within 24h)	to validate CE as an effective tool in diagnosing patients with UGIB and identifying those who require hospital admission.	Hospital admission CE group: 7/34 ST group: 34/34 Findings CE: 5 (1 gastric ulcer with visible vessel missed by CE, admitted later) EGD: 11 (9 forrest III ulcers)	Small sample size Doubtful cost-effectiveness of use of CE at triage	CE offers a safe and effective method in triaging patients presenting with UGIB that do not require hospital admission.
Scholag et al 2016	Prospective	88 patients with ongoing severe overt bleeding (19 out of 20 patients with negative EGD	Rate of patients in whom emergency VCE correctly guided further diagnostic and therapeutic procedures	Positive findings: 15/20 75% (95% CI, 51-91) (all positive pts underwent further examination with	Single-center Non-randomized small sample size short FU (4w)	In patients with acute severe GI bleeding and negative upper endoscopy results, emergency CE

Supplementary material

		received immediate VCE)		positive findings in 14/15). Negative findings: 5/20 underwent colonoscopy (detection of presumed bleeding source in 3 of 5 cases in the left colon)		can be useful for the immediate detection of the bleeding site and is able to guide further therapy
Pérez-Cuadrado Robles et al 2015	Retrospective	27 patients with overt bleeding underwent emergency DBE(<24h) -16 pts had previous CERT -11 pts did not received CERT Comparison group (DBE > 24h): 334 pts	To evaluate the usefulness of emergency DBE combined with Real Time CE (CERT) in patients with overt acute OGIB analyzing the causes, treatment and outcome.	Therapeutic intervention in urgent DBE: 77.8% Dieulafoy lesion detection: DBE <24h: 40.7% DBE >24h: 0.9% P < 0.001 Combined approach with RT viewing by CE correctly modified DBE management in four patients (25%)R	Retrospective Small sample size	CERT was carried out in 16 cases and truly modified the initial approach and/or management by DBE in four cases (25%).
Innocenti et al 2021	Retrospective Single center cohort study	290 Patients with OGB referred for CE after negative bidirectional endoscopy	Cleanliness Completion of procedure Capsule retention Diagnostic Yield Percentage findings outside the small bowel/ bleeding potential	Caecum was reached in 92.4%. Capsule retention occurred in 0.7. Diagnostic yield was 73.8%. An actively bleeding lesion was noticed in 39.3% of positive tests. Capsule endoscopy revealed clinically significant non-small-bowel lesions missed at gastroscopy or colonoscopy in	Retrospective design No randomization	Demonstrates missed lesions Authors suggest to consider second look endoscopy prior to CE

Supplementary material

				30.3% of patients, 43.2% of which were bleeding.		
Akin et al 2016	Retrospective	Patients ref for SBCE for suspected SB Bleeding	Diagnostic yield	In 58 patients (50.9%) bleeding lesion could be determined. Among these 58 patients 8 patients' lesions were in the reach of conventional endoscopes. Overall these 8 patients comprised 7% of patients in whom VCE was performed for potential small bowel bleeding. Among these 8 patients 5 had colonic lesions (4 angiodysplasia, 1 ulcerated polypoid cecal lesion), 2 had gastric lesions (1 GAVE, 1 anastomotic bleeding), and 1 patient had a bleeding lesion in the duodenal bulbus.	retrospective	Clinicians should review non SB segments carefully on CE
Juanmartiñena Fernández et al 2018	Retrospective	2217 CE- all indications	Non SB lesions- gastroduodenal	Gastroduodenal abnormalities were detected by capsule endoscopy in 696 (31.4%) of 2,217 patients. The most common types of missed gastric and duodenal lesions found were gastric	Retrospective & minor findings such as gastritis and duodenal erythema included	Review gastric images too

Supplementary material

				erosions (35.4%), findings suggestive of chronic gastritis (22.9%), duodenal erosions (28.1%) and duodenal erythema (23.5%). This information had a clinical or diagnostic impact of 26.2% and a therapeutic impact of 15.5%.		
Juanmartiñena Fernández et al 2017	Retrospective	464 patienst ref for VCE for OGB & IBD	Non SB-colonic lesions	Colonic abnormalities were detected by capsule endoscopy in 47 (9%) of 464 patients. The most common types of missed lesions were vascular lesions (34%) and colonic ulcers (32%). This information had a clinical or diagnostic impact of 7.55% and a therapeutic impact of 6.03%.	retrospective	Review colonic images too
Juanmartiñena Fernández et al 2017	Retrospective	2217 patienst ref for CE for OGB & IBD	Non SB lesions-oesophageal	Esophageal abnormalities were detected in 105 out of 2217 patients (4.7%). The most common lesions detected were peptic esophagitis (58.1%) and esophageal varices (17.1%). This information had a clinical/diagnostic impact of 3.3% and a	Retrospective and using same database	Careful look at oesophagus

Supplementary material

				therapeutic impact of 3.2%.		
Stone et al 2020	Retrospective	1351 patients underwent CE in Manitoba between the years of 2005-2016. In 620 pts (46%) CE was indicated for occult GI bleeding or IDA. Positive findings on CE were separated into 'definite' and 'possible'.	Diagnostic yield of CE in diagnosing the cause of IDA Clinical parameters that predict higher diagnostic yields	Of the 620 included subjects: - mean age: 62.9 years - mean hemoglobin: 89 g/L - mean ferritin: 32 uMol/L - 17.2% of patients were taking ASA - 5% of patients were on an antiplatelet agent - 5.3% of patients were on an anticoagulant VCE diagnostic yield: 33.9% (definite findings 23%; possible findings 10.8%) Vascular ectasias were the majority of definite findings (47.5%) Predictors of definite findings were: -age (RR 1.04) -male sex (RR 1.88)	Retrospective study	33.9% positive yield. 65.8% of patients underwent further workup as a result of CE 12.7% of patients required therapeutic intervention. Age and male sex are predictors of definite findings on CE
Tran-Duyet al 2018	Retrospective	26,806 cases: - 2,960 PFU - 6,607 PLU - 17,239 PNU 26,806 controls:	Risk of iron deficiency (ID) associated with the use of PPIs Dose-response relationship	Crude ORs of ID in: - PFUs compared to PNUs: 3.88 - PLUs compared to PNUs: 1.73.	Observational study Presence of covarieties that can lead to blood loss and ID	Long-term PPI use is associated with iron deficiency

Supplementary material

		- 1,091 PFU - 5,058 PLU - 20,657 PNU PFU = PPI "full" user= received PPIs for a continuous duration of at least one year prior to the index date PLU = PPI "limited" users = intermittently received PPI therapy PNU = PPI non-users = subject who received no PPIs prior to the index date	Time-response relationship	- PFUs compared to PLUs: 2.24 Dose-response relationship: - if defined daily doses (DDDs) 0.10-0.99 → higher risk of ID compared to non-exposed subjects (OR, 2.60). - if DDDs > 1.00 → an increase in the dosage did not further increase the risk of ID. Time-response relationship: - PPI use ≥ 1 year: higher risk of ID compared to non-exposed patients or patients with a period of PPI use < 1 year. - PPI use between 0.10 and 0.99 years: risk of ID higher than in non-exposed individuals (OR, 2.69).	ID may have occured prior to PPIs use No stratification according to PPIs metabolism rate	
Okam et al 2017	Pooled data analysis of 5 RCT	738 patients	To compare oral and IV iron-replacement therapy for IDA To evaluate demographic and clinical characteristics for association with hemoglobin response	72.8% responders Hemoglobin increases 1.0, 2.0, and 3.0 g/dL was greatest among those with postpartum anaemia, intermediate among those with heavy uterine bleeding or	Post hoc design Multiple comparisons create the chance of a type 1 error ("false positive") Compliance with the use of oral iron	Hemoglobin responses <1.0 g/dL at day 14 of oral iron identify subjects with IDA who should be transitioned to IV iron supplementation .

Supplementary material

			at multiple timepoints.	gastrointestinal-related causes of anaemia, and lowest among those with other causes; A 1.0-g/dL increase in hemoglobin on day 14 most accurately predicted satisfactory overall hemoglobin response to oral iron on day 42/56 (sensitivity 90.1%; specificity 79.3%; positive and negative predictive values of 92.9% and 72.7%, respectively). Responders achieved increases in Hb and experienced improvements in quality of life	observed in the present studies ranged from 83.9% to 98.5% and may be higher than what is typically observed in the real-world setting	
Contaldo et al 2019	Retrospective	109 patients with negative bidirectional endoscopy and a positive fecal occult blood test (FOBT). Exclusion criteria: - overt GIB; - menorrhagia; - any overt source of extra-intestinal bleeding; - IBD; - CD; - Chronic liver disease; - Inherited polyposis syndromes.	Primary aim: prevalence and the spectrum of small bowel injury features detected by VCE in a cohort of inpatients with IDA and obscure-occult small bowel bleeding. Secondary aim: potential predictive factors related to the presence or absence and the severity of lesions detected by VCE	73.4% of patients showed ≥1 small bowel lesions The Lewis score was calculated in 41 patients: -13 (31.7%) showed a mild (<135) score -28 (68.3%) a moderate-severe (135–790 and >790, respectively) score In analysis, the small bowel transit time (6.2 ± 2.9 versus 5.2 ± 2.1 h; p = 0.049) and NSAIDs use for at	Retrospective study	VCE can reveal the source of obscure-occult bleeding in a high percentage of unexplained IDAs. A wide spectrum of endoscopic pictures may be found. Known as well as supposed risk factors for small bowel lesions may be detected.

Supplementary material

				least two weeks (17.5% versus 0%; p = 0.01) were significantly higher in subjects with injuries. The severity of a lesion directly correlated with PPI use and duration.		
Romeo et al 2021	Prospective	50 patients - Group A: ongoing overt SSBB - Group B: previous overt SSBB - Group C: occult bleeding Inclusion criteria: age between 18-85, diagnosis of OGIB, non-diagnostic standard bidirectional endoscopy Exclusion criteria: deglutition impairment, SBCE contraindications, pregnancy.	Diagnostic yield of SBCE in a cohort of consecutive patients with OGIB Diagnostic yield of SBCE according to bleeding characteristics Impact of SBCE on the diagnostic and therapeutic work up during a follow-up 3-28 months	Overall DY: 92% DY according to bleeding characteristics: > 85% in all groups No immediate procedural adverse outcomes Treatment was: medical (60%), endoscopic (14%), surgical (36%) or conservative (18%) Clinical follow-up: - Complete resolution: 63.2%, - Partial or absent resolution: 18.4%	Single center study Small number of patients Limited number of patients requiring a second procedure Lack of long-term follow-up	High DY of SBCE, useful as first line investigation in patients with OGIB. The relevance of a dedicated gastroenterologist to optimize the DY of SBCE
Chang et al 2020	Prospective	144 patients Inclusion criteria: age>18 years with IDA and a precedent complete evaluation with EGD and colonoscopy. Exclusion criteria: overt GI bleeding, such as melena	- Assess diagnostic yield of CE in unexplained IDA without overt bleeding - Evaluate long-term outcomes and related clinical factors at a mean follow up 18.3 months	CE DY was 34% GI bleeding was found in 6.3% of the patients (occult bleeding in four patients and overt bleeding in five patients) during a mean follow-up of 17.8 months.	The study evaluated prospectively collected data, but these data were analyzed in a retrospective manner Some bleeding cases may have been missed in asymptomatic	Diagnostic yield for CE in patients with unexplained IDA without overt intestinal bleeding is 34%. Positive FOBT is a predictive factor for GI bleeding during follow-up after CE in patients with

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		and hematochezia; any positive result of active or/and recent bleeding stigmata in EGD or colonoscopy before CE; history of inflammatory bowel disease; extraintestinal conditions related to IDA; poor-quality examination.		Patients with positive FOBT at the initial diagnosis had a higher rate of GI bleeding after CE (p=0.004). A positive FOBT was the only independent predictive factor for GI bleeding (p=0.013).	patients because not all patients were evaluated for their symptoms or with FOBT in the specific period The CE registry includes only cases from tertiary hospitals (accounting for a third of all cases) Relatively small number of the patients.	unexplained IDA without overt bleeding.
Singeap et al 2020	Retrospective	224 inpatients with OGIB and negative upper and lower endoscopy were evaluated by SBCE. OGIB was either proved by a fecal test or resumptively incriminated as a cause for IDA.	DY of SBCE in overt and occult OGIB Causes of OGIB Impact of SBCE on clinical management Outcome	Overall DY for OGIB: 62% DY for overt OGIB: 75% DY for IDA: 37% Most frequent findings: SB angioectasias (62.2% in overt OGIB, 78.5% in IDA) Hb level <10 g/dL and anticoagulants/antiplatelet therapy were the variables independently associated with positive findings All patients received medical, endoscopic or surgical treatment	Retrospective study design Single center study Lack of long-term follow up for all patients	SBCE has good performance parameters for OGIB and proved itself as a safe technique SBCE has a high diagnostic yield and a positive impact on the management of patients with OGIB

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				and had good clinical outcome during follow-up.		
Olano et al 2018	Retrospective	118 patients (120 CE) Inclusion criteria: non diagnostic standard bidirectional endoscopy, unexplained IDA Exclusion criteria: age <18 years, Crohn's disease, pregnancy, gynecological causes for IDA, coeliac disease	DY of VCE Factors predicting positive findings in patients with IDA	DY of VCE for IDA: 50 %, Male sex (OR 3.93), age (OR 1.03), Hb levels (OR 0.73) had independent effect on the probability of positive findings Age > 50 years (OR 14.05;) and male sex (OR 3.63) increased the risk of diagnosing angiodysplasia	Retrospective, single-center, cohort study The institution, a tertiary referral center, may have taken a disproportionate number of complex patients Inclusion of nonspecific diagnosis as potentially explaining IDA No data about treatment	CE is a useful technique in patients with IDA. To improve its yield, it is necessary to select patients carefully. Male sex, older age, low Hb levels were associated with a risk of positive finding The risk of diagnosing angiodysplasia increased with male sex and older age.
Yung et al 2017	Retrospective	220 patients Inclusion criteria: - Age 19–50 - Recent complete gynecological evaluation - IDA (Hb <13 g/dl in men and <12 g/dl in women) - Iron deficiency: MCV <80 or ferritin <12–15 mg/l - Negative upper and lower GI endoscopy evaluation. Exclusion criteria:	DY of CE Factors predicting SB pathology	DY of CE : 32.3% (71/220) The most common significant but non-neoplastic pathologies were angioectasias (22/61) and Crohn's disease (15/61) Weight loss and lower MCV were associated with significant SB pathology (OR: 3.87 and 0.96)	-Retrospective study design -Many centres were high-volume or tertiary referral centres, which may have taken a disproportionate number of complex patients -MCV as a marker of IDA (current guidelines state that MCV alone is not enough to make a diagnosis of IDA)	In patients younger than 50 years old presenting with IDA, the overall DY of SBCE for significant SB findings was 32.3%. Around 5% were diagnosed with SB neoplasia. Lower MCV and weight loss were associated with higher risk of a diagnosis of significant SB findings.

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		- Previous or ongoing obscure-overt GI bleeding - Presence of any comorbidity that could also cause IDA				In young patients with certain clinical features such as low MCV and weight loss, CE should be prioritized
Sidhu et al 2015	Retrospective	1324 patients -971 recurrent IDA →Group 1: age <50 years →Group 2: age ≥50 years -353 overt bleeding	VCE DY VCE significant findings Elements associated with increased DY	VCE DY: - Group 1: 28% - Group 2: 38% Significant diagnoses: -erosions and ulcers: 26% - SB angioectasia: 10%, commoner in Group 2 -SB tumours: 3%, equally common in Group 1 and Group 2 -Crohn's disease: 3% -SB bowel strictures: 1% -SB varices: 1% The presence of diabetes (P = 0.02) and the use of warfarin (P = 0.049) was associated with increased DY.	-Retrospective study -All referrals made were taken at face value -Patients's history was not revisited to scrutinise any previous investigation undertaken -Not have the menopausal status for all the females <50 years of age -No long-term follow-up data on patients	Although the DY in patients <50 years is lower compared to those ≥50 years, significant pathology is found in this age group. CE is advisable in patients <50 years old with recurrent IDA and negative bidirectional endoscopies
Xavier et al 2018	Retrospective	118 patients - ≤60 yo - >60 yo	SBCE DY according to age Incidence of specific findings that could account for IDA were considered relevant, and presented according to age	Overall DY: 49% DY among patients >60 years: DY 60% DY among patients ≤60 years: 34% Angioectasias were more frequent in patients >60 years (45% vs 9%, p<0.01)	Retrospective, single-centre study	SBCE diagnosed clinically relevant findings in the setting of IDA in almost half the patients The DY was higher in patients older than 60 years, with vascular lesions being more

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				Significant inflammation (Lewis score >135 in 10.3% vs 1.7%, p<0.05) and other non-vascular lesions (24% vs 10%, p=0.04) were more frequent in patients ≤60 years		frequent in this age group. Despite the lower DY in patients ≤60 years, significant pathology is also found in this age group, mainly of inflammatory type
Limrisvilai et al 2016	Prospective	52 patients Inclusion criteria: age > 18, overt bleeding (melena/hematochezia) or occult bleeding (IDA/ FOBT+ and anaemia), non-diagnostic standard bidirectional endoscopy within 3 months Exclusion criteria: known allergy to contrast material, non dialyzed CKD stage 3, history of gut obstruction, uncontrolled bleeding with unstable vital signs	DY and sensitivity of CE and CTE (performed within a 1-week interval) Factors associated with higher DY in CTE Patients' outcome at follow-up (at least 6 months)	CE DY: 59.6% CTE DY: 30.8% CE sensitivity: 72.2% CTE sensitivity: 44.4% Combined sensitivity of CE and CTE: 88.9% Age below 40 years and severe bleeding were significantly associated with a higher diagnostic yield for CTE Clinical follow-up: - Complete resolution: 63.2% -Partial/absent resolution: 18.4% - Recurrent bleeding: 11.5%	Single-center study Small number of patients The institution, a tertiary referral center, may have taken a disproportionate number of complex patients Capsule reader and radiologist known patients ' clinical data CT enteroclysis not selected because less convenient than CTE	VCE had a higher DY and sensitivity than CTE in patients with potential SB bleeding, but CTE and VCE can complement each other. Age below 40 years and presentation with severe bleeding were independent predictors of positive diagnosis by CTE
Efthymakis et al 2016	Prospective	26 patients Inclusion criteria: presence of IDA at coeliac disease (CD) onset, a GFD of at least 24 months,	Compare the DY of endoscopy (EGD and colonoscopy) and SBCE in adult CD patients with persisting IDA	Endoscopy DY for lesions potentially causing anaemia: 42.3%	Single-center study Small number of patients	SBCE yielded significant findings in 23% of coeliacs with persistent IDA despite adequate gluten-free diet

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		negative serum IgA anti-TG and EMA work-up Exclusion criteria: major extraintestinal causes of IDA, abnormal menstrual blood loss, overt bleeding, chronic NSAIDs use, common contraindications for CE.	despite adequate gluten-free diet (investigations perfomed within 1 month from inclusion) Potential correlations between serology and SBCE outcome	SBCE DY for lesions potentially causing anaemia: 23.1% Severe disease found at SBCE and not at EGD: 11.5% Hypoalbuminemia was significantly associated with a positive SBCE outcome ($p < 0.01$).	Absence of a control group Inclusion of female subjects only	Hypoalbuminemia was associated with a positive SBCE outcome
Almilaji et al 2020	Prospective	2390 patients Inclusion criteria: confirmed IDA; high GI cancer risk based on age and Hb (≥ 70 years and <100g/L respectively); listed for investigation with gastroscopy and colonoscopy/ colonography Exclusion criteria: incomplete investigations; incomplete records	Predictive value of age, sex, Hb, MCV and iron studies on the probability of underlying GI cancer in patients with IDA Study the benefit of adding FIT into the model (FIT performed prior to invasive investigation, using the HemascreenSPECIFIC kit (detection limit 50µg Hb/g faeces).	ORs for the four predictive variables: - Age: 1.05 per year - Sex: 2.86 for men - Hb: 1.03 for each g/L reduction - MCV: 1.03 for each fL reduction FIT was predictive of GI cancer (OR 6.6), but the sensitivity was low at 23.5%	Single-center study The predicted GI cancer risk is in all cases greater than 0% and less than 50% While GI cancer is the most important cause of IDA, it is not the only one, and the model is not useful in predicting the likelihood of other causes	Age, sex and Hb are strong and independent predictors of the risk of underlying GI cancer in subjects with IDA Incorporating MCV into the risk stratification model increases its predictive value In combination, these variables can identify 10% of the study population who are at ultra-low risk of GI cancer FIT is a strong predictor of underlying GI cancer, but it has low sensitivity

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Yung et al 2018	Retrospective	170 inpatients Group 1: CE following negative upper and lower gastrointestinal endoscopy Group 2: CE following negative upper gastrointestinal endoscopy (UGIE) only	Effect of earlier CE in inpatients with IDA or melena with negative UGIE, with no other signs or symptoms suggesting lower gastrointestinal tract pathology Comparison in hospital stays between 2 groups	DY Group 1: SB 48.4%; stomach 16.8%; colon 12.6% DY Group 2: SB 44.0%; stomach 16.0%; colon 14.7% Group 2 had shorter mean times from admission to CE (5.08 ± 3.80 vs. 6.38 ± 3.80 days; p = 0.02) and hospital stays (10.5 ± 9.58vs. 12.5 ± 11.4 days; p = 0.04) compared to Group 1	Retrospective, single-center study The institution, a tertiary referral center, may have taken a disproportionate number of complex patients In 2005 CE had already been approved for conventional clinical use with acceptable image quality from the first models. The choice of investigative pathway and CE timing was determined by consultant preference.	Inpatient CE for IDA or melena had a DY of 52.3% Earlier use of CE in the investigative pathway significantly reduced the number of colonic investigations performed without compromising clinical outcomes Earlier use of CE also shortened hospital stays.
Yung et al 2017	SRMA	607 patients	Correlation betweem FOBT and CE findings to examine the predictive value of positive FOBT for CE findings.	Five of the 6 studies were suitable for statistical analysis. For all positive FOBT, sensitivity for small-bowel findings was 0.60 (95%CI 0.50-0.69), specificity was 0.72 (95%CI 0.52-0.86), and DOR was 3.96 (95%CI 1.50-10.4). For the 4 studies using only FIT, sensitivity was 0.48	small number of included articles lack of standardization between the included studies in lesion classification definition of a positive SBCE is not homogeneous	FOBT does not offer a comprehensive solution. Further work is required to refine screening methods, such as combining other fecal or serum markers, for the selection of patients for SBCE

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				(95%CI 0.36-0.61), specificity was 0.60 (95%CI 0.42-0.76), and DOR was 1.41 (95%CI 0.72-2.75).		
Judge et al 2019	Prospective	51 patients Inclusion criteria: adults (≥ 18 years) referred for investigation of suspected SB bleeding following negative EGD, colonoscopy and investigation for other possible causes of iron-deficiencyanaemia Exclusion criteria: age < 18 years of age and those who declined or were unable to participate.	Investigate if FIT could predict likelihood of small bowel pathology on SBCE Postulate whether FIT, alone or in combination with serum Hb, could be used to triage patients referred for investigation of suspected SB blood loss.	Statistically significant association between positive FIT and pathology on SBCE (p=0.001). Sensitivity of positive FIT in predicting SBCE findings: 69% Specificity of positive FIT in predicting SBCE findings: 84% Combining Hb and FIT was statistically significant in predicting pathology on SBCE (p=0.025).	Relatively low number of Patients Relatively low DY for SBCE versus some other studies (25.5% vs 63%) Inclusion of overt and occult bleeding cases within the same cohort	FIT ≥ 45 ug Hb/g is a useful tool in predicting small bowel pathology on SBCE. Use of FIT alone, or in combination with serum Hb, has value as a screening tool and may help to triage patients referred for SBCE.
Endo et al 2016	Prospective,	157 patients (low-dose aspirin users Inclusion criteria: patients with a history of daily low-dose aspirin use for at least 3 months. Exclusion criteria: common contraindication to CE; severe comorbidities;	Association between FIT results and CE findings in patients with negative bidirectional endoscopy	53.5% of patients had positive FIT results Sensitivity, specificity, PPV and NPV of positive FIT results for small bowel ulcers were 0.56, 0.47, 0.30, and 0.73, respectively The NPV of positive FIT results for severe small bowel injury was 0.90	Many patients underwent a 1-day FIT gFOBT was not examined	CE does not need to be performed to investigate the possibility of SB injury in all patients taking low-dose aspirin. SBCE is not recommended in FIT-negative, low-dose aspirin users. SBCE should be considered in both

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		ongoing overt bleeding; use of NSAIDs within 3 months prior to the study; failure to access the full length of the SB; presence of SB lesions that could cause occult bleeding (e.g. angioec-tasia, tumours)		When the analysis was performed only in low-dose aspirin users with anaemia, the sensitivity of the positive FIT results was notably improved (0.72)		FIT-positive and anemic low-dose aspirin users.
Clere-Jehl et al 2016	Retrospective	69 inpatients Inclusion criteria: proven IDA; no significant initial GI lesion known to lead to IDA; minimum of 12 months of follow-up Exclusion criteria: active chronic disease potentially inducing severe anaemia; end-stage kidney disease; hemoglobinopathies; hematological malignancy; aplastic anaemia; metastatic cancer; autoimmune diseases resulting in anaemia	Outcomes of IDA patients aged ≥65 with negative bidirectional endoscopy in terms of: - Death - Persistent anaemia - Further investigations - Final diagnosis for IDA Follow-up of 41±22 months	- Death: 23/69 (33%). 5 deaths were linked with IDA - Persistent anaemia: 45/69 (65%). Persistent anaemia was significantly associated with death (P=0.007) - Further investigations: 45/69 (65%). 64% of the second-look GI endoscopies led to significant changes in treatment, compared with 25% for the CE - Final diagnosis for IDA ultimately established for 19/69 (27%). It included 3 cancer patients. Among the other 50/69 patients, 40 (58%) had antithrombotics	Retrospective study	In endoscopy-negative IDA over the age of 65 years, further investigations should be reserved for patients with persistent anaemia. Second-look GI endoscopy should be favored. If the results of these investigations are negative, the role of antithrombotics should be considered.

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Kunihara et al 2018	Retrospective	357 patients Group A: 98/357 patients who had positive SB findings and indication for treatment Group B: 59/357 patients who had positive SB findings but no indication for treatment Group C: 200/357 who had negative SB findings	Rate of positive CE findings Detection rate and details of bleeding sources Overt bleeding rate Anaemia exacerbation rate Mean follow-up period 50.1 months)	Positive CE findings rate: 44% (157/357) Detection rate of bleeding source: 27% (98/357) Details of Group A bleeding sources: angioectasia (61/98), nonspecific ulceration (10/98), NSAID-induced ulcer 8/98), and others (19/98) Details of Group B bleeding sources: erythema (31/59), angioectasia (25/59), others (3/59); no patients with overt bleeding Overt bleeding rate: 0% (0/98) in Group A, 0% (0/59) in Group B Anaemia exacerbation rate after treatment for bleeding sources: 0% (0/98) in Group A, 10% (6/59) in Group B	Retrospective, single-centre study Relatively small sample size Relatively short observation period	OGIB patients who underwent treatment for bleeding sources did not have overt bleeding or anaemia exacerbation during the follow-up period OGIB patients who had no bleeding sources did not have rebleeding during the follow-up period OGIB patients without a confirmed bleeding source may not require follow-up CE
Sealock et al 2018	Retrospective	116 patients Exclusion criteria: CE performed after 180 days from the	Long-term outcomes in patients undergoing VCE for suspected obscure	Abnormal VCE findings (VCE DY): 87.9% of patients (37.9% for P1	Retrospective, single-center study	The diagnostic yield of VCE is high among patients with obscure GI bleeding.

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		request; no follow-up visits; alternative etiologies of anaemia or bleeding	bleeding (IDA or overt) at a mean follow-up duration of 571 days Need for additional intervention for persistence or recurrence of symptoms in patients undergoing VCE	lesions, 44.8% for P2 lesions) Additional diagnostic testing: 47.4% of patients, 67.7% of GI procedures. Hb restored to normal range by end of follow up: 50.9% of patients; normalization of Hb levels was attributed to iron supplementation and/or discontinuation of NSAIDs in a majority. Rebleeding: 22.4% of patients The need for a blood transfusion at the time of presentation was the only significant determinate of rebleeding during the follow-up period (OR 18.9)		More than 50% of patients achieve normal Hb in the long term with conservative measures such as iron supplementationand the discontinuation of NSAIDs.
Van de Bruaeneet al 2016	Retrospective	458 patients	Long term outcome of patients with a negative CE (prior to negative bi-directional endoscopy) at a median follow up of 4.4 years	57.4% of patients had negative CE and were included in the analysis: -65.9% True Negative -9% False Negative	Retrospective, single-center study No comparison between an equal number FN and TN CEs could be made	Further diagnostics can initially be deferred if negative CE Persisting anaemia should be investigated by

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				Continuous bleeding of unknown cause: 25.1% Further diagnostics after negative VCE because of ongoing bleeding/ anaemia: 45.5% Diagnosis of cause of bleeding through further examination: 59.4%	The number of FN CEs remained relatively small (n=19) Heterogeneity in patient population could not be avoided No data on the period between CE and re-bleeding was available	repeating bidirectional endoscopy (if no other approach is indicated). If negative, re-investigation of the SB with imaging as first-choice diagnostic tool might be necessary. In stabilized patients with IDA without OGIB diagnosis, no further diagnostic nor therapeutic procedures are needed, in the absence of alarm symptoms.
Yung et al 2017	SRMA	3657 patients	The primary outcome evaluated was the pooled odds ratios (ORs) for rebleeding after a negative CE for obscure GI bleeding (OGIB).	The pooled rate of rebleeding after negative CE was .19 (95% CI, .14-.25; P < .0001) The pooled OR of rebleeding was .59 (95% CI, .37-.95; P < .001) The effect was more pronounced in studies with a short follow-up (OR, .47; 95% CI, .24-.94; P < .001).	Heterogeneity of the studies No specific and standardized outcomes No standardized treatment after SBCE, follow-up modality	Negative CE provides adequate evidence of a subsequently low risk of rebleeding. Such patients can therefore be safely managed with watchful waiting. However, patients who rebleed after 2 years may need to be investigated for a new source of blood loss.
Cúrdia Gonçalves et al 2016	Retrospective	222 patients referred for SBCE for the study of IDA. 122: P2 lesions,	Risk factors for P1 lesions on SBCE Describe the natural history of anemic	From the 87 patients followed: - 39: additional studies for investigation of IDA,	Retrospective, case-control study	P1 lesions are commonly found in patients with IDA submitted to SBCE.

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		excluded from the final analysis 37: P1 lesions (cases) 63: P0 lesions or negative examinations (controls) From Sep 2008 to Aug 2013 13 patients had follow-up intervals shorter than 12 months and were excluded from this analysis	patients with such type of lesions.	significantly more common in patients with no findings on SBCE (53.7% vs 30.3%, P = 0.033) - 29: at least one rebleeding or IDA recurrence episode - 9: death of non-anaemia related causes but no differences were found between cases and controls		The use of NSAID seems to be a risk factor for P1 lesions. The outcomes of patients with P1 lesions do not differ significantly from those with P0 lesions or normal SBCE. P1 lesions had no gender predominance. The presence of P1 lesions does not seem to be influenced by age.
Robertson et al 2019	Retrospective	92 patients multiple (n2) CE examinations	Evaluate the utility of repeat CE with on-going concern of SB bleeding, following the initial SB investigation with CE.	45.8% of patients had initially normal CE; on repeat examination, abnormalities were detected. 14.2% of patients with angioectasia on first CE had alternative causes for IDA or GI bleeding detected on repeat CE. 83.3% of patients with active bleeding, without an identifiable source on initial CE, undergoing repeat CE had a cause isolated.	Retrospective study design Single-center study Cohort is heterogenous, with a wide range of time intervals between initial and repeat CE examinations Various capsule models have been used over the 13 years and reviewers experience has increased.	Patients with an initially negative or inconclusive CE frequently have a cause of SB bleeding detected on repeat CE. The DY of repeat CE is highest in those with bleeding on their initial CE (83.3%) and lower in those with initially normal examinations (45.8%) or when an alternative cause, such as angioectasia, is seen (14.2%).

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				Changing CE device did not affect diagnostic yield (DY) compared to repeat CE using the same device (27.5% to 26.8%).		
Zhang et al 2015	Prospective	88 patients (70 with OGIB) All pts underwent both CE and DBE Exclusion criteria: common contraindications to CE and severe comorbidities	To compare CE and DBE in the diagnosis of obscure SB diseases in terms of: - Detection rate - Diagnostic yield - Difference in the etiologies	Detection rates: - VCE 60.0% - DBE 59.1% Etiological DY: - VCE 42.0% - DBE 51.1% CE better than DBE in diagnosing: scattered small ulcers and small vascular malformations, but with no significant differences DBE was better than CE in diagnosing larger tumours and diverticular lesions with bleeding ulcers	Single-center study	CE and DBE each have their own advantages and disadvantages. The appropriate choice depends on the patient's age, tolerance, and clinical manifestations. Sometimes CE followed by DBE is necessary.
Lipkaet al 2015	SRMA	375 patients	Primary outcomes: diagnostic yield (DY) and therapeutic yield (TY) of SBE and DBE. Secondary outcomes were failure rates, adverse events, complete enteroscopy, anterograde/retrograde insertion depths, and procedure times.	DBE did not offer an advantage over SBE in: -TY (RR 1.11; 95% confidence interval (CI): 0.90, 1.37; P=0.33)] -DY (RR=1.08; 95% CI: 0.89, 1.32; P=0.42) -failure rates (RR=0.68; 95% CI: 0.23, 2.05; P=0.5)	4 out of 1 RCT were performed in western countries Heterogeneity in devices and operators experience	Performance of SBE and DBE appears to be similar in terms of DY / TY, insertion depths, procedure time, complete enteroscopy, failure rates, or adverse events

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				-overall adverse events (RR=1.41; 95% CI: 0.32, 6.3; P=0.65) -complete enteroscopy rates (RR=1.73; 95% CI: 0.86, 3.48; P=0.12).		
Beynaet al 2021	Prospective	132 patients Inclusion criteria: suspected SB disease with a positive or suggestive finding on prior SB imaging (VCE, radiology) or other clinical indication for deep antegrade enteroscopy Exclusion criteria: < 18 years of age Comorbidities (≥ 4 ASA) Common contraindication to CE antiplatelet agents or anticoagulants (other than aspirin) within last 7 days	- DY of PSE - Technical success rate of antegrade PSE (defined as successful insertion of the endoscope at least to the ligament of Treitz) - Depth of maximum insertion (DMI), measured in cm beyond the ligament of Treitz on withdrawal of the endoscope - Procedure time until DMI is reached and total procedural time - Adverse events during and after the procedure within a follow-up (FU) interval of 30 days.	140 procedures performed on 132 patients Overall DY of PSE: 74.2% 68.2% of procedures included some form of endotherapy Technical success rate of PSE: 97% Median DMI: 450 cm (0–600) Median insertion time to DMI: 25min (3–122) Overall adverse event rate: 14.4% Major serious adverse events: 1.5%	The study was conducted at two highly experienced endoscopic referral centers with extensive experience in deep enteroscopy and interventional endoscopy Retrograde and bidirectional approach for PSE and examination of patients with altered GI anatomy were not part of the trial	PSE is effective for diagnostic and therapeutic antegrade enteroscopy and may compare favourably with traditional methods of deep enteroscopy in ease of use and procedural duration.
Segarajasingamet al 2015	Prospective	79 patients -40 CE -39 PE (randomly assigned)	Compare CE to PE in terms of: - Diagnostic yield - Lesion detection rate	82.3% overt OGIB CE DY 72.5% PE DY 48.7% (P<0.05)	Single-center study Choice of DY as outcome, rather than true, more	A VCE-first approach had a significant diagnostic advantage over PE-first in patients with OGIB

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		Inclusion criteria: Patients ≥18 years of age with OGIB and negative bidirectional endoscopy Exclusion criteria: Common contraindications to perform CE and ingest erythromycin or PEG -Significant cardio-pulmonary disease preventing endoscopy -recent CE or PE examinations	-Bleeding outcomes at follow-up (at 12 months)	*in the distal small bowel CE DY 58% PE DY 13% (P<0.01) CE-identified lesions were rated possible or certain causes of bleeding (79.3% versus 35.0% of PE; P<0.05) No differences in the rates of ongoing bleeding (acute [40.0% versus 38.5%; P not significant], chronic [32.5% versus 45.6%; P not significant]), nor in health resource utilization, at FU - Fewer VCE-first patients crossed over due to ongoing bleeding (22.5% versus 48.7%; P<0.05)	downstream patient endpoints	There were no subsequent differences in bleeding or resource utilization outcomes in follow-up
Jia et al 2020	Retrospective	58 patients underwent CE before retrograde DAE: -39 CE → SBE -19 CE → TTSE Overall, 81 retrograde enteroscopy procedures were	Compare the clinical utility and safety of retrograde TTSE with retrograde SBE	50.6% IDA 45.7% OGIB Technical success was comparable in TTSE [23/27 (85.2%)] and SBE [41/54 (75.9%) Positive findings (35/39 and 17/19)	Retrospective study Non- randomized design Modest sample size Lack of a gold standard for measurement of depth of insertion	Both retrograde TTSE and SBE are feasible and safe, with comparable technical success TTSE showed a lower capacity of small bowel insertion

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		performed in 75 patients: -54 SBE in 49 pts -27 TTSE in 26 pts		were higher on CE, but lower on both types of enteroscopy (15/54, 6/27)		CE confirms to be more accurate than DAE when performed as first-line examination.
Lee et al 2018	Retrospective	130 IDA pts > 65 years	Diagnostic yield, subsequent management	Fifty-one studies (40.6%) had positive findings, and from this group, 30 (58.8%) recommended active intervention (i.e., EGD, n = 8; colonoscopy, n = 12; push enteroscopy, n = 3; double-balloon [DB] enteroscopy, n = 2; small bowel resection, n = 3; escalation of Crohn's therapy, n = 2), while 21 (41.2%) were managed supportively, typically with iron supplementation. Most negative studies (73 of 79) recommended supportive therapy (other recommendations included hematological workup, n = 3; hiatal hernia repair, n = 1; proton-pump inhibitors [PPI] initiation, n = 1; stop donating blood, n = 1).A history of	retrospective	CE importnat, key factors

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				cardiac disease had a significant association with positive findings (0.54 versus 0.33, P = 0.001).		
Garrido Durán et al 2015	Retrospective	249 pts with IDA	Diagnostic yield in women vs men. Pre vs post menopausal women	. The diagnostic yield of VCE for the diagnosis of IDA was 44.6% (95% CI 39.9 - 50.8). Diagnostic yield was 50.8% vs 38.9% in men vs women (p=0.05) and was 55% vs 13.7% in postmenopausal vs premenopausal women (p<0.001). No predictors of small bowel lesions were found in premenopausal women. The most common findings in the postmenopausal group were angioectasias (70.5%) and erosions (57.1%) in the premenopausal group. The cost in premenopausal women was 44.727€ and 86.3% of the procedures had no clinical impact	retrospective	The diagnostic yield of VCE is low in the etiological study of IDA in premenopausal women and there is no cost-effectiveness in relation to clinical impact. No predictors of small bowel lesions were found in this group.
Silva et al 2018	Retrospective	CE in IDA N=183	Diagnostic yield pre vs post menopausal	The DY was 30.4% in PMW and 63.8% in MW. The most common findings were angiodysplasias	retrospective	: PMW with suspected OGIB are less likely to have significant findings in CE. In MW DY, need

Supplementary material

				in both groups (PMW: 21.4%, MW: 44.9%) (P = 0.003). In PMW, only 1.8% required therapeutic endoscopy. In 17.3% of MW, CE findings led to additional endoscopic treatment. Rebleeding at 1, 3 and 5 years in PMW was 3.6%, 10.2%, 10.2% and 22.0%, 32.3% and 34.2% in MW. Postmenopausal status was significantly associated with higher DY (P < 0.001), TY (P = 0.003), rebleeding (P = 0.031) and lower time to rebleed (P = 0.001).		for endoscopic treatment and rebleeding were significantly higher while time to rebleed was lower.

Supplementary material

Task force 2 - Crohn's disease

Despott**(Leader)**, Rosa, McNamara, González-Suárez, Carretero, Kunovsky, Neumann

Author, year	**Study design**	**Study objective**	**Participants**	**Intervention / Comparison**	**Outcomes**		**Results - Conclusion**	**Level of evidence**	**Remarks**
Choi et al 2017	Meta-analysis	Compared the effectiveness of VCE compared with other diagnostic modalities in small bowel CD patients	24 studies included studies with suspected CD only, established CD only, and studies with suspected and established CD combined	focus on: VCE vs IC comparison (5 studies only)	<u>diagnostic yield of detection lesions of terminal ileum:</u> **VCE vs. IC** 60% vs. 48% 95% CI, 0.00 to 0.22, p=0.004 my note: the diamond (overall effect estimate) touches the line of zero effect – so the clinical significant difference is very low		In the detection of lesions in terminal ileum (established CD pts), VCE exhibits <u>marginally a significant increased detection</u> rate compared with IC (p=0.004)	Low/moderate	VCE vs IC comparison only in CD established group! Low quality meta-analysis
Mitselos et al 2016	ObservationalRetrospectivestudy (2005-2015)	compared VCE and IC as primary tools for diagnosis in suspected CD patients (irrespective of its location)	91 patients with suspected CD	VCE vs IC	<u>small bowel or colonic CD:</u> **VCE vs. IC** Sensitivity: 64% v.s. 82% (p=0.375) Specificity: 93% v.s. 78% (p=0.008)	<u>small bowel or colonic CD:</u> **IC+VCE vs. IC** Sensitivity: 91% v.s. 82% (p=0.500) Specificity: 74% v.s. 78% (p=0.125)	IC should be the initial diagnostic test in patients with suspected CD <u>The discriminatory ability of the combination (IC+VCE) was not shown to be superior to</u>	Low	Study evaluating small bowel and/or colonic disease VCE used only for small bowel

Supplementary material

							that of IC. On the basis of this outcome, the 'blind' initial use of VCE in all patients under evaluation for suspected CD is not advised. VCE offers additional information on small bowel mucosa and the extent of disease		
Garcia-Bosch et al 2016	Single-centre prospectivestudy, (2006-2010	Compared the diagnostic accuracy and impact of management of MRI and IC as first- and second-line examination in already diagnosed CD patients	100 pts with established CD (active CD)	focus on: MRI vs. IC in diagnostic accuracy	Disease activity * **MRI vs. IC** 87% vs 87% (not significant) Stenosis * **MRI vs. IC** 90% v.s 66% ($p < 0.001$)	Fistula * **MRI vs. IC** 98% v.s 39% ($p < 0.001$) Abscess * **MRI vs. IC** 99% v.s 40% ($p < 0.001$)	The assessment of disease activity were similar, however in comparing complications MRI showed better results information provided by MRI has a higher impact on patient management than IC	Low	Only diagnosed CD patients!! *after assessment of clinical data + adding data from MRI or IC
Taylor et al 2018	Multicentrep rospectivestu dy, (2013-2016)	compared accuracy in assessing the extent and activity of small bowel diseasein CD patients between MRE	284 pts with CD 133 pts with newly diagnosed CD	focus on: comparing MRE and ultrasound in newly diagnosed CD patients and only small bowel	small bowel extent: **MRE vs. US** Sensitivity: 77% v.s. 66% (difference 11%) Specificity: 98% v.s. 88%	Against an ileocolonosco pic standard of reference (available in 186 patients – combined newly diagnosed CD	Both MRE and ultrasound have high sensitivity for detecting small bowel CD However, MRE had higher sensitivity and	Low	ileocolonoscop y was used as a standard of reference. Not comparative study with ileocolonoscop y.

Supplementary material

		and ultrasound (US)	215 ptsestablished CD	results evaluated	(difference 10%) small bowel presence: **MRE vs. US** Sensitivity: 96% v.s. 92% (difference 4%) Specificity: 99% v.s. 91% (difference 8%)	and established CD patients!): terminal ileum disease presence: **MRE vs. US** Sensitivity: 97% v.s. 91% (difference 6%) Specificity: 41% v.s. 33% (difference 8%)	specificity than ultrasound Against a ileocolonoscopic standard of reference MRE showed a quite low specificity (41%)		Small bowel disease present at the time of diagnoses of CD in 83%
Bruining et al 2020	Multicentreprospectivestudy, (2018-2019)	assessedtheaccuracy of panenteric VCE in Crohn's disease as compared with ileocolonoscopy (IC) and/or magneticresonance enterography (MRE)	99 pts included with established CD	panenteric VCE v.s. MRE and/or IC in assessing CD activity	Overall (proximal small bowel, terminal ileum, colon): **VCE vs. MRE and/or IC** Sensitivity: 94% v.s. 100% (p=0.125) Specificity: 74% v.s. 22 % (p=0.001) Proximal small bowel: **VCE vs. MRE** sensitivity: 97% v.s. 71% (p=0.021) Specificity: 87% v.s. 66 % (p=0.020)	Terminal Ileum: **VCE vs. IC** Sensitivity: 94% v.s. 89% (p=0.688) Specificity: 81% v.s. 92% (p=0.289) **VCE vs. MRE** Sensitivity: 94% v.s. 79% (p=0.057) Specificity: 82% v.s. 44 % (p=0.001)	In overall assessment (small and large bowel) VCE had higher sensitivity and specificity than MRE and/or IC However, in terminal ileum the results comparing VCE and IC were similar in assessing CD activity VCE had higher sensitivity and specificity in proximal small bowel and also	Low	Panenteric capsule! Only diagnosed CD patients!!

Supplementary material

							in terminal ileum than MRE		
Leighton et al 2017	Multicentreprospectivestudy, (periodduration notspecified)	compared the diagnostic yield of a pan-enteric VCE (small-bowel colon [SBC] capsule) versus IC in patients with active CD	66 pts	panenteric VCE v.s. IC in known active CD patients	<u>Small bowel + colon:</u> per-subject diagnostic yield rate **VCE vs. IC** 83% v.s. 70% for IC (yield difference, 13.6%; 95% confidence interval [CI], 2.6%-24.7%) <u>Small bowel + colon:</u> the per-segment diagnostic yield rate **VCE vs. IC** 41% v.s. 33% (yield difference 7.9%; 95% CI, 3.3%-12.4%)	<u>Only terminal ileum:</u> lesion detection rate **VCE vs. IC** 70% v.s. 54% for IC (yield difference 16%; 95% CI, 3%-26%)	the diagnostic yields for panenteric VCE might be higher than IC however, the magnitude of difference between the two is difficult to estimate	Low	Panenteric capsule! Only diagnosed CD patients!!
Prichard et al 2020	Observationalprospectivestudy (2010-2014)	compared the ability of VCE and MRE to detect small bowel inflammation (and in the terminal ileum separately) in	20 pts with newly diagnosed CD	focus on: VCE v.s. IC	<u>whole small bowel (pan-enteritis):</u> diagnostic yield **VCE v.s. MRE** 75% pts v.s. 5% pts ($p<0.001$)	<u>Only terminal ileum:</u> diagnostic yield **VCE v.s. IC** 80% pts v.s. 60% pts	VCE is at least equivalent to IC in its ability to identify active CD in terminal ileum VCE is as sensitive as	Very Low	Pediatricpopulationonly!

Supplementary material

		children with newly diagnosed CD, and compared their performance with IC			<u>Only terminal ileum:</u> diagnostic yield **VCE v.s. MRE** 80% pts v.s. 60% pts	VCE and IC agreement regarding mucosa findings in 89% of pts (p=0.01)	MRE for identifying active TI inflammation, but appears more sensitive in identifying more proximal small bowel inflammation		
Freitas et al 2020	Observational Retrospective study (2016-2019)	evaluated thediagnosticvalue of smallbowel VCE forisolated terminal ileitisdetecteddduring IC	102 ptsisolated terminal ileitis	perform VCE after IC with isolated terminal ileitis findings	positive findings on VCE in 82.4%	VCE supported definitive diagnoses in two-thirds of patients (61.8%), being CD in 35 pts (34.3%)	In patients with isolated terminal ileitis on IC, in one-third (34.3%) of patients has been finally diagnosed as CD (VCE used as a supporting diagnostic tool)	Very low	

Author,year	**Study design**	**Study objective**	**Participants**	**Intervention/ Comparison**	**Outcomes**		**Results/Conclusion**	**Level of evidence**	**Remarks**
Kopylov et al 2017	Meta-analysis	Compared diagnostic yield of VCE to MRE and US in small bowel CD patients	13 studies included studies with suspected CD only, established CD only, and studies with suspected	focus on: VCE vs MRE in suspected CD patients	<u>diagnostic yield:</u> **VCE was similar to that of MRE** (2 studies, 85 patients, OR 3.24; 95% CI 0.14–72.76; P = 0.46) **and US** (1 study, 30	<u>diagnostic yield:</u> **VCE was superior to MRE** for the detection of <u>proximal small bowel</u> disease (7 studies, 251 patients, OR 2.79; 95% CI	Diagnostic yield of VCE and MRE was similar for <u>suspected small bowel CD patients</u> VCE is superior to MRE in detection of proximal small	moderate	low number of studies including only suspected CD patients

Supplementary material

			and established CD combined		patients, OR 1.00; 95% CI 0.36–2.81; P = 1.00) for suspected CD patients	1.2–6.48; P = 0.02), (mostly established CD patients)	bowel disease (this subanalysis includes patients with established CD and patients with established or suspected CD patients combined)		
Choi et al 2017	Meta-analysis	Compared effectiveness of VCE compared with other diagnostic modalities in small bowel CD patients	24 studies included studies with suspected CD only, established CD only, and studies with suspected and established CD combined	focus on: VCE vs SBFT/CE/CTE/MRE comparison (<u>suspected CD patients only</u>)	<u>diagnostic yield:</u> **VCE vs. SBFT** 66% vs. 21% 95% CI, 0.29 to 0.59, p<0.00001, (3 studies) **VCE vs. EC** 76% vs. 29% 95% CI, 0.21 to 0.79, p=0.0008, (2 studies)	<u>diagnosticyield:</u> **VCE vs. CTE** 72% vs. 23% 95% CI, 0.18 to 0.90, p=0.19, (2 studies) **VCE vs. MRE** 86% vs. 100% 95% CI, -0.63 to 0.32, p=0.52, (2 studies)	In cases of suspected CD, CE demonstrated a superior diagnostic yield compared with SBFT and EC, however, there was no difference compared with CTE or MRE	Low	Low quality meta-analysis (high heterogeneity, low number of studies included to subanalysis!)
González-Suárez et al 2018	Observational Retrospective study (2011-2013)	compared VCE and MRE for diagnostic yield and assessment of CD	47 pts with CD 32 pts with established CD	compared VCE and MRE for the diagnostic yield and assessment of CD	<u>whole small bowel:</u> **VCE v.s. MRE** lesions detection: 77% v.s. 45%	<u>Jejunum:</u> **VCE v.s. MRE** lesions detection: 32% v.s.6% (p=0.03)	VCE was significantly superior to MRE in detecting small bowel lesions, mainly	Low	mixed group of suspected and established CD patients

Supplementary material

			15 pts with suspected CD		(p=0.001)	Ileum: **VCE v.s. MRE** lesions detection: 57% v.s. 21% (p=0.04) Terminal ileum: **VCE v.s. MRE** lesions detection: 68% v.s. 38% (p=0.002)	superficial lesions		
Bruining et al 2020	Multicentreprospectivestudy, (2018-2019)	assessedtheaccuracy of panenteric VCE in Crohn's disease as compared with ileocolonoscopy (IC) and/or magneticresonance enterography (MRE)	99 pts included with establishe d CD	panenteric VCE v.s. MRE and/or IC in assessing CD activity	Overall (proximal small bowel, terminal ileum, colon): **VCE vs. MRE and/or IC** Sensitivity: 94% v.s. 100% (p=0.125) Specificity: 74% v.s. 22 % (p=0.001) Proximal small bowel: **VCE vs. MRE**	Terminal Ileum **VCE vs. MRE** Sensitivity: 94% v.s. 79% (p=0.057) Specificity: 82% v.s. 44 % (p=0.001)	In overall assessment (small and large bowel) VCE had higher sensitivity and specificity than MRE and/or IC VCE had higher sensitivity and specificity in proximal small bowel and also in terminal ileum than MRE	Low	Panenteric capsule! Only diagnosed CD patients!!

Supplementary material

					sensitivity: 97% v.s. 71% (p=0.021) Specificity: 87% v.s. 66 % (p=0.020)				
Calabrese et al 2020	Observationalretrospectivestudy (2010-2015)	compared the ability of VCE and cross-sectional imaging techniques in the detection of small bowel lesions in established CD patients	102 pts with established CD	VCE v.s. CTE/MRE in detection of small bowel lesions in established CD patients	<u>whole small bowel:</u> **VCE v.s. CTE** sensitivity: 100% v.s. 55% (p<0.001) specificity: 84% v.s. 80% (p<0.5) **VCE v.s. MRE** sensitivity: 100% v.s. 60% (p<0.001) specificity: 84% v.s. 82% (p<0.5)	<u>Proximal small bowel</u> **VCE v.s. CTE** sensitivity: 100% v.s. 16% (p<0.001) specificity: 94% v.s. 100% (p<0.5) **VCE v.s. MRE** sensitivity: 100% v.s. 41% (p<0.001) specificity: 94% v.s. 100% (p<0.5) <u>middle small bowel</u> **VCE v.s. CTE** sensitivity: 100% v.s. 17% (p<0.001)	VCE has a superior sensitivity in detecting CD lesions in the proximal and medium small bowel compared with CTE/MRE. In the terminal ileum, MRE and CTE displayed similar performance to CE Extra-luminal complications were detected more accurately by CTE/MRE compared with VCE	Low	Onlydiagnosed CD patients!!

Supplementary material

						specificity: 94% v.s. 100% (p<0.5) **VCE v.s. MRE** sensitivity: 100% v.s. 38% (p<0.001) specificity: 94% v.s. 82% (p<0.5) <u>terminal ileum</u> **VCE v.s. CTE** sensitivity: 100% v.s. 90% (p<0.001) specificity: 100% v.s. 80% (p<0.5) **VCE v.s. MRE** sensitivity: 100% v.s. 82% (p<0.001) specificity: 100% v.s. 83% (p<0.5)			

Supplementary material

Prichard et al 2020	Observationalprospectivestudy (2010-2014)	compared the ability of VCE and MRE to detect small bowel inflammation (and in the terminal ileum separately) in children with newly diagnosed CD, and to compare their performance with IC	20 pts with newly diagnosed CD	focus on: VCE v.s. MRE	<u>whole small bowel (pan-enteritis):</u> diagnostic yield **VCE v.s. MRE** 75% pts v.s. 5% pts (p<0.001) <u>Jejunum:</u> diagnostic yield **VCE v.s. MRE** 80% pts v.s. 20 pts (p=0.003) <u>Ileum:</u> diagnostic yield **VCE v.s. MRE** 80% pts v.s. 35% pts (p=0.007)	<u>Only terminal ileum:</u> diagnostic yield **VCE v.s. MRE** 80% pts v.s. 60% pts	VCE is as sensitive as MRE for identifying active TI inflammation, but appears superior in identifying proximal small bowel inflammation	Very Low	Pediatricpopulationly!
Freitas et al 2020	ObservationalRetrospectivestudy (2016-2019)	evaluated thediagnosticvalue of VCE forisolated terminal ileitisdetecteddduring IC	102 ptsisolated terminal ileitis	perform VCE after ileocolonoscopy with isolated terminal ileitis findings	In patients with isolated terminal ileitis on ileocolonoscopy, in 35 patients (34.3%) has been finally diagnosed as CD (VCE	in these 35 new diagnosed CD patients 19 patients (54%) had proximal small bowel involvement on VCE	VCE can add important information of proximal small bowel involvement in newly diagnosed CD patients	Very low	

Supplementary material

					used as a supporting diagnostic tool)				
Nehra et al 2020	Observational Retrospective study (2002-2011)	determined the importance of ileal inflammation on CTE/MRE in CD patients with normal IC	1471 CD patients underwent CTE/MRE and IC	evaluated patient with negative IC and positive CTE/MRE in terminal ileum	6% (1471/88) of patients with negative IC and with negative biopsies had positive inflammatory findings in terminal ileum on CTE/MRE (included patients with suspected CD who subsequently received diagnosis of CD patients) 67 % (59/88) of these patients were subsequently confirmed to have inflammatory changes and disease progression		CD patients with unequivocal imaging findings of ileal inflammation at CTE/MRE despite negative IC and biopsy are likely to have active inflammatory CD	Low	

Supplementary material

Huang et al 2020	Observationalprospectivestudy (2014-2018)	Assessed the value of DBE for suspected isolated small CD patients	18 pts with suspected small bowel isolated CD Pts underwent EGD, IC, CT and additional imaging modalities such as CTE or VCE	Pts with suspected small bowel isolated CD underwent DBE	CD was finally confirmed in 14 pts	DBE assisted in diagnosis in 86% patients (12/14)	DBE was useful in diagnosing and confirming small bowel CD in patients after exclusion of abnormal changes in upper gastrointestinal tract and colon DBE is suitable when VCE or radiological examination reveals abnormal lesions, or when the results of these two methods are negative but small bowel CD is highly suspected	Very low	Low number of patients

Author, year	**Study design**	**Study objective**	**Participants**	**Intervention/ Comparison**	**Outcomes**		**Results/Conclusion**	**Level of evidence**	**Remarks**
Pasha et al 2020	Meta-analysis	evaluatingthe VCE retention in CD patients	35 studies suspectedandestablished CD	focus on: evaluatingthe VCE retention in suspected CD pts	<u>retention rate:</u> <u>Overall CD:</u> **3.32%** (95% CI,	<u>retention rate:</u> <u>Established CD:</u> **4.63%** (95% CI, 3.42%–6.25%; 32 studies)	Patientswithestablished CD were 3.5 times more likelytoexperience retentionthan	Moderate	

Supplementary material

			adult andpediatric CD patients	(adult poputaion)	2.62%–4.2%; 35 studies)	<u>Suspected CD:</u> **2.35%** (95% CI, 1.31%–4.19%; 16 studies)	those withsuspected CD		
Rezapour et al 2017	Meta-analysis, (1995-2015)	evaluatethe VCE retention	25 studies including pts with GI bleeding, suspected and established IBD	focus on: evaluatingthe VCE retention in suspected IBD patients	<u>retention rate (sub-analysis 1):</u> **established IBD** (11 studies): **8.2%** (95% CI, 6.0%-11.0%) **suspected IBD** (9 studies): **3.6%** (95% CI, 1.7%-8.6%) note: Patients with strictures demonstrated on MRE and/or CTE or retention of the patency capsule were excluded from this sub-analysis	<u>retention rate (sub-analysis 2):</u> patients included after the completion of either a patency capsule or CTE/MRE and exclusion of those patients who were found to have retention with patency capsule or CTE/MRE: <u>VCE retention rate decreased to **2.7%**</u> in IBD patients (95% CI, 1.1%-6.4%). suspected and established IBD counted together in this sub-analysis	VCE retention rates in IBD were detected to be 8.2% in established IBD and 3.6% in suspected IBD, rates that may be higher than previously reported Performing a patency capsule study or CTE/MRE in patients suspected of having a stricture or other potential reason for VCE retention is useful because they lower the potential retention rate by more than half	Low/Moderate	significant heterogeneity between the studies with suspected IBD (I^2 = 69%)! in the sub-analysis 2 there is no distinguished if patency capsule or CTE/MRE were used

Supplementary material

Tontini et al 2020	Observationalprospectivestudy (2017-2018)	evaluated a new VCE panoramic 344°-viewing	41 pts with suspected (30) andestablished (11) CD	focus on: VCE retention in suspected CD patients	30 suspected CD patients In suspected CD patients group no capsule patency were performed prior to VCE	retention rate: no VCE retention in 30 patients with suspected CD	no VCE retention	Low	
Mitselos et al 2016	ObservationalRetrospectivestudy (2005-2015)	compare VCE and IC as primary tools for diagnosis in suspected CD patients	91 patients with suspected CD	focus on: VCE retention in suspected CD patients	91 patients with suspected CD Patients with suspected strictures and at high risk of VCE retention ingested a patency capsule (10 patients) one week before VCE	retention rate: no VCE retention in 91 patients with suspected CD	no VCE retention	Low	
Tai et al 2020	Observationalmulticentricprospectivestudy (2017-2019)	examine feasibility, safety and impact on patients' outcomes of panenteric VCE in CD patients	71 patients with established CD and 22 with suspected CD were included	focus on: VCE retention in suspected CD patients	21 patients with suspected CD 20 patients out of 22 with suspected	retention rate: no VCE retention in 91 patients with suspected CD 2.8% retention rate (2/71) in established CD	no VCE retention in suspected CD	Very Low	Panenteric capsule!

Supplementary material

					CD had patency capsule or small bowel imaging (no further specified). Two patients with suspected CD had no imaging or patency capsule.				
Prichard et al 2020	Observationalprospectivestudy (2010-2014)	compared the ability of VCE and MRE to detect small bowel inflammation in children with newly diagnosed CD	20 pts with newly diagnosed CD	focus on: VCE retention in suspected CD patients	20 pts with newly diagnosed CD Exclusion criterium was suspicion for high grade small bowel stricture	<u>retention rate:</u> no clinically significant (surgical/endoscopic intervention) VCE retention occurred in 20 newly diagnosed CD patients in one patient VCE was halted, that resulted in spontaneous VCE passage after corticosteroid treatment	no clinically significant (surgical/endoscopic intervention) VCE retention	Very Low	Pediatricpopulationonly!
Eliakim et al 2018	Observationalmulticentricprospectivestudy (2016-2017)	evaluate the functionality of panenteric capsule	41 patients (29 with established CD, 5 with established UC and 7 with	focus on: VCE retention in suspected CD patients	Patency capsule were used only in established CD patients	<u>retention rate:</u> no VCE retention in 7 patients with suspected CD	no VCE retention	Very Low	Panenteric capsule!

Supplementary material

			suspected CD)						

Author, year	**Study design**	**Study objective**	**Participants**	**Intervention / Comparison**	**Outcomes**		**Results/Conclusion**	**Level of evidence**	**Remarks**
Ahmed et al 2015	Meta-analysis	MRI in detecting small bowel activity as well as extramural complications in CD patients	a total of 19 studies with 1020 patients	focus on: MRI in detectingstenosis (only 6 studies)	stenosis **MRI** sensitivity 65% (95% CI 0.53 to 0.76)	stenosis **MRI** specificity 93% (95% CI 0.89 to 0.96)	MRI showed high specificity in detectingstenosis	Low/Moderate	patients' group either with established CD or established/suspected CD were included only 6 studies in evaluating stenosis
Garcia-Bosch et al 2016	Single-centre prospective study, (2006-2010)	Compared the diagnostic accuracy and impact of management of MRI and IC as first- and second-line examination in already diagnosed CD patients	100 pts with established CD (active CD)	focus on: MRI in diagnostic accuracy of complications	Stenosis * **MRI** 90%	Fistula * **MRI** 98% Abscess * **MRI** 99%	MRI provided high diagnostic accuracy of CD complications	Low	Only diagnosed CD patients!! *after assessment of clinical data + adding data from MRI
Pasha et al 2020	Meta-analysis	evaluatingthe VCE retention in CD patients	35 studies suspectedandestablished CD	focus on: evaluatingthe VCE retentionrate when	retention rate (sub-analysis 1):	retention rate (sub-analysis 2): after either MRE/CTE or a negative PC	Retention rates in established CD patients were lower after	Moderate	Only established CD patients in this sub-analysis!

Supplementary material

			adult andpediatric CD patients	MRE/CTE or patency capsule performed prior to VCE	Established CD: **4.63%** (95% CI, 3.42%–6.25%; 32 studies) Suspected CD: **2.35%** (95% CI, 1.31%–4.19%; 16 studies)	Established CD: **2.75%** (95% CI, 1.76%–4.28%; 19 studies)	negative PC or MRE/CTE		
Al-Bawardy et al 2015	retrospective study (2002-2013)	determine the incidence and risk factors for capsule retention and define cross-sectional imaging findings predictive of capsule retention	including pts with GI bleeding, CD and other diagnosis	focus on: comparison of CT findings in patients with retained VCE v.s. patients with spontaneous passage	partial small bowel obstruction retained VCE v.s. passed VCE 63% v.s. 38% small bowel anastomosis retained VCE v.s. passed VCE 88% v.s. 23%	stricture retained VCE v.s. passed VCE 63% v.s. 23%	Patients with VCE retention were more likely to have small bowel anastomosis and strictures compared with patients who passed the capsule	Very Low	Patients with OGIB, CD and other diagnosis included!

	Study design			**Intervention/**	**Outcomes**	**Results/Conclusion**		**Remarks**

Supplementary material

Author, year		**Study objective**	**Participants**	**Comparison**				**Level of evidence**	
Rondonotti et al 2016	Observational prospective multicenter study (2011-2013)	compare VCE retention rates in high-risk patients with negative patency capsule (PC) or dedicated small-bowel cross-sectional imaging (SBCSI)	total 3117 pts 2942 (94.4%) classified as low-risk 175 (5.6%) classified as high-risk	compare VCE retention rates in high-risk patients with negative PC or dedicated small-bowel cross-sectional imaging	<u>high-risk patients:</u> **PC** 151/175 (86.3%) **SBCSI** 24/175 (13.7%)	<u>capsule retention:</u> **PC v.s. SBCSI** 1/151 (0.7%) v.s. 2/24 (8.3%)	high-risk patients with negative SBCSI have a significantly higher capsule retention rate in high-risk patients with negative SBCSI, PC should be performed prior to VCE	Low	Patients with OGIB, CD and other diagnosis included! high-risk patients (obstructive symptoms, previous surgery, suspected stenosis on imaging methods, etc.)
Rozendorn et al 2016	Observational prospective study (?)	evaluate the ability of MRE to predict PC retention in patients with CD	57 pts with established CD	evaluate the ability of MRE to predict PC retention in patients with CD	radiologist predicted PC retention in 30 patients, 30/57 (52.6%) In 13 patients PC retained PC retention was predicted in 12 of 13 cases (92.3%)	<u>MRE prediction for PC retention:</u> sensitivity: 92.3% specificity: 59% PPV: 40% NPV: 96.3%	MRE had a high NPV and sensitivity for PC retention When VCE retention is suggested by MRE, PC should be performed before the VCE examination (low specificity an PPV of MRE)	Low	Only established CD patients!

Supplementary material

Herrerias et al 2008	Observational multicenterstudy	assess the ability/patency of VCE in patients with known strictures	106 pts with known strictures	assess the ability/patency of VCE in patients with known strictures	PC demonstrated functional patency in **59/106 (56%)**	There were no VCE retention in any of the 59 patients with negative PC tests	Higher false-positive rate of SBFT/CT compared to PC test	Low	Mostly CD patients (54%), however also other diagnoses included
Yadav et al 2011	Observational Retrospective study (2006-2010)	Comparison of PC and radiological examinations to detect clinically significant small bowel strictures	42 pts with known or suspected strictures	Comparison of PC and radiological examinations to detect clinically significant small bowel strictures	<u>sensitivity:</u> **PC v.s radiology** 57% v.s. 71% p=1.00 <u>specificity:</u> **PC v.s radiology** 57% v.s. 71% p=0.22	<u>PPV:</u> **PC v.s radiology** 44% v.s. 93% (no significant difference) <u>NPV:</u> **PC v.s radiology** 91% v.s. 94 (no significant difference)	NPV for the PC and radiological tests were not significantly different	Very Low	Mostly CD patients (60%), however also other diagnoses included radiology methods used (CT, CTE, MRE, SBFT)
González-Suárez et al 2018	Observational Retrospective study (2011-2013)	compared VCE and MRE for diagnostic yield and assessment of CD	47 pts with CD 32 pts with established CD <u>15 pts with suspected CD</u>	Focus on: evaluate gastrointestinal patency (VCE retention risk) by MRE prior to PC and VCE	VCE performed in 47 patients	MRE found stenosis in 10/47 patients (prior to VCE) all 10 pts with suspected stenosis	Intestinalstricturesdetectedby MRE (prior to PC and VCE) overestimatedthe VCE retention risk	Very Low	mixed group of suspected and established CD patients excludes pts with previous history of previous known

Supplementary material

						detected by MRE underwent PC with negative results and then a successful VCE was performed without retention in these 10 pts			intestinal stricture! evaluate gastrointestinal patency (VCE retention risk) by MRE prior to PC and VCE wasn´t the aim of the study

Author, year	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
Kopylov et al 2016	Systematic review and meta-analysis	Seven studies (463 patients with suspected or established CD), 2000-2015	Diagnostic accuracy of FC for diagnosis of SBCD or evidence of active inflammation in the small-bowel in established CD. Evaluated three FC level cut offs: 50, 100, and 200 µg/g	For an FC cut-off of 50 µg/g, sensitivity and specificity were 0.83 and 0.53, respectively (diagnostic odds ratio, DOR-5.64); PPV was 56.1% (47–61) and NPV was 49.8% (48.5–51.1); For an FC cutoff of 100 µg/g, the sensitivity was 0.68 and the specificity was 0.71 (DOR-5.01), PPV was 62.9% (54.7–67.5), and NPV was 60.5% (58–64.2); For an FC cut-off of 200 µg/g, sensitivity and specificity were 0.42 and 0.94, respectively (DOR-13.64); PPV was 83.5% (78.2–86.1); and NPV was 69.1% (64.6–75.8).	Majority of the studies were retrospective Different definitions of CD on SBCE The criteria used to establish the diagnosis of CD were not identical.	Fecal calprotectin has a significant diagnostic accuracy for the detection of small-bowel CD. In patients with suspected CD with normal ileocolonoscopy and calprotectin < 50 µg/g, the likelihood of positive diagnosis is very low.

Supplementary material

				For studies including patients with suspected CD only, the overall accuracy for FC cut-off 50 µg/g was further increased (sensitivity 0.89, specificity 0.55, DOR-10.3), with a negative predictive value of 91.8%.		
Jung et al 2021	Systematic review and meta-analysis	Fourteen studies (1094 patients with suspected or established CD), 2000-2020	Diagnostic accuracy of FC for diagnosis of SBCD or evidence of active inflammation in the small-bowel in established CD. Evaluated three FC level cut offs: 50, 100, and 200 µg/g	The cutoff valueof 50 µg/g had a sensitivity of 83% (95% CI, 74% to 90%); specificity of 50% (95% CI, 36% to 64%),and DOR of 5.52 (95% CI, 3.31 to 9.19). The partialAUC of the HSROC was 0.81; At the cutoff value of 100 µg/g, FC had a sensitivity of 73% (95% CI,66% to 78%); specificity of 73% (95% CI, 62% to 81%) andDOR of 7.89 (95% CI, 4.32 to 14.44). The partial AUC of the HSROC was 0.72; At thecutoff value of 200µg/g, FC had a sensitivity of 50% (95% CI, 36% to 63%); specificity of 88% (95% CI, 74% to 95%)and DOR of 7.21 (95% CI, 2.68 to19.37). The partial AUC of the HSROC was 0.58. The highest DOR was observed at 100 µg/g (sensitivity, 0.73; specificity, 0.73; and DOR, 7.89). The studies for patients with suspected Crohn's disease had a sensitivity of 0.75 and specificity of 0.74 (DOR of 8.96). The studies that included only patients with normal ileocolonoscopies	Included retrospective studies along with prospective studies Different definitions of CD on SBCE The criteria used to establish the diagnosis of CD were not identical	Although the sensitivity of the 50 µg/g cutoff was the highest among the three cutoffs, the specificity was relatively low (0.50). A cutoff of 100 µg/g had relatively high sensitivity and specificity, and the DOR was higher than the 50 µg/g cutoff. FC has significant diagnostic accuracy for detecting small bowel inflammation, and an FC cutoff of 100 µg/g can be used as a tool to screen for small bowel Crohn's disease.

Supplementary material

				had a sensitivity of 0.76 and specificity of 0.75 (DOR of 10.07).		
Xiang et al 2021	Systematic review and meta-analysis	Twenty-one studies (1198 patients with suspected or established CD), 2000-2020	Diagnostic accuracy of FC for diagnosis of SBCD or evidence of active inflammation in the small-bowel in established CD. Evaluated three FC level cut offs: 50, 100, and 200 µg/g	Diagnostic accuracy of the disease was calculated for fecal calprotectin values of 50, 100 and 200 ug/g; the sensitivity values were 0.84, 0.66 and 0.45; specificity values were 0.49, 0.74 and 0.87; diagnostic odds ratio were 5, 5 and 5; and area under curve were 0.74, 0.76 and 0.75, respectively. A fecal calprotectin level of 100-140 ug/g for the prediction of relapse had a pooled sensitivity of 0.68, specificity of 0.91, diagnostic odds ratio of 21, and area under curve of 0.77.	Baseline CE studies not scored using the same method such as different scoring systems Separate analysis for patients with suspected or established CD, isolated SBCD or ileocolic CD could not be performed	Capsule endoscopy is effective and FC an adequate surrogate in diagnosing small bowel Crohn's disease and predicting relapse.
Egea-Valenzuela et al 2018	Multicenter, retrospective observational study	410 patients from 12 Spanish hospitals Inclusion criteria: (1) Patients with suspected CD of the SB, matching the International Conference on Capsule Endoscopy criteria. (2) All the patients had undergone a previous lower endoscopy, with no inflammatory lesions.	To develop and validate a scoring index to assess the risk of the patients with suspected Crohn's disease (CD) of the small bowel on the basis of biomarkers	Biomarkers Odds Ratio / points: Fecal calprotectin 10.30 / 10 C-reactive protein 6.00 / 6 Thrombocytosis 2.97 / 3 Anaemia 2.39 / 2 Leukocytosis 1.85 / 2 Erythrocyte sedimentation rate 0.34 / 1 Three risk groups for the diagnosis of CD at SBCE have been established (low, intermediate, and high): - Group A (5 or less points) Sensitivity 13.1 (10.1–18.9), Specificity 47.7 (41.4 54), NPV 42.4 (36.6–48.5), PPV 15.8	Retrospective and observational study; All the patients had undergone a previous lower endoscopy, but in some cases, it was not possible to determine whether ileoscopy had been carried out;	Patients in groups B and C should be referred for CE studies as they have a high risk for presenting inflammatory lesions. CE studies not recommended in patients included in the low risk group.

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		(3) Patients had been investigated before CE including all the required biomarkers (FC, CRP, hemoglobin levels, leukocytes and platelets count, and ESR).		(10.7–22.5), AUC 0.304 (0.244–0.364); Group B (6-15 points) Sensitivity 56 (48.6–63.1), Specificity 57.9 (51.5–64), NPV 63.8 (57.2–70), PPV 49.7 (42.8–56.7), AUC 0.570 (0.513–0.626); Group C (16 or more points) Sensitivity 30.9 (24.5–38.1), Specificity 94.5 (90.8–96.7), NPV 64.7 (59.5–69.3), PPV 80.6 (69.6 88.3), AUC 0.627 (0.522–0.721) In external validation analysis the probability of CD was 15.8%, 49.7%, and 80.6% for the low-risk, intermediate risk, and high-risk groups, respectively.	The three groups are heterogeneous in terms of population. Despite the good rate of positive studies found in the high-risk group, sensitivity is low as a result of false positives.	
Monteiro et al 2015	Retrospectivecohort study	95 patients with suspected Crohn's Disease Group 1: 37 patients not fulfilling International Conference on Capsule Endoscopy criteria; Group 2: 58 patients with 2 or more International Conference on Capsule Endoscopy criteria.	- Lewis Score ≥ 135 at SBCE - Diagnosis of CD	The diagnostic yield of SBCE was lower in group 1 (patients not fulfilling ICCE criteria for suspected CD) compared with group 2 (patients with higher level of suspicion of CD based on ICCE criteria), 18.9% versus 67.2%, respectively. The diagnosis of CD was established in 38 patients (40%): 8 (21.6%) from group 1 and 30 from group 2 (51.7%) (P = 0.003). ICCE criteria Sensitivity 78.9 (62.2–89.9), Specificity 50.9 (37.4–64.2), PPV 51.7 (38.3–64.9), NPV 78.4 (61.3–89.7) and overall diagnostic accuracy 62.1%	Retrospective Single center	LS≥135 as the cutoff value for significant inflammatory activity in patients undergoing SBCE for suspected CD useful to establish the diagnosis of CD. In patients with LS <135, the probability of having CD confirmed on follow up is low.

Supplementary material

				In patients with ICCE criteria + LS ≥135 at SBCE, overall diagnostic accuracy was 80% with a sensitivity, specificity, positive predictive value, and negative predictive value for the diagnosis of CD of 76.3%, 82.4%, 74.4%, and 83.9%, respectively.		

Author, year	**Study type**	**Patient group**	**Key outcomes**	**Key results**	**Limitation**	**Conclusion**
Chen et al 2018	Case-control prospective study	26 patients taking enteric-coated aspirin and 26 healthy controls (control group) recruited between September 2017 and May 2018, were submitted to magnetically controlled capsule endoscopy	Mucosal injury Lanza scores: 0, no visible lesion; 1, mucosal erythema only; 2, 1–2 erosions; 3, several (3–10) erosions; 4, large number (>10) of erosions or ulcers.	In total, 84.6% (22/26) of patients taking enteric-coated aspirin suffered both gastric and small intestinal injuries Gastric and intestinal mucosal injury were significantly associated (Spearman correlation coefficient, 0.662, $P < 0\ 001$). Median gastric Lanza scores 2.50 vs. 1.00 control group ($P <$ 0,001); Small intestinal Lanza scores 1.00 vs. 0.00 control group ($P <$ 0,001)	Single center Possible selection bias	Rates of gastric and small intestinal mucosal injury in patients taking enteric-coated aspirin significantly higher than those in the healthy controls.

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Endo et al 2017	Multicentric prospective cohort	157 consecutive low-dose aspirin users for at least 3 months, negative colonoscopy and esophagogastroduodenoscopy, submitted to CE. Excluded patients taking NSAIDs in the last 3 months	Incidence of small bowel inflammatory lesions assessed with the Lewis score: normal or clinically insignificant change (<135), mild change (between 135 and 790), and moderate or severe change (≥790).	The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of positive FIT results for small bowel mucosal breaks were 0.53, 0.45, 0.61, 0.37, and 0.50, respectively. The NPV of positive FIT results for severe small bowel injury (Lewis score ≥790) was high (0.90).	Time discrepancy between the FIT and the CE One-day FIT allowed	Small bowel evaluation using CE should be considered in FIT-positive low-dose aspirin users

Author, year	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
Kyaw et al 2018	Double-blind, randomized, placebo-controlled trial	84 aspirin users with either occult or overt GI bleeding, no evidence of significant pathology in either the upper tract or colon, and evidence of small bowel damage on CE. Aspirin was continued (100mg id) and subjects were randomized to misoprostol 200 mg 4 times daily or placebo for 8 weeks	Primary endpoint: complete ulcer healing at follow-up CE; Secondary end points: changes in hemoglobin level and number of ulcer/erosions from baseline.	Complete healing of SB ulcers in 12 patients in the misoprostol group (28.6%; 95% CI, 14.9%–42.2%) and 4 patients in the placebo group (9.5%; 95% CI, 0.6% 18.4%), P = 0,026. Reduction in medium number of ulcers or erosions was significantly greater in the misoprostol group (from 6.5 [range, 1–85] to 2 [range, 0–25]) than in the placebo group (from 7 [range, 1–29] to 4 [range, 0-19] (P = 0,005). A significant number of patients still had large erosions or ulcers		Misoprostol was superior to placebo in promoting healing of small bowel ulcers among patients who require continuous aspirin therapy.

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		(42 patients in each arm), when CE was repeated		after 8 weeks of treatment (misoprostol 21%, placebo 29%).		
Taha et al 2018	Randomised, double-blind, placebo-controlled, phase 3 trial	Patients with SB ulcers and evidence of obscure GI bleeding who were taking low-dose aspirin, NSAIDs, or both for a minimum of 4 weeks Randomly assigned (1:1) to receive 200 µg oral misoprostol (50 patients) or placebo (52 patients) four times daily for 8 weeks	Primary endpoint: complete healing of SB ulcers and erosions assessed with CE at baseline and after 8 weeks of treatment.	Complete healing of SB ulcers and erosions at week 8 in 27 (54%) of patients in the misoprostol group and 9 (17%) of patients in the placebo group, p=0,0002.	Single center Aspirin and NSAID were non-enteric coated Excluded patients with severe or unstable systemic diseases	Misoprostol is effective for the treatment of small bowel ulcers and erosions in patients using low-dose aspirin and NSAIDs.
Niikuraet al 2018	Retrospective case-control study	850 patientseligible for inclusion	Prevalence of drug-induced mucosal injuries at small bowel CE	Multivariate analysis: age >65 ys, use of NSAIDs (mainly low dose aspirin), and use of H2RAs significantly associated with an approximately two-fold risk of mucosal injuries at SB CE	Potential selection bias	The use of NSAIDs, mainly low dose aspirin, was significantly associated with an increased risk of small-bowel mucosal injury No significant associations were observed between the use of the drug and small-bowel overt bleeding
Watanabe et al 2015	Multicenter, randomized, double-blind, placebo-controlled trial	38 patients who received 100 mg of enteric-coated aspirin daily for more than 3 months and with more than 3	Primary endpoint: change in the number of mucosal breaks	After 8 weeks of treatment, rebamipide, but not placebo, significantly decreased the number of mucosal breaks (p = 0.046).	Relatively small sample size Exclusion of patients with	High-dose rebamipide is effective for the treatment of low dose aspirin (LDA) induced

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		SB mucosal breaks at CE; Received rebamipide 300 mg (triple dose) 3 times daily (25 patients) or placebo (13 patients) for 8 weeks in a 2:1 ratio and CE was repeated.	from baseline to 8 weeks. Secondary endpoints: complete healing of mucosal breaks at 8 weeks; changes in Lewis score from baseline to 8 weeks.	Rate of complete mucosal break healing in the rebamipide group (32%) tended to be higher than that in the placebo group (7.7%), p = 0.13.	active small intestinal bleeding	moderate to severe enteropathy
Teutsch et al 2021	Systematic review and meta-analysis of randomized controlled trials	18 RCTs included in the quantitative synthesis	NSAID-associated small intestinal injuries comparing mucoprotective drugs (MP), antibiotic and probiotic treatments to placebo, proton-pump inhibitors (PPIs) or histamine-2 (H2) receptor antagonists. Main outcomes were mucosal integrity, mucosal breaks after treatment, mucosal injury improvement and complete healing	MP medications administered preventively reduced the number of mucosal erosions (weighted mean difference = −1.24, CI: −2.15 to −0.34) and significantly lower chance of developing mucosal breaks after treatment (OR = 0.38, CI: 0.16–0.93). MP therapy associated with a higher rate of complete healing of mucosal breaks (OR = 5.39, CI: 2.79–10.42).	RCTs used different NSAIDs, interventions and controls with different dosages Small sample sizes and short follow-up periods Some RCTs had crossover design Most of the studies conducted in Asia. Moderate risk of bias and high heterogeneity within studies.	MP treatment administered with NSAIDs can prevent and reduce small intestinal mucosal lesions

Supplementary material

			of mucosal breaks			

Supplementary material

Author, year	Study Objective	Participants/ Setting	Intervention	Comparisons	Outcome	Study Type	Results	Conclusion	Quality assessment (for RCTS)*
Eliakim et al 2020	to compare the correlation and reliability of the novel PillCam Crohn's score with the existing small bowel capsule Lewis inflammatory score.	54 PillCam Crohn's studies (41 patients)	Eliakim score	Lewis score	Correlation between scores	Randomized Clinical trial	The median LS was 225 for both readers. The median PillCam Crohn's score was six (0-14) and four (3-15) for readers 1 and 2, respectively. There was a high inter-rater reliability coefficient between the two readers for Lewis inflammatory and PillCam Crohn's score (0.9, $p < 0.0001$ for both). The correlation between PillCam Crohn's score and fecal calprotectin was stronger than for Lewis inflammatory score ($r = 0.32$ and 0.54 respectively, $p = 0.001$ for both).	The novel panenteric capsule score correlates well with the Lewis inflammatory score, has excellent reliability, and may be potentially more accurate in estimation of the panenteric inflammatory burden	
Melmed et al 2018	to assess the correlation between changes in CE scores compared with the Physician Global Assessment (PGA) as well as the validity and responsiveness of serial CE, as compared with ileocolonoscopy, regardless	74 Crohn's disease patients	CE	ileocolonoscopy	Correlation between endoscopic scores and clinical parameters	Prospective, cohort study	The SES-CD ileocolonoscopy score correlated with the Lewis score ($P < .001$, $\rho = .59$) and CECDEIS capsule score ($P = .002$, $\rho = .48$). None of the 3 endoscopic scores correlated with PGA, CDAI, HBI, C-reactive protein, erythrocyte sedimentation rate, or fecal calprotectin. Approximately 85% of subjects had proximal small-bowel inflammation identified on CE.	There was high correlation between CE and ileocolonoscopy scores for the assessment of mucosal disease activity over time; however, there were no correlations between endoscopic scores and	

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	of medical therapy							clinical parameters.	
Yablecovitch et al 2018	to compare the quantitative evaluation of small- bowel inflammation by LS and CECDAI.	50 CD patients	Lewis score	CECDAI	Correlationbetwn scores	Prospective cohort study	There was a moderate correlation between the worst segment LS and CECDAI (Pearson's r = 0.66, p = 0.001), and a strong correlation between C-LS and CECDAI (r = 0.81, p = 0.0001). CECDAI < 5.4 corresponded to mucosal healing (LS < 135), while CECDAI > 9.2 corresponded to moderate-to-severe inflammation (LS ⩾ 790). There was a moderate correlation between capsule scores and FCP levels (r = 0.39, p = 0.002 for LS, r = 0.48, p = 0.001 for C-LS, and r = 0.53, p = 0.001 for CECDAI, respectively). CRP levelswerenotsignificantlycorrelated with either score.	CECDAI and C-LS are strongly correlated and perform similarly for quantitative assessment of mucosal inflammation in established CD.	
Nishikawa et al 2021	To investigate prognostic predictors in patients undergoing capsule endoscopy and determined the optimal LS cut-off value	102 patients	clinical course and the patients' characteristics, Crohn's Disease Activity Index, laboratory findings, LS, and Prognostic Nutritional Index (PNI) for factors potentially		clinical outcomes according to these factors	Retrospective, cohort	LS ≥ 270 and PNI < 45 were identified as independent predictors of Crohn's disease-related emergency hospitalization with hazard ratios of 9.48 and 3.01, respectively. Even in patients with LS ≥ 270, cumulative hospitalization rates decreased after intervention based on capsule endoscopy findings. The prospective study confirmed that patients with LS ≥ 270 or PNI < 45 had a significantly higher risk of Crohn's disease-related	LS and PNI are the best available prognostic predictors in patients with Crohn's disease without gastrointestinal stenosis and can guide decisions on treatment escalation.	

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			associated with Crohn's disease-related emergency hospitalization				emergency hospitalization and that additional treatment reduced the risk of relapse.	Patients with LS ≥ 270 and PNI < 45 were at increased risk for exacerbation, and additional treatments should be considered for this group.	
He et al 2017	To explore the correlations between LS and clinical disease activity indices, CRP, SBTT in pediatric, and adult patients with small bowel CD	120 CD patients	CE	Harvey-Bradshaw	correlations between LS and clinical disease activity indices	Retrospective, single-center study	Weak correlations were found between LS and HBI, (r1 = 0.213; P1 = .019). Correlation between LS and CRP was moderate (r = 0.326; P < .001). Strong correlations were found between CRP and HBI (r1 = 0.522 P < .001).	The role of capsule endoscopy should be emphasized both in pediatric and adult patients with small bowel CD	
Santos-Antunes et al 2015	To analyze therapeutic changes in Crohn's disease (CD) patients following video capsule endoscopy (VCE) and to assess the usefulness of Lewis score and the	106 patients	CE		the impact of VCE findings on the therapeutic management of CD patients and to evaluate the utility of the Lewis score	Cohorts, retrospective	VCE determined changes in the treatment of 40% of patients: 21% remained free of immunosuppressors after VCE compared to 44% before VCE (P < 0.001). The differences in therapy before and after VCE achieved statistical significance in the Staging and Flare groups. A higher Lewis score was associated with therapeutic modifications (P < 0.0001); where a score higher than	VCE significantly changed the therapeutic management of CD patients, even in those with long-term disease.	

Supplementary material

	Patency Capsule						1354 was related to 90% probability of changing therapy [area under the receiver operative characteristic (AUROC) 0.80 (95%CI: 0.69-0.88)].		

Supplementary material

Author, year	Study Objective	Participants/ Setting	Intervention	Comparisons	Outcome	Study Type	Results	Conclusion	Quality assessment (for RCTS)*
Elosua et al 2022	To evaluate therapeutic impact of SBCE in an 11-year real-life cohort of known CD patients	432 CE	VCE		The change in CD-related treatment recommended based on SBCE results.	Cohort, retrospective	A change of management was guided by SBCE in 51.3% of procedures: 199 (46.1%) escalation and 23 (5.3%) de-escalation, with significant changes in all groups. Escalation increased with disease activity: 57.8% in mild and 89.5% in moderate-to-severe disease. De-escalation was conducted in 13.9% procedures with mucosal healing and 1.1% with mild disease.	SBCE is a useful tool for guiding therapeutic management in CD patients both for treatment escalation and de-escalation	
Nishikawa et al 2021	To investigate prognostic predictors in patients undergoing capsule endoscopy and determined the optimal LS cut-off value	102 patients	clinical course and the patients' characteristics, Crohn's Disease Activity Index, laboratory findings, LS, and Prognostic Nutritional Index (PNI) for factors potentially associated with Crohn's disease-related emergency hospitalization		clinical outcomes according to these factors	Retrospective, cohort	LS ≥ 270 and PNI < 45 were identified as independent predictors of Crohn's disease-related emergency hospitalization with hazard ratios of 9.48 and 3.01, respectively. Even in patients with LS ≥ 270, cumulative hospitalization rates decreased after intervention based on capsule endoscopy findings. The prospective study confirmed that patients with LS ≥ 270 or PNI < 45 had a significantly higher risk of Crohn's disease-related emergency hospitalization and that additional treatment reduced the risk of relapse.	LS and PNI are the best available prognostic predictors in patients with Crohn's disease without gastrointestinal stenosis and can guide decisions on treatment escalation. Patients with LS ≥ 270 and PNI < 45 were at increased risk for exacerbation, and additional treatments should be	

Supplementary material

								considered for this group.	
Tai et al 2021	To examine the role in the assessment of disease severity and extent by a comparison with existing clinical and biochemical markers.	71 patients with established CD	Panenteric capsule	CRP, calprotectine	Changes in Montreal classification, mucosal healing	Multicenter, observational	The use of capsule resulted in management change in 64.6% (32/48) of patients with an established diagnosis . Montreal classification was upstaged in 33.8% of patients with established Crohn's disease and mucosal healing was demonstrated in 15.5%. Proximal small bowel disease upstaged disease in 12.7% and predicted escalation of therapy (odds ratio 40.3, 95% confidence interval 3.6-450.2). Raised C-reactive protein and faecal calprotectin were poorly sensitive in detecting active disease (0.48 and 0.59 respectively).	The ability to detect proximal small bowel disease may allow better estimation of prognosis and guide treatment intensification. Panenteric capsule endoscopy may be a suitable non-invasive endoscopic investigation in determining disease activity and supporting management decisions	
Le Berre et al 2019	To investigate the impact of SBCE in a treat-to-target strategy in patients with CD	47 papers reviewed	VCE		Correlation between activity indexes, disease reclassification, evaluation of mucosal healing, detection of postoperative recurrence	Systematic review	Good correlation between indexes. SBCE useful for disease reclassification, with a significant incremental diagnostic yield compared to other diagnostic modalities. Nine studies also demonstrated that the mucosal healing can be evaluated by SBCE to monitor the effect of medical treatment in patients with CD. SBCE can detect post-operative	SBCE could be incorporated in the treat-to-target algorithm for patients with CD.	

Supplementary material

							recurrence to a similar extent as ileocolonoscopy, and proximal SB lesions that are beyond the reach of the colonoscope in over half of the patients.		
Ben-Horin et al 2019	To evaluate the accuracy, safety, and tolerability of an intensive monitoring strategy designed to predict the future course of Crohn's disease in patients with quiescent disease	61 patients	VCE	MRE, biormarkers	The ability of the different Crohn's disease monitoring methods used to predict the occurrence of a flare during the 24-month follow-up period.	Prospective, observational	No clinicodemographic parameter predicted future flare. A baseline VCE Lewis score of 350 or more identified patients with future flare (area under the curve [AUC] 0·79, 95% CI 0·66-0·88; p<0·0001; hazard ratio 10·7, 3·8-30·3). C-reactive protein at baseline had an AUC of 0·73 (0·6-0·84; p=0·0013) for predicting flare. The AUC of baseline faecal calprotectin for the prediction of flare occurring within 2 years was 0·62 (0·49-0·74; p=0·17), but progressively improved for shorter timespans and reached an AUC of 0·81 (0·76-0·85) for the prediction of flare occurring within 3 months. Of four MRE-based indices, only MRE global score correlated with 2-year flare risk (AUC 0·71, 0·58-0·82; p=0·024). During follow-up, a Lewis score increase of 383 points or more from baseline predicted imminent disease exacerbation within 6 months (AUC 0·79, 0·65-0·89; p=0·011)	In patients with quiescent Crohn's disease involving the small bowel, faecalcalprotectin predicts short-term flare risk, whereas VCE predicts both short-term and long-term risk of disease exacerbation	

Supplementary material

Yablecovitch et al 2018	to compare the quantitative evaluation of small-bowel inflammation by LS and CECDAI.	50 CD patients	Lewis score	CECDAI	Correlationbetwn scores	Prospective cohort study	There was a moderate correlation between the worst segment LS and CECDAI (Pearson's r = 0.66, p = 0.001), and a strong correlation between C-LS and CECDAI (r = 0.81, p = 0.0001). CECDAI < 5.4 corresponded to mucosal healing (LS < 135), while CECDAI > 9.2 corresponded to moderate-to-severe inflammation (LS ⩾ 790). There was a moderate correlation between capsule scores and FCP levels (r = 0.39, p = 0.002 for LS, r = 0.48, p = 0.001 for C-LS, and r = 0.53, p = 0.001 for CECDAI, respectively). CRP levelswerenotsignificantlycorrelated with either score.	CECDAI and C-LS are strongly correlated and perform similarly for quantitative assessment of mucosal inflammation in established CD.	
Niv 2017	to determine whether mucosal healing assessment by CE may serve as a predictor of clinical remission in patients with Crohn's disease.	5 studies, 142 patients	CE		Mucosalhealing	Meta-analysis	The mucosal healing CE score was found to be significantly associated with improved outcome after a follow-up of 12 weeks to 24 months, with an odds ratio of 11.06 (95% confidence interval: 3.74-32.73, P<0.001). The degree of heterogeneity among the studies was small (Q=2.014, d.f.[Q]=3, P=0.569 and I=0). Endoscopy scores may play a role in the long-term prognostic evaluation of patients with Crohn's disease	This review suggests that the CECDAI score may be predictive of long-term clinical remission and may therefore serve as an essential tool in the management of CD	
Kopylov et al 2015	to evaluate the prevalence of mucosal healing and	56 patients	CE		Small bowelinflammation	Observational, prospective	SBMH was demonstrated in 8/52 (15.4%) of patients in clinical remission. Moderate-to-severe SB inflammation was demonstrated in 11/52 (21.1%)	SB inflammation is detected in the majority of CD patients in	

Supplementary material

	deep remission in quiescent CD						of patients in clinical remission and in 1/21 (4.7%) of patients in clinical and biomarker remission. Only 7/52 (13.5%) patientswere in DR	clinical and biomarker remission. SBMH and DR were rare and were independent of treatment modality. Our findings represent the true inflammatory burden in quiescent patients with SBCD	

Supplementary material

Author, year	Study Objective	Participants/ Setting	Intervention	Comparisons	Outcome	Study Type	Results	Conclusion	Quality assessment (for RCTS)*
Servais et al 2021	To compare the value of intestinal ultrasonography (US) coupled with contrast agent injection with that MRE in the assessment of small bowel CD activity using surgical histopathology analysis as reference. ESTABLISHED CD	17 CD patients	CEUS & MRE	MRE vs histopatologic findings CEUS vs histopatologic findings	Disease activity	Cohort study, prospective	The median wall thickness (CEUS) differed significantly between patients with non-severely active CD and those with severely active CD [7.0 mm, IQR (6.5–9.5) vs 10.0 mm, IQR (8.0–12.0), respectively; p = 0.03]. The area under the ROC curve (AUROC) of the wall thickness assessed by US and MRE to identify patients with or without severely active CD on surgical specimens were 0.85, 95% CI (0.64–1.04), p = 0.03 and 0.80, 95% CI (0.56–1.01), p	The accuracy of intestinal CEUS is close to that of conventional US to detect disease activity. A thickened bowel and shortened time to peak and rise time were the most accurate to identify CD patients with severe histological disease activity.	

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							= 0.07, respectively. Among the param-eters derived from the time-intensity curve during CEUS, time to peak and rise time were the two most accurate markers [AUROC = 0.88, 95% CI (0.70–1.04), p = 0.02 and 0.86, 95% CI (0.68–1.04), p = 0.03] to detect patients with severely active CD assessed on surgical specimens		
Pous-Serrano et al 2017	To assess the accuracy of magnetic resonance enterography in predicting the extension, location and characteristics of the small bowel segments affected by	38 CD patients	MRE	MRE vs surgical & pathological findings	Detection of disease	Cohort, prospective	During surgery, 12 lesions (14.8%) not described on MRE were found. MRE had 90% accuracy in detecting the location of the stenosis (75.0% sensitivity,	MRE is a useful tool in the preoperative assessment of patients with Crohn's disease. However, a thorough intra-operative exploration of the entire	

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	Crohn's disease. ESTABLISHED CD						95.7% specificity). Accuracy for detection an inflammatory phlegmon (46.2%), but it was more accurate in detecting abscesses or fistulas (accuracy 89.9% and 98.6%, respectively).	small bowel is still necessary.	
Tai et al 2021	To determine the feasibility, safety and impact on patient outcomes of panenteric capsule endoscopy in routine clinical practice ESTABLISHED+ SUSPECTED	93 CD patients (71 with established CD)	Panenteric capsule endoscopy	Impact of panenteric capsule compared to clinical&biochemical markers	Management change. Montreal classification	Multicenter observational	Panenteric capsule resulted in management change 64.6% (32/48) of patients with an established diagnosis whose disease was active, Montreal classification was upstaged in 33.8% of patients with established Crohn's disease. Proximal small bowel disease upstaged disease in 12.7% and	Panenteric capsule endoscopy was feasible in routine practice and the ability to detect proximal small bowel disease may allow better estimation of prognosis and guide treatment intensification ..	

Supplementary material

							predicted escalation of therapy (odds ratio 40.3, 95% confidence interval 3.6-450.2		
Bruining et al 2020	Accuracy and safety of panenteric CE in Crohn's disease ESTABLISHED CD	158 patients	PEC	IC and MRE	Accuracy parameters	Clinical Trial	Overall sensitivity for active enteric inflammation (CE vs MRE and/or IC) was 94% vs 100% (p=0.125) and specificity was 74% vs 22% (p=0.001). Sensitivity of CE was superior to MRE for enteric inflammation in the proximal small bowel (97% vs 71%, p=0.021), and similar to MRE and/or IC in the terminal ileum and colon (p=0.500-0.625).	PEC demonstrates high performance of the panenteric CE as compared to MRE and/or IC without the need for multiple tests in non-stricturing Crohn's disease.	

Supplementary material

Nehra et al 2020	To determine the importance of ileal inflammation at CTE or MRE in CD patients with normal ileoscopy. ESTABLISHED CD	112 CD patients with imaging findings suggesting inflammation & negative ileoscopy. 88 CD patients with negative ileoscopy and ileal biopsy	Cross-sectional studies (MRE or CTE)	Negative ileoscopy		Retrospective Cohort	50% of patients with negative biopsy had moderate/severe inflammation at enterography, with 45%, 32% and 11% having proximal small bowel inflammation, stricture or fistulas, respectively.	Crohn's disease patients with unequivocal imaging findings of ileal inflammation at enterography despite negative ileoscopy and biopsy are likely to have active inflammatory Crohn's disease.	
González-Suárez et al 2018	To compare MRE and (CE) for the assessment of Crohn's disease (CD). The secondary objectives were to compare the diagnostic accuracy of both CE modalities and changes in Montreal classification after each examination.	47 patients with established (n = 32) and suspected CD (n = 15)	MRE	VCE	Diagnostic yield	Cohort Prospective	CE detected more patients with lesions than MRE (87.5% vs 56.2%, respectively, P = 0.01). Results by segments: jejunal inflamma-tion was detected by CE in 37.5% of patients and by MRE in 9.4% of patients (12/32 vs 3/32; P = 0.01); lesions	CE was significantly superior to MRE for detecting SB lesions, mainly superficial and proximal lesions. CE is useful for an appropriate patients' classification according to Montreal classification.	

Supplementary material

	ESTABLISHED+SUSPECTED						in the ileum were detected in 68.7% of patients by CE, and in 28% of patients by MRE (22/ 32 vs 9/ 32; P = 0.01). Finally, in terminal ileum, CE showed lesions in 78.1% (25/32) of patients, whereas MRE detected lesions in 46.9% (15/32 patients), (P = 0.005). Regarding the Montreal classification, the original classifi-cation was changed in 46.8% of patients (15/32) after CE and in 15.6% of patients (5/32) based on MRE findings (P < 0.05)		
Lang et al 2015	To evaluate the diagnostic benefit of small bowel	347 MR examinations	MR enteroclisis or MRE		diagnostic yield, significant additional	Cohort, retrospective	In every second patient, new relevant	MRE and MRY presented high	

Supplementary material

	MRI in Crohn's disease according to Montreal Classification, in routine practice. ESTABLISHED CD				information, and alterations in the assessment of disease behaviour and location		diagnostic information was provided. Incorporation of the MRI results caused significant shifts in Montreal Classification, specifically higher L-levels [+21.2%; $p < 0.05$] and higher B-levels: [+24.6%; $p < 0.05$].	diagnostic yields, often detected significant additional information, and significantly caused shifts in Montreal Classification, both techniques are confirmed to be excellent tools in diagnosing and monitoring Crohn's disease in its daily course.	
Kopylov et al 2015	To evaluate the impact and safety of VCE on the clinical management of patients with established CD. ESTABLISHED CD	187 patients	VCE	Inflammatory biomarkers	VCE diagnostic accuracy and correlation ofelevated biomarkers (FCP, CRP, and combination) with significantSB inflammation (LS.790).	retrospective, multicenter, cross-sectional study	No SB inflammation was observed in 28.4%, mild-to-moderate inflammation in 26.6%, and moderate-to-severe inflammation in 45% of the patients. A change in management was recommended in 52.3% of patients based	VCE results often have a significant clinical impact. VCE should not be limited to CD patients with positive inflammatory markers because their predictive value for significant SB inflammation is poor	

Supplementary material

							on VCE findings. Elevated C-reactive protein, fecal calprotectin, or the combination of both were poorly correlated with significant SB inflammation.		
Kopylov et al 2017	To compare the diagnostic yield (DY) of CE to MRE and SICUS in detection and monitoring of SB CD through SUSPECTED +ESTABLISHED	112 studies	MRE, VCE, SICUS	MRE, VCE, SICUS	Diagnostic yield	meta-analysis	The DY of CE for detection of active SB CD was similar to that of MRE (10 studies, 400 patients, OR 1.17; 95% CI 0.83–1.67) and SICUS (5 studies, 142 patients, OR 0.88; 95% CI 0.51–1.53). CE was superior to MRE for proximal SB CD (7 studies, 251 patients, OR 2.79; 95% CI 1.2–6.48); the difference vs SICUS was not significant	CE, MRE and SICUS have similar DY for detection of SB CD in both suspected and established CD. CE is superior to MRE for detection of proximal SB disease.	

Supplementary material

Taylor et al 2018	Accuracy for assessing disease extent and activity ESTABLISHED CD	248 patients	MRE	IUS	per-patient difference in sensitivity between MRE and ultrasound for correct identification and localisation of small bowel Crohn's disease	RCT	The sensitivity of MRE for small bowel disease extent (80% [95% CI 72–86]) and presence (97% [91–99]) were significantly greater than that of ultrasound (70% [62–78] for disease extent, 92% [84–96] for disease presence); a 10% (95% CI 1–18; p=0·027) difference for extent, and 5% (1–9; p=0·025) difference for presence. The specificity of MRE for small bowel disease extent (95% [85–98]) was significantly greater than that of ultrasound (81% [64–91]); a	Both MRE and ultrasound have high sensitivity for detecting small bowel disease presence and both are valid first-line investigations, and viable alternatives to ileocolonoscopy.	

Supplementary material

							difference of 14% (1–27; p=0·039). The specificity for small bowel disease presence was 96% (95% CI 86–99) with MRE and 84% (65–94) with ultrasound (difference 12% [0–25]; p=0·054). There were no serious adverse events		
Greener et al 2016	to examine whether VCE or MRE performed after the initial diagnosis may alter the original disease classification ESTABLISHED	79 underwent MRE and in 56 VCE was also performed	VCE	MRE	Changes in disease extension/localization	Clinical trial	Previously unrecognized disease locations were detected with VCE and MRE in 51 and 25%, respectively ($p < 0.01$) and by both modalities combined in 44 patients (55%). 22 (27%) were reclassified as having an advanced phenotype (B2/B3).	VCE and MRE may lead to reclassification of the original phenotype in a significant percentage of CD patients in remission. VCE was more sensitive for detection of previously unrecognized locations, while MRE was superior for detection	

Supplementary material

							MRE and VCE reclassified the phenotype in 26 and 11% of cases, respectively ($p < 0.05$). Overall, both modalities combined altered the original Montreal classification in 49/76 patients (64%).	of phenotype shift. The described changes in the disease classification may have an important impact on both clinical management and long-term prognosis in these patients	

Author, publication, year	**Study design**	**Study objective**	**Participants**	**Intervention / Comparison**	**Outcomes**		**Results/Conclusion**	**Level of evidence**	**Remarks**
Rondonotti et al 2016	Prospective Observational Multicenter	Analyze SBCE retention rates in low risk and high-risk patients (after negative patency capsule, CT or MRE)	3117 patients Low risk: 2942 p (94.4%) High risk: 175 p (5.6%) 1% only with established Crohn's Disease	Compare SBCE retention rates in high-risk patients after patency or radiologic techniques (CT&MRE)	Retention rate: 1. Low risk patients: 0.7% (20 pts) 2.High-risk patients: Patency 151/175 (86.3%) CT or MRE 24/175 (13.7%) Retention: 1.7% (3pts: 2 previous	<u>Retention rate after</u> Patency vs radiologic techniques 1/151 (0.7%) vs 2/24 (8.3%)	Patency capsule seems more effective than radiologic techniques preventing capsule retention in high-risk patients	Low	Patients with OGIB, CD and other diagnosis included! high-risk patients (obstructive symptoms, previous surgery, suspected stenosis on imaging

Supplementary material

					CT and 1 previous patency)				methods, etc.)
Rezapour et al 2017	Meta-analysis andsystematic review	Evaluate SBCE retentionrate	25 studies (n=5876p) 11 studies in established IBD patients (n=558p)	SBCE retentionrate in established IBD patients	Retention rate: 8.2% (95% CI, 6.0%-11.0%) Patients submitted to MRE and/or CTE or patency capsule were excluded	Retention rates after patency capsule or CT/MR enterography: 2.7% patients (95% CI, 1.1%-6.4%). Probably suspected+ established	SBCE retention rate was 8.2% in established CD patients, higher than previously reported Performing a patency capsule study or CTE/MRE decrease retention rate	High	
Silva et al 2019	Prospective Single center (2015-2017)	- Patency capsule retention in established CD -FP rate RFIT scanner 30 hrs - CT for location of patency	54 patients with established CD	Retention rate of patency capsule after RFIT scanner (after 30 hrs) & CT	Retention rates: -20% after RFIT (11 patients) -9% after patency +CT (5 patients) CT identified 6 patency capsules in colon		False positive retention rates with RFIT may be avoid. CT can be used to localize retained capsule	Low	Only established CD patients!
Nemeth et al 2016	Retrospective Multicenter	Evaluate capsule retention in 2 groups: selective	406 patients Established CD. -Patency capsule in 274 pts	Selective patency (180 pts) vs non-selective (162 pts)	SBCE retention rate:	Selective vs non-selective retention rate: 1.3 vs	- Risk of SBCE retention was notreducedbythe non-selectivestrategy	Low	

Supplementary material

		(obstructive symptoms or abdominal surgery) or non-selective patency capsule administration	-SBCE without patency in 132 pts		-Without patency: 1.5% -Prior patency: 2.1% (p=0.9)	1.6% (p=0.9)	- SBCE retentionrateafter a positivepatency test was associated a high risk of retention		
Nakamura et al 2021	Prospective Multicenter	-Evaluate SBCE retention after a negative patency test. -Identify factors related to SBCE retention	-1096 pts Patients with suspected or established SB strictures -366 pts with established CD	Patency capsule test + SBCE	Patency test in study population: -Positive: 133/1096 (12.1%) -Negative: 963/1096 (88%) Patency test in established CD: -Positive: 76/366 (20.8%) -Negative: 290/366(79.2%)	SBCE retention rate in study population : 5/963 (0.5%) SBCE retention rate in Established CD after negative patency test: Established CD: 3/290 (1%) Suspected CD: 0%	Appropriate PPC evaluation contributed to safer SBCE examinations in patients with suspected small bowel stenosis.		
González-Suárezet al 2018	Retrospective Observational	compared VCE and MRE for diagnostic	47 pts with CD (32 pts established CD; 15 pts suspected CD)	To evaluate gastrointestinal patency (SBCE retention	SBCE performed in 47 patients	MRE found strictures in 10/47 patients	Intestinalstricturesmaybeoverestimatedby MRE	Low	mixed group of suspected and

Supplementary material

		yield and assessment of CD		risk) by MRE prior to PC and VCE		(prior to SBCE). These pts underwent patency capsule with negative results and then a successful SBCE was performed.			established CD patients excludes pts with previous history of previous known intestinal stricture! evaluate gastrointestinal patency (VCE retention risk) by MRE prior to PC and VCE wasn´t the aim of the study
Pasha et al 2020	Meta-analysis	Toevaluate SBCE retentionrate in CD patients (suspected + established) Adult + pediatric population	35 studies suspectedandestablished CD adult andpediatric CD patients	Toevaluate SBCE retention in establishedadults CD pts	Retention rate: -Total Cohort: 3.32% (95% CI, 2.62%–4.2%; 35 studies) -Established CD: 4.63% (95% CI, 3.42%–	Retention rate: -After SB imaging (CT or MRE): 2.32% (95% CI, 0.87%–6.03%; 4 studies)	Patientswithestablished CD were 3.4 times more likelytoexperienceretentionthan those withsuspected CD Confirmsutility of patency capsule and cross-sectional imaging in lowering SBCE retention	High	

Supplementary material

					6.25%; 32 studies) -Suspected CD: 2.35% (95% CI, 1.31%–4.19%; 16 studies)	-After patency capsule: 2.88% (95% CI, 1.74%–4.74%; 15 studies)			

Author, year	Study design	Study objective	Participants	Intervention/ Comparison	Outcomes	Outcomes	Results/Conclusion	Level of evidence
Mitsui et al 2016	Retrospective Cohort study 5 yrs FU	-Effective of DBE for retrieval SBCE -Adverse events -Rate of surgery for strictures where SBCE are retained	12 pts	DBE or Surgery	91.6% (11/12) successful retrieved 75% (9/12pts) non-surgery in 5 years No AE		-Retrieval of SBCEs using DBE had a high success rate -75% patients with small bowel stricture did not require surgery through FU	Low
Lee HS et al 2019	Retrospective Multicenter	Outcomes for capsule retention	2705 pts. SBCE retention: 20 pts (0.7%) 11/169 CD (6.5%) 2/140 NSAIDs No patency capsule	Medical treatment Endoscopic treatment Surgery	Medical treat: 9/20 (45%) Endoscopic treat: 6/20 (30%) Spontaneous 3/20 (15%) Steroids 2/20 (10%)	Predictive fc surgery or endoscopic treatment: Abdominal symptoms	75% pts were managed with endoscopic or surgical intervention, particularly those with abdominal symptoms after retention	Low
Nemeth et al 2017	Retrospective Single center (2001-2011)		2401 pts	Treatment of capsule retention	Emergency treatment: 20% (5/25 cases ; 2	Elective treatment: 80% Surgery: 6p	80%	Low

Supplementary material

			25 capsule retention (1%)		surgery and 3 endoscopy)	Endoscopy: 8 p Spontaneous: 3 p Steroid:3 p	patients can be electively managed with non-surgical	
Gao et al 2020	Systematic review Retrospective studies	Use of DBE for retrieval of retained capsule	12 studies 150 pts	Double balloon enteroscopy	Pooled retrieval success rate was 86.5% (95% confidence interval [CI], 75.6–95.1%) with significant heterogeneity (I2 47.4%, p .034)	Factors associated higher success: -Anterograde approach (62/83 [74.7%] vs. 10/38 [26.3%], p<.001 -Malignant strictures (21/21 [100.0%]vs 65/83 [78.3%] p .043) SAE: 2 SB perforations	DBE is a reliable and safe method for removing retained capsules DBE could decrease the need for surgery and facilitate surgery for those with malignant strictures.	High??

Author, year	**Study design**	**Study objective**	**Participants**	**Intervention/ Comparison**	**Outcomes**	**Outcomes**	**Results/Conclusion**	**Level of evidence**
Nemeth et al 2016	Retrospective Multicenter	Evaluate capsule retention in 2 groups: selective (obstructive symptoms or abdominal surgery) or non-selective patency capsule administration	406 patients Established CD. -Patency capsule in 274 pts -SBCE without patency in 132 pts	Selective patency (180 pts) vs non-selective (162 pts)	SBCE retention rate: -Without patency: 2.3% -Prior patency: 2.1% (p=0.9)	Selective vs non-selective retention rate: 1.3 vs 1.6% (p=0.9)	Risk of SBCE retention was notreducedbythe non-selectivestrategy SBCE retentionrateafter a positivepatency test was associated a high risk of retention	Low
Rondonotti et al 2016	Prospective Observational Multicenter	Analyze SBCE retention rates in low risk and high-risk patients (after negative patency capsule, CT or MRE)	3117 patients Low risk: 2942 p (94.4%) High risk: 175 p (5.6%) 1% only with established Crohn's Disease	Compare SBCE retention rates in high-risk patients after patency or radiologic techniques (CT&MRE)	Retention rate: 1. Low risk patients: 0.7% (20 pts) 2.High-risk patients: Patency 151/175 (86.3%)	Retention rate after Patency vs radiologic techniques 1/151 (0.7%) vs 2/24 (8.3%)	Patency capsule seems more effective than radiologic techniques preventing capsule retention in high-risk patients In high-risk patients, negative radiologic explorations doesn't exclude capsule retention	Low

Supplementary material

					CT or MRE 24/175 (13.7%) Retention: 1.7% (3pts: 2 previous CT and 1 previous patency)			
Rezapour et al 2017	Meta-analysis andsystematic review	Evaluate SBCE retentionrate	25 studies (n=5876p) 11 studies in established IBD patients (n=558p)	SBCE retentionrate in established IBD patients	Retention rate: 8.2% (95% CI, 6.0%-11.0%) Patients submitted to MRE and/or CTE or patency capsule were excluded	Retention rates after patency capsule or CT/MR enterography: 2.7% patients (95% CI, 1.1%-6.4%). Probably suspected+ established	SBCE retention rate was 8.2% in established CD patients, higher than previously reported Performing a patency capsule study or CTE/MRE decrease retention rate	High
Pasha et al 2020	Meta-analysis	Toevaluate SBCE retentionrate in CD patients (suspected + established) Adult + pediatric population	35 studies suspectedandestablished CD adult andpediatric CD patients	Toevaluate SBCE retention in establishedadults CD pts	Retention rate: -Total Cohort: 3.32% (95% CI, 2.62%–4.2%; 35 studies) - Established CD:	Retention rate: -After SB imaging (CT or MRE): 2.32% (95% CI, 0.87%–6.03%; 4 studies)	Patientswithestablished CD were 3.4 times more likelytoexperienceretentiont han those withsuspected CD Confirmsutility of patency capsule and cross-sectional imaging in lowering SBCE retention	High

Supplementary material

					4.63% (95% CI, 3.42%–6.25%; 32 studies) -Suspected CD: 2.35% (95% CI, 1.31%–4.19%; 16 studies)	-After patency capsule: 2.88% (95% CI, 1.74%–4.74%; 15 studies)		
Kopylov et al 2016	Retrospective Multicenter Case series	Symptomaticretention of patency capsule	20/1615 pts (1.5%) -19 SB -1 esophagus (schatsky ring) 30% suspected CD 65% established CD 5% mesentericisquemia	Evaluate cases of symptomaticretention of patency capsule	Surgery 5% Spontaneous 65% Steroids therapy 25%		Symptomatic patency capsule retention is a rare complication with a favorable prognosis.	Low
Silva M et al 2019	Prospective Single center (2015-2017)	- Patency capsule retention in established CD -FP rate RFIT scanner 30 hrs - CT for location of patency	54 patients with established CD	Retention rate of patency capsule after RFIT scanner (after 30 hrs) & CT	Retention rates: -20% after RFIT (11 patients) -9% after patency +CT (5 patients) CT identified 6 patency capsules in colon		False positive retention rates with RFIT may be avoid. CT can be used to localize retained capsule	Low

Supplementary material

Author, year	Study design	Study objective	Participants	Intervention/ Comparison	Outcomes	Outcomes	Results/Conclusion	Level of evidence
Fernández-Uriénet al 2015	Retrospective Multicenter	To evaluate incidence, clinical outcomes and therapeutic approaches of CE-related AEs	5428 procedures	Adverse events	Retention rate 1.8% (104/5428) More frequent in IBD patients 61.5% asymptomatic retention 25% abdominal pain	Resolution: 64% non- surgical: -Spontaneous passage 37% -Medical therapy 20% -DBE 7%	Capsule retention without acute obstructive symptoms should be managed conservatively whenever possible.	Low
Juan Du et al 2015	Retrospective Case-control	To evaluate capsule retention and risk factors	204 capsules in CD patients	Retention rate Risk factors	Retention rate: 8.3% (17/204)	Resolution: -23.5% (4/17): IQ for obstruction -70.5% (12/17) spontaneous passage after medical treatment -1 still retained	Most of the patients with SBCE retention can excrete the capsule endoscopy after medical conservative treatment	Low
Mitsui et al 2016	Retrospective Cohort study 5 yr FU	-Effective of DBE for retrieval SBCE -Adverse events -Rate of surgery for strictures where SBCE are retained	12 pts	DBE or Surgery	91.6% (11/12) successful retrieved 75% (9/12pts) non-surgery in 5 years No AE		-Retrieval of SBCEs using DBE had a high success rate -75% patients with small bowel stricture did not require surgery through FU	Low
Nemeth et al 2017	Retrospective Single center (2001-2011)	To investigate incidence, causes, risk factors, management and clinical outcomesof capsule retention	2401 pts 25 capsule retention (1%)	Treatment of capsule retention	Emergency treatment: 20% (5/25 cases; 2 surgery and 3 endoscopy)	Elective treatment: 80% Surgery: 6p Endoscopy: 8 p Spontaneous: 3 p Steroid:3 p	80% patients can be electively managed with non-surgical intervention	Low
Han et al 2018	Retrospective	To analyze risk factors for surgery	5348 consecutive patients	Evaluate risk factors for surgery	1.4% (77/5348p) capsule	Finally, Surgery: 64.9% (50/77)	1.Asymptomatic patients. Medical treatment	Low/moderate?

Supplementary material

		in patients with capsule retention			retention. 46/77 CD patients. Spontaneous passage: 20.8% (16/77) DBE: 18% (14/77)	Factors associated: -Intestinal obstruction - Overt SB bleeding Protective factors: -Medical treatment - Successful endoscopic retrieval	2.Slight abdominal pain: DBE 3.Intestial obstruction or bleeding: Surgery	
Lee HS et al 2019	Retrospective Multicenter	Outcomes for capsule retention	2705 pts. SBCE retention: 20 pts (0.7%) 11/169 CD (6.5%) 2/140 NSAIDs No patency capsule	Medical treatment Endoscopic treatment Surgery	Medical treat: 9/20 (45%) Endoscopic treat: 6/20 (30%) Spontaneous 3/20 (15%) Steroids 2/20 (10%)	Predictive fc surgery or endoscopic treatment: Abdominal symptoms	75% pts were managed with endoscopic or surgical intervention, particularly those with abdominal symptoms after retention	Low
Gao et al 2020	Systematic review Retrospective studies	Use of DBE for retrieval of retained capsule	12 studies 150 pts	Double balloon enteroscopy	Pooled retrieval success rate was 86.5% (95% confidence interval [CI], 75.6–95.1%) with significant heterogeneity (I2 47.4%, p .034)	Factors associated higher success: -Anterograde approach (62/83 [74.7%] vs. 10/38 [26.3%], p<.001 -Malignant strictures (21/21 [100.0%]vs 65/83 [78.3%] p .043) SAE: 2 SB perforations	DBE is a reliable and safe method for removing retained capsules DBE could decrease the need for surgery and facilitate surgery for those with malignant strictures.	High

Supplementary material

Author, publication, year	Study design	Study objective	Participants	Intervention/ Comparison	Outcomes	Outcomes	Results/Conclusion	Level of evidence
Monteiro et al 2017	Retrospective Multicenter	Role of SBCE in the Re-classification of IBDU	36 patients with IBDU	Lewis Score	LS>135: 9p(25%) CD LS<135: -16 UC (44%) -1CD (2.7%) -10 IBDU (27%)	Lewis Score: Sens 90% Spec 100% PPV 100% NPV 94%	Absence of significant inflammatory activity in the small intestine (Lewis Score) allowed exclusion of CD in 94% of cases.	Low
Han et al 2018	Retrospective Cohort	Recurrence of CD after 1 year of Ileocolonic resection with no profilaxis. If recurrence: medical treatment and evaluation in 1 yr	83 pts included Group 1: IC+SBCE 37 pts Group 2: IC 46 pts Evaluation of recurrence 1 yr later	Group 1: IC+SBCE Group 2: IC	Group 1: Recurrence identified 24/37 pts (13 SBCE+IC; 11 SBCEonly) Group 2: Recurrence in 15/46 pts Those with recurrence started pharmacological prophylaxis	Recurrence in 1 yr: Group 1: 2.7% (1/37) Group 2: 21.7%	If endoscopic remission identified by ileocolonoscopy was confirmed by CE, patients could remain free of pharmacologic prophylaxis. If recurrence outside the scope of ileocolonoscopy was detected by CE, initiation of active pharmacologic therapy would be needed.	Low
Kusaka et al 2018	Prospective Cohort	Effect of residual lesions after surgery on postoperative recurrence	27 patients	Patency first 25pts negative patency test 25 SBCE 3 months after surgery	20/25 complete SBCE studies 84% residual lesions	5/25 presented postoperative recurrence in 10 months Higher incidence in pts with lesions in third tertile	Many cases with CD have residual inflammatory lesions immediately surgery. These residual lesions in the distal small intestine, were associated withpostoperativeclinicalrecurrence	Low
Hausmann et al 2017	Prospective Multicenter	Evaluation of postoperative recurrence with panenteric	22 patients	D1.-PICE 4-8 weeks after surgery D2.-PICE + IC 6-2 months after surgery	D1:3/16 disease activity (19%) D2: -PICE: 6/12 (50%) -IC: 5/15 (33%)		Pan-intestinal capsule endoscopy seems to be feasible in the postoperative surveillance of Crohn's disease. Detect lesions in SB with impact in clinical recurrence	low

Supplementary material

		capsule (PICE)						
Jung et al 2021	Meta-analysis and systematic review	Accuracy of CE,MRE &US for post-operative recurrence	14 studies		Sensitivity, specificity for: SBCE: 100%, 69% MRE: 97%, 84% US: 89%,86%		CE, MRE, and US provide accurate assessment of postoperative endoscopic recurrence in CD	High
Shiga et al 2022	Prospective	to assess the postoperative activity using CE. Start treatment based on findings	105 patients	2 groups: CE group: 48 pts Patency first 42 CE Non-CE group: 57 pts 3 months/follow up	3 months: 85.7% (36/42) pts with inflamm activity 8 months: 79.2% (19/24) inflammatory activity	-CE group had significantly fewer primary outcomes -Multivariate analysis: CE group as an independent protective factor (hazard ratio = 0.45, 95% CI = 0.20–0.96)	Postoperative repeated CE enables to assess residual and recurrent lesions accurately before clinical symptoms.	High?

Supplementary material

Task force 3 - Inherited polyposis syndromes and suspected small bowel tumours
Keuchel **(Leader)**, Saurin, Vlachou, Tacheci

Author, year	**P (patient, problem, population**	**I (intervention)**	**C (comparison, control)**	**O (outcome)**	**limits**
Kazuhitoet al 2022	37 FAP patients	Retrospective analysis 13.8 yrs median FU after surgery	-	15 cancers, 2 duodenal cancers No distal SB cancer	
Sekiya et al 2021	8 pts with FAP	Retrospective analysis, DAE, 72 sessions, 77.5 months period	-	1237 polyps 11 SAE (15 %, 7 bleeding, 4 pancreatitis) 1 intramucosal duodenal cancer Median 6 DBE/pts, median 81 pol/pt; median 99 min/procedure (32-210)	No precision of the length of SB examined, no distinction of jejunal versus duodenal polyp
Matsumotoet al 2016	41 FAP pts, 1-43 yrs after colectomy (excluding 7 with obstructive symptoms within 1 year)	Prospective evaluation of CE after positive patency evaluation	-	Retention 3 cases (7 %), no pain. 1 advanced SB lesions (Treitz ligament, 25 mm, intra mucosal cancer) No distaladvancedlesion	Exclude patients with obstructive symptoms

Author, year	**Study design**	**Participants**	**Intervention**	**Outcomes**	**Results**	**Comments**
Han et al 2015	retrospective, comparative, multi-centre study	79 patients with small-bowel tumour diagnosis, 10 % patients with polyposis, hamartomas 33 %	CT, SBFT, SBCE as diagnostic methods (in 32 patients all procedures) , DBE and histology in 65 patients	Diagnostic yields of SBFT, CT, and SBCE for small bowel tumours (using DBE as reference)	Diagnostic yield: CT: 56 %, SBFT: 46 %, SBCE: 83 % sensitivity CT: 40 %, SBFT: 44 %, SBCE: 80 %	

Supplementary material

Author, year	Study design	Participants	Intervention	Outcomes	Results	Comments
Sulbaran et al 2016	Meta-analysis	15 comparative studies, 821 patients	Device Assisted Enteroscopy (DBE, SE, SBE) vs SBCE	sensitivity, specificity, positive and negative likelihood ratio for the diagnosis of small-bowel polyps and tumours (DAE) rates of diagnostic concordance and discordance between DAE and SBCE	DAE: sensitivity: 0.89 (95% CI 0.84–0.93) specificity: 0.97 (95 %CI 0.95–0.98) positive likelihood ratio: 17 (95 %CI 3.74–73.82) negative likelihood ratio: 0.14 (95 %CI 0.05–0.35) 93 % concordance rate between DAE and SBCE	20 cases detected by SBCE - missed by DAE 16 cases missed by SBCE – detected by DAE CE complete examinations: ranged from 68 %to 91 % DAE complete examination: ranged from 17 % to 70 %

Author, year	Study design	Participants	Intervention	Outcomes	Results	Comments
Faggian et al 2016	retrospective study	67 patients with a clinical suspicion of intestinal neoplasia	MRE (2 readers) followed (in positive cases) by surgery, SBCE, colonoscopy or enteroclysis after 6 months	sensitivity, specificity, for the diagnosis of small-bowel polyps and tumours	malignant neoplasms: 17 cases benign lesions: 2 leiomyomas, 1 adenoma, 3 hamartomas sensitivity (MRE, reader 1 and 2): 88 % and 92 %, specificity (MRE, reader 1 and 2): 93 % and 98 %	agreement between the readers, with a κ value > 0.9 for MR enteroclysis

Author, year	Study design	Participants	Intervention	Outcomes	Results	Comments
Belsha et al 2016	prospective, single-centre study	16 PJS patients with small-bowel polyps (diameter ≥ 15 mm) diagnosed by means of SBCE	polypectomy of the 45 small-bowel polyps in 14 PJS patients: DBE (11 patients) or laparoscopy-assisted DBE (in 3 high-risk large polyps)	small bowel polyp clearance, confirmed by SBCE or MRE and clinical symptoms during follow-up period (1–60 months,	polyps: 14% duodenum, 69% jejunum, 16% ileum, polyps ≥ 10 mm confirmed in 14 patients, successful clearance of polyps ≥ 10 mm	one complication: pelvic abscess after the laparoscopy assisted DBE

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				median: 26 months)	achieved in all patients, all patients (except one complicated case) were asymptomatic during follow-up	
Perrodet al 2020	retrospective, single-centre study	25 PJS patients	polypectomy of the 216 small-bowel polyps (SE, DBE, PE) based on the SBCE (42 in 23 patients) or MRE (23 in 14 patients) screening	complete treatment rate: the absence of residual polyps ≥ 1 cm detected at initial screening	complete treatment rate in 19 patients (SE, DBE, PE): 76% in 16 % indicated IOE (4 cases) and surgical resection in 8 % (2 cases) complications rate (DAE): 6 % (delayed bleeding: DBE, acute pancreatitis: SE), no complications during IOE or surgical resection	IOE improved the complete treatment rate by 16 % (92% clearance of the residual small bowel polyps ≥ 1 cm by combined approach)
Cortegoso Valdivia et al 2020	retrospective, single-centre study	24 PJS patients	polypectomy of the 247 small-bowel polyps during DAE (47) or IOE (9) based on the SBCE, MRE, CTE, SB series/ enteroclysis, size of the small bowel polyps: 5 – 60 mm, 181 (73 %) ≥ 15 mm	safety and impact on the reduction of the polyp burden, complication rate during follow-up (108 months)	small bowel polyp-related complications requiring emergent surgery in 2 (9 %) patients during follow-up, complications rate: 6 patients - 13 % (9 % during DAE: pneumothorax, minor intraprocedural bleeding, 22 % during IOE: minor	3 deaths during the follow-up period (13 %): all related to extra-GI neoplasms (lung, pancreatic, and ovarian cancers)

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					intraprocedural bleeding, delayed perforation)	
Wang et al 2019	retrospective, single-centre study	97 PJS patients	320 DBE (185 oral, 135 anal approach), 1661 small bowel polys resected 45 patients hospitalized > twice, 12 patients > thrice	the maximum size and number of the resected polyps, reduction of the maximum size of the resected polyps during time	maximum size of the resected polyps significantly smaller during 2nd hospitalization (vs 1st hospitalization): antegrade DBE: P = 0.012; retrograde DBE: P = 0.03 and significantly larger (vs 3rd hospitalization): antegrade DBE: P = 0.012; retrograde DBE: P = 0.048. complications rate: 4 % (delayed bleeding perforation, intussusception, transmural syndrome)	total enteroscopy rate 58 %

Author, year	Study design	Participants	Intervention	Outcomes	Results	Comments
Goverde et al 2017	prospective, comparative study	15 PJS patients	MRE and proximal DBE	identification of significant small bowel	significant polyps identified by MRE and/or	significantly more pain during preparation for MRE than for

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			within 20 weeks endoscopistsblinded to the MRE results	polyps (≥ 15 mm) sensitivity of methods	DBE 80% patients no significant difference in the detection of polyps (38 by MRE vs. 50 by DBE, P=0.37). Sensitivity 62% (38/61) for MRE, 82% (50/61) for DBE	DBE (moderate vs. no pain, P=0.02) periprocedural pain comparable (both mild, P=0.89).

Author	P	I	C	O	Design
Pérez-Cuadrado Robles et al 2015	89 pts with SBT, of them 28 had SBT distal of Treitz diagnosis at DBE	Bleeding indication	Other indication	19 bleeding 1 diarrhea 8 obstructive symptoms	Retrospective, single center
Chung et al 2018	103 pts with >SBT /1070 DBE procedures	malignant SBT	Benign SBT	Age Malignant SBT 62.2 ± 15.6 years benign SBT 50.7±21.4 y, p < 0.01	Retrospective multicenter
		Indication		Bleeding (43.7%), abdominal pain (40.8%) and ileus (10.7%)	
Wang et al 2021	1291 consecutive patients with 1531 DBE s (1375 diagnostic and 156 therapeutic)	Duodenum/Jejunum	Ileum	of CD was the ileum (199/236, 84.3%), while that of tumours was the proximal small bowel (duodenum and jejunum, 115/164, 70.1	Retrospective, single center
		SSBB	pain	The diagnostic yields for occult gastrointestinal bleeding (SSBB) and abdominal pain were 57.3% and 52.4%,	

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		< 45 years	≥ 45 years	%). In the young group (< 45 years), the majority of patients had CD, whereas tumours were the most common disease in the older group (≥ 45 years).	
Zhang et al 2020	1102 pts. with DBE and diagnosis SBT	Bleeding indication 44.4%	Pain indication 39.4 %	Further symptoms with pain e.g. weight loss not mentioned	Retrospective, single center
Tang et al 2018	DBE	Bleeding indication	Pain indication	120/596 malignant SBT (20.1%) 9 / 369 malignant SBT (2.4%)	Retrospective, single center
Fujita et al 2015	558 consecutive pts undergoing US before SBCE/DBE	Ultrasound	SBCE/DBE	Sensitivity of US for SBT >20mm 91.7% (44/48) SBTs <20mm was only 14.3% (7/49)	Retrospective, single center
Yoo et al 2021	438 pts. with 510 SBCEs and 126 DBEs	SBCE/ DBE	CT	28/438 SB malignant tumour 27/28 (96.4%) pos. CT findings Abdominal pain and obstructive symptoms were the most common findings in metastatic cancers (4/5, 80%). SSBB most common symptom of GIST (6/7, 85.7%) and adenocarcinoma (3/8, 37.5%).	Retrospective, single center
Chen et al 2016	729 DBE procedures	SBT	Crohn´s	SSBB: 24.9% - SBT 20.9% Crohn´s Abdominal pain: Crohn´s 61.8	retrospective
Chu et al 2016	27 SBTs (121 total)	SBCE	CTE DBE	Miss rate CE 38.9%, DBE 16.7% CE 52.4%, CTE 33.3% CE 50%, CTE 50% DBE 25%	retrospective
Iwamuro et al 2015	110 pts with GI involvement in	Enteroscopy DAE or SBCE	No enteroscopy	No significant difference in WHO or Lugano grading	Retrospective multicenter Japan

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	follicular lymphoma				
Miura et al 2018	51 pts with NHL involving GIT undergoing SBCE or DBE	19 pts with involvement of duodenal bulb or terminal ileum	32 pts without involvement	SB lesions in 13 / 19 pts. with involvement (68.4%) 6 /32 (18.8%) without involvement of bulb or TI	Retrospective, single center Japanese
Maruyama et al 2021	190 pts with GI lymphoma 29 with whole GI investigation	Single lesion (GI segment)	Overlap lesions (>1 GI segment involved)	SB lesions were found in 25 (13.2%) cases: 9 (5.5%) cases in the single lesion group and 16 (64.0%) in the overlap group 32 patients underwent BAE or CE, (7 pathol. Imaging, 7 SSBB, 18 screening)	Retrospective, single center
Noujaim et al 2017	16 pts. Treated surgically for SB NET	SBCE 12/16	Other diagnostic modalities	Diagnostic SBCE 10/12 (83.3%) CT 5/8 to 62.5% colonoscopy 21.4% (3/14) Deep enteroscopy44% (4/9), EGD 0% (0/9)	Retrospective, single center (87.5%) of pts presented with either occult gastrointestinal bleeding or anaemia
Manguso et al 2018	85 Sb NET	DBE	Other modalities	sensitivity 59.7% for CT, 54% for MRI, 56% for SRI, 88.1% for DBE.	Retrospective, single center
Ethun et al 2016	93 pts. With resected SB NET	SBCE	DBE Octreoscan	45% had octreoscans (85% diagnostic yield); 11% had SB-enteroscopy (10% yield); 19% had capsule endoscopy (83% yield but identified the correct tumour number in only 21%).	Single center cohort
Rossi et al 2021	6 pts with suspected NET undergoing DBE	DBE (3 antegrade, 2 retrograde, 1 combined)	Surgery	DBE: Sensitivity 60%	Single center, prospective cohort
Gangi et al 2018	85 pts with SB NET included	Single SB NET	Multifocal SB NET	Multifocality has no impact on survival or recurrence outcomes (primary study aim)	Single center cohort study with prospectively maintained database

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				Secondary: %). Of DBE patients, 28 (62.2%) had additional lesions identified, of which 23 (82.1%) had NET confirmed on pathology	
Furnari et al 2017	24 pts with Hepatic NET metastasis without localization of primary	16 SBCE	16 Laparotomy	Sensitivity=75%; Specificity=37.5%; PPV=55%; NPV=60%	Retrospective, single center
Nakano et al 2017	25 pts with GIST undergoing DBE	DBE	none	The diagnostic result of biopsy was 46.7% (7/15), detected by antegrade approach in 91.3%.	Retrospective, single center
Martinez et al 2021	10 pts with SB GIST	DBE	none	5/9 biopsies positive	Retrospective, single center
Zhou et al 2018	32 pts. with surgically resecte4d SB GIST (R0)	Clinical follow-up	none	No endoluminal recurrence during follow-up (3 -54 months, mean 30 months)	Retrospective, single center
Zhang et al 2020	1102 pts. undergoing 1140 DBEs – 99 SBT	DBE	CTE	Of 99 SBTs, 33 were not found by CTE while DBE had positive findings. Using CTE and MRI, nine malignant SBTs and three benign polyps were diagnosed, whereas DBE and CE had negative findings.	Retrospective, single center
Tomba et al 2016	24 complicated coeliac cases / 1000 controls	DBE		2 adenocarcinomas, 1 NET (all with IDA)	Retrospective, bi-centric (Milano/Sheffield)
Perez-Cuadrado-Robles et al 2018	189 pts with unresponsive coeliac disease or additional alarm symptoms	SBCE	none	7 SB lymphomas (confirmed in 5/7 cases by biopsy and 1 NET (confirmed) detected	Retrospective multicenter
Ferretti et al 2020	130 pts. with suspected	SBCE	DBE	25 patients with premalignant/malignant	Prospective cohort

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	complicated coeliac disease			lesions: 12 type 1 refractory CD (RCD-1), 7 type 2 RCD (RCD-2), 6 EATL	
Zammit et al 2021	60 pts with RCD	SBCE	none	5 pts with ulcerative jejuno-ileitis, 3 EATL	2 Centers, retrospectively
Awadieet al 2021	101 pts with duodenal adenoma (10-80mm)	SBCE	SBCE in 100 controls (for SSBB or IDA)	No SB polyps in both groups. More colonic adenomas in pts. with duodenal adenomas	Single center prospective
Simon et al 2017	101 pts with longstanding SB disease without resection > 10 years	Surveillance enteroscopy	none	2 cases with Indeterminate small bowel dysplasia SB Adenocarcinoma was confirmed in one after surgical resection. With an at least 1-year follow-up duration, two additional cases of SBA were identified in patients who underwent surgery for obstruction, resulting in a 33% sensitivity rate for SBA endoscopic screening prevalence of dysplasia and SBA on CD was 4%.	Prospective cohort, 10 centers
Baba et al 2020	29 (0f 169) with SB rebleeding	Rebleeding (n=29)	No rebleeding	Risk factors in univariate analysis: chronic kidney disease, vascular lesion, and overt previous bleeding	Retrospective, single center
Otani et al 2018	359/652 pts with negative CE and repeat SB investigation for ongoing bleeding /anaemia	CE (n=41)	DBE (n=48)	CE 5 tumours (total pos. findings 30/41 73.2%) DBE 5 tumours (total pos. 19/48 (39.6%)	Retrospective, single center
Perez-Cuadrado Robles et al 2018	2311 pts undergoing SBCE	SBCE	none	Polyp/mass $\geq$ 75 years: 37 (6.13%) < 75 years: 88 (5.62%) p 0.650	Retrospective, single center

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He et al 2014	532 Chines patients with SSBB	SBCE or SBE	none	erosions/ulceration (27.1%) Mass lesion (19.4%) and angiodysplastic/vascular lesions (13.9%). Most common etiology per age 21-40-years: erosions/ulceration (27.1%) 41-60-years: Mass lesion >60 years: vascular lesions	Retrospective, single center

Author, year	**Type**	**Patient group**	**Key outcomes**	**Key results**	**limitations**	**Conclusion**
Benmassaoud et al 2018	Retrospective study	453 patients that underwent BAE for various indications	To quantify local diagnostic and therapeutic yields of BAE in patients with suspected small bowel diseases.	Amongst patients with CD or suspected tumour evaluation, the presence of SBCE or imaging prior to the enteroscopy tended towards increased diagnostic yield, but was not statistically significant (69.7% versus 48.7%, p=0.07). The diagnostic yield improved with suspected small bowel neoplasia (OR: 2.45; 95% CI, 1.06–5.65) The therapeutic yield increased with suspected small bowel neoplasia (OR: 6.97; 95% CI, 2.90–16.77) The impact of BAE on the management of the patient was not significantly higher in patients with a pre-endoscopic diagnosis of suspected small bowel neoplasia (OR: 1.73; 95% CI, 0.83– 3.57),	• retrospective nature. •the impact of BAE on the management of patients was determined retrospectively using the procedural reports, making this a posteriori analysis. •Data in patients that were BAE-naïve so it may not reflect the overall clinical course of a patient with multiple balloon enteroscopies.	SB investigations prior to BAE showed a trend towards increased diagnostic yield. Suspected small bowel neoplasia was related with increased diagnostic and therapeutic yield of BAE, nevertheless BAE did not have higher impact on the management of patients with a pre-endoscopic diagnosis of suspected SB neoplasia.

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Chen et al 2016	Retrospective	674 patients that underwent DBE	to evaluate the diagnostic and therapeutic value of double balloon enteroscopy (DBE) in small bowel diseases (SBDs) in China.	Small bowel tumours were detected in 18.8%, of patients (127/674) yielding a positive detection rate of 81.1% (104/127)	single center study the selection of patients may have been biased in many aspects. patients with endoscopic treatment relatively few compared to diagnostic DBE.	A total of 40 cases of small bowel tumours had the CE examination with the detection rate of 84.6%, comparable to DBE (81.1%, P>0.05)
Johnston et al 2017	retrospective	1949 patients that underwent CE	to determine the frequency, indications and diagnostic work-up of patients with small bowel malignancy found by capsule endoscopy	There were 7 cases of SB tumours diagnosed by CE. The median age was 50 years (range 34 – 67). 4 patients had prior to CE, CT CAP that were normal or non-diagnostic. The most common indication for CE was IDA (71.4% Malignancy was diagnosed more frequently in younger patients (≤ 55y) with IDA (3 of 312 CE cases, 0.96 %) compared with those older than age 55 years (2 of 682 CE cases, 0.29 %)	retrospective design and the fact that information on follow-up was only available for a limited number of patients	SB tumours are a rare diagnosis on CE for IDA. Nevertheless, in this study it was mor frequently observed in younger patients that were investigated for IDA.
Calabrese et al 2015	Retrospective, single-center study, based on prospective database	Consecutive patients that underwent CE for occult gastrointestinal bleeding during 2004–2014 (n=849)	To characterize frequency, clinical and laboratory signs, endoscopic findings related to SB tumours detected in patients who underwent CE.	SB tumours were detected in 75 patients (8.8 %). The most frequent tumours were adenocarcinomas (n=14; 18.7 %), gastrointestinal stromal tumours (GIST) (n=9; 12 %), and lymphoma (n=5; 6.7 %) Benign neoplasms included dysplastic adenomatous polyps (n=27; 36 %). Non-neoplastic lesion included an inflammatory	Retrospective study No distinctive information regarding history and/or symptoms prior to CE	CE detected SB tumours in 75/78 patients (70.5 %) and identified only active bleeding in two patients (2.6 %) that were

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				polyp (n=1) and hyperplastic polyps (n=19; 25.3 %).		diagnosed by surgery. CE failed to find any lesion in only 1 patient (1.3 %) that was diagnosed by SBE. The SSBB was occult in 69 patients (92 %) and overt in 6 (8 %). The percentage of tumours found is 6.5 %, higher than in other CE series, which may be explained by well-defined diagnostic criteria according to the authors.
Chu et al 2016	Retrospective study	121 patients who underwent capsule endoscopy, DBE and/or CTE before or after CE at Ruijin Hospital (between July 2007 and July 2014) with the indication of SSBB. CE was	To evaluate the complimentary value of CTE and DBE combined with CE in the diagnosis of obscure gastrointestinal bleeding (SSBB).	The overall diagnostic yield of CE was comparable with DBE (73.9% versus 60.9%) but was significantly higher than the yield of CTE (87% versus 25%, $p<$ 0.001) Specifically regarding SB tumours, CE detected tumours in 15/27 cases (sensitivity 55.6%, 95% confidence interval [CI] 35.3%–74.5%; specificity 100%, 95% CI	Retrospective comparative study, and the subjects investigated were patients who underwent CE plus CTE and/or DBE procedures; thus they were not a true representation of the population with SSBB. The study design likely resulted in selection bias of patients with small bowel diseases that were indicated for combination of several techniques for diagnosis.	The diagnostic yields of CE and DBE were comparable in patients with SSBB, which were significantly higher than

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		performed in all patients; CTE and DBE were performed in 100 (82.6%) and 46 (38.0%) of the patients, respectively.		96.2%–100%), CTE was positive in 15/21 cases (sensitivity 71.4%, 95% CI 47.8%–88.7%; specificity 97.5%, 95% CI 91.2%–99.7%), and DBE identified tumours in 15/17 cases (sensitivity 88.2%, 95% CI 63.6%–98.5%; specificity 100%, 95% CI 88.1%–100%).	Among those patients who underwent DBE, not all patients received total balloon enteroscopy, which led to underestimated yield of DBE procedure as compared with CE. The CE, CTE, and DBE procedures were not performed in a fixed sequence, and the order of CE and DBE tests could affect their diagnostic yields. Twenty-five patients received all three examinations in this study, and SBT was diagnosed in 12 of them. CE and CTE each detected 6/12 tumours (sensitivity 50%; 95% CI 21.1%–78.9%), and DBE found 9/12 tumours (sensitivity 75%; 95% CI 42.8%–94.5%).	the yield of CTE. CE proved to be superior in the detection of angiodysplasia. The three approaches showed comparable performances in the identification of small bowel tumours. DBE and CTE identified small bowel diseases undetected or undetermined by CE. Conversely, CE improved diagnosis in the cases with negative CTE and DBE, and positive findings at initial CE directed further diagnosis made by DBE. Combination of the three

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						diagnostic platforms in a properly integrated manner based on individual patient conditions provides complementary value in the diagnosis of SSBB. Twenty-five patients received all three examinations in this study, and SBT was diagnosed in 12 of them. CE and CTE each detected 6/12 tumours (sensitivity 50%; 95% CI 21.1%–78.9%), and DBE found 9/12 tumours (sensitivity 75%; 95% CI 42.8%–94.5%).
Deepak et al 2019	Retrospective study	All mpCTEs performed between January 1, 2006, and December 31, 2014, for suspected	To estimate the diagnostic yield and efficacy of multiphase computed	A definitive diagnosis of small bowel bleeding was established in 340 patients (31.3%) through surgical, endoscopic, angio-graphic, or pathologic findings. In	retrospective nature of the study with selection bias, a heterogeneous clinical population, and a	Overall sesnsitivity and PPV of mpCTE in the setting of

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		small bowel bleeding (n=1087)	tomographic enterography (mpCTE) for suspected small bowel bleeding. The reference standard for a definitive diagnosis of small bowel bleeding was defined as a finding on endoscopy, angiography, surgery, or pathology that could cause small bowel bleeding.	this cohort, 165 patients had their definitive cause of small bowel bleeding identified on mpCTE, 56 had indeterminate findings, and 119 did not have the lesion identified at mpCTE, resulting in an overall sensitivity of 58.1% (165 of 284; 95% CI, 50.0%-66.0%). For patients who had a positive finding on mpCTE as well as a definitive diagnosis, the over- all PPV was 88.2% (165 of 187; 95% CI, 83.0%- 92.0%). The highest sensitivity and positive predictive value of CTE were for small bowel masses (90.2% [55 of 61] and 98.2% [55 of 56], respectively) *especially for age <40 years old (see table 2) +3 for sensitivity & PPV	heterogeneous reference standard, probably due to the wide spectrum of diagnoses that cause GI bleeding. The original test interpretations were performed by multiple abdominal radiologists with varying experience, which may have affected the study results. Another potential limitation is verification bias, although it was minimized by using more than one method to verify mpCTE results such as information derived from surgical, endo- scopic, angiographic, or pathologic data.	suspected SB bleeding were 58.1% (165/284) and 88.2% (165/187) respectively. The highest sensitivity and positive predictive value of CTE were for small bowel masses (90.2% [55 of 61] and 98.2% [55 of 56], respectively)
Dohan et al 2018	Prospective	17 patients that underwent VE for suspected SBT	To evaluate the feasibility, tolerance and performance of virtual enteroscopy (VE) using carbon dioxide for small-bowel distension in patients with suspected small-bowel tumours (SBTs)	On a per-patient analysis, the sensitivity, specificity, PPV, NPV, accuracy and Youden index of VE for SBT >5 mm were 92% (95% CI: 65–99), 80% (95% CI: 38–96), 92% (95% CI: 65–99), 80% (95% CI: 52–94), 88% (95% CI: 61–97) and 72% (95% CI: 44–89), respectively. On a per-lesion analysis, the sensitivity and PPV of VE was 92.0% (95% CI: 76–98) and 92.0% (95% CI: 76–98), respectively	limited number of patients standard of reference was not blinded.	VE is a feasible and well-tolerated technique with high sensitivity and specificity for the diagnosis of SBT.

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Dohan et al 2016	retrospective	The MR-enterography studies of 19 patients with 27 pathologically confirmed NETSB were blindly reviewed.	To determine the sensitivity of MR-enterography for the detection of neuroendocrine tumours of the small-bowel (NETSB) and analyze the imaging presentation of NETSB on MR-enterography	On a per-patient basis, MR-enterography had an overall sensitivity of 95% (18/19; 95%CI: 74-100%) for the detection of NET. On a per-lesion basis, overall sensitivity for NET detection was 74% (20/27; 95%CI: 54-89%). Regarding detection of NET ≥10 mm, the sensitivity was 94% (15/16; 95%CI: 70%-100%). Regarding detection of NET < 10 mm, the sensitivity was 45% (5/11: 95%CI: 17%-77%). Seven NETs in three patients were not visible on MR-enterography; they had a mean diameter of 5.2 mm ± 2.5 (SD) [range: 3 - 15 mm].	All patients had surgery so only patients with resectable NETs were included and that patients with unresectable NETs were excluded. It is thus assumable that the MR imaging presentation may be different in a more general population. Inclusion of patients with confirmed NET, so that the issue of specificity and accuracy was not addressed because of the absence of control subjects without NET. retrospective design of the study, Absence of comparison between MR-enterography with other imaging techniques.	MR-enterography shows highly suggestive features for the diagnosis of NETSB and has high degrees of sensitivity for the diagnosis of NETSB on a per-patient basis. Significantly lower sensitivity for lesions <10mm
Yung et al 2017	retrospective, multicentrestudy	220 young patients (□50 years) from 18 centres/12 countries, with negative bidirectional gastrointestinal (GI) endoscopy undergoing SBCE for IDA	to estimate the diagnostic yield (DY) of SBCE for SB pathology – in particular, the prevalence of SB neoplasia – in a large cohort of young patients (age □50 years) with IDA and negative bidirectional GI endoscopy. Also to assess possible predictive factors	Among the 220 patients, 71 had a positive CE (DY 71/220; 32.3%). patients with neoplastic SB pathology (10/220; 4.5%), and non-neoplastic albeit clinic- ally significant CE findings (61/220; 27.7%). In the patients with neoplasia, 6/10 had undergone computed tomography (CT) or magnetic resonance (MR) imaging prior to CE with no pathology yield (hence the investigation with CE).	retrospective study design high-volume or tertiary referral centres, which would therefore have taken a disproportionate number of complex patients or those suspected of having sinister pathology. MCV was used as a marker of iron deficiency in anaemic patients, although drawbacks exist to the use of MCV to quantify iron deficiency.	overall DY of SBCE for clinically significant findings was 32.3%. 4.5% of our cohort was diagnosed with SB neoplasia

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			associated with the occurrence of significant SB pathologies.			
Segarajasingam et al 2015	Randomized controlled study	80 patients undergoing either CE (n=40) or PE(n=40) for SSBB	To evaluate diagnostic yields and downstream clinical outcomes comparing video capsule endoscopy (SBCE) with push enteroscopy (PE).	Diagnostic yield for SB tumours/polyps was 17.2% for CE and 5.3% for PE (P=0.22)		CE had a higher diagnostic yield than PE for detection of SB tumours/polyps
Lim et al 2015	Retrospective study	A total of 2,914 CE examinations in the capsule registry from October 2002 to September 2012	To estimate the indications for and detection, completion, and retention rates of small intestine CE based on the 10-year data from the Korean Capsule Endoscopy Registry.	Small bowel tumours were detected in 278/2914 (9.5%) CE examinations. The overall capsule retention rate was 3% (90/2,914). The rate was high in patients with small bowel tumours (5.7%) and Crohn's disease (3.4%)	This is a retro- spective analysis. There might be differences in interpretation of CE findings between institutions. Data were selected from the registry, therefore selection bias is possible.	Small bowel tumours were detected in 278/2914 (9.5%) CE examinations. In the present study, small bowel tumours were identified as high-risk factors for capsule retention (5.7%).

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						Nevertheless, previous history, symptoms of SB obstruction, previous imaging and assessment of SB patency are not mentioned.
Rezapour et al 2017	Systematic review and metanalysis	systematic review of 33 studies consisting of 8,513 patients undergoing video capsule endoscopy		Small-bowel neoplasms were present in 17 (17%) of cases and were due to neuroendocrine tumour in 1 (6%) case, lymphoma in 2 (11.8%) cases, metastases from endometrial cancer in 1 (6%) case, and adenocarcinoma in 7 (41%) cases.	lack of systematic approach to SBCE retentions causes of stricture were not listed in many of the studies. There was lack of randomization in all the studies which lowered the overall study quality The majority of the analyses demonstrated a high degree of heterogeneity between studies based on I^2 values.	SBCE retention rates varied from 0-7%. Using a random effects model, the pooled retention rate was 2.1% (95% CI 1.5-2.8%, p=0.000) Small-bowel neoplasms were present in 17 (17%) of cases and were due to neuroendocrine tumour in 1 (6%) case, lymphoma in 2 (11.8%) cases, metastases from endometrial cancer in 1

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						(6%) case, and adenocarcinoma in 7 (41%) cases.
Fujita et al 2015	Retrospective	558 consecutive patients who underwent ultrasonography before capsule endoscopy and/or balloon-assisted endoscopy. Ninety-seven tumours (52 benign, 45 malignant) detected by capsule endoscopy and/or balloon-assisted endoscopy were retrospectively analyzed.	the usefulness of ultrasonography in the detection of small bowel tumours.	The sensitivity and specificity of ultrasonography in the detection of small bowel tumours were 50.5% (47/93) and 100% (465/465), respectively. If we restricted patients to those with a tumour>20 mm in size, its detection ratio would become higher (91.7%): the ratio of submucosal tumour>20mm in size was 85.7% (6/7) and that of partial and circumferential ulcerative tumours> 20 mm in size was 96.9% (31/32), respectively. Small bowel tumours detected by ultrasonography (mean 33.2 mm) were significantly larger than those undetected by ultrasonography (mean 8.7 mm). The percentage of small bowel tumours located in the ileum detected by ultrasonography (70.6%) was significantly higher than those undetected by ultrasonography (29.4%). Of the 46 small bowel tumours undetected by ultrasonography, 42 (91.3%) were benign tumours with good clinical prognosis.	the detection rate of SBTs in asymptomatic patients has been unclear The correlation between US operator experience and the rate of SBT detection is unclear excluded patients unable to undergo CE and/or BAE after US. Inclusion of these patients may have increased the sensitivity and specificity of US. Fourth, SBT detectability by US examination was not compared with detectability by CT and/or MR. Small number of patients	sensitivity and specificity of ultrasonography in the detection of small bowel tumours were 50.5% (47/93) and 100% (465/465), respectively and especially higher for ulcerative lesions >20mm. Those that were not detected were mostly benign lesions
Gangi et al 2018	retrospective	178 patients with SBNET were identified from our prospectively maintained database, between January 2006 and February 2013	to evaluate the incidence of multifocality in primary small bowel neuroendocrine tumours (SBNETs) and to examine the	Preoperatively, 11 patients (10.6%) underwent capsule endoscopy and 45 (53%) patients had a DBE (retrograde and antegrade) performed. These procedures were performed to rule out multifocal disease. Of the patients who underwent DBE, 28 (62.2%) had additional lesions identified, of	Retrospective. Small number of patients that underwent CE, therefore not enough evidence to compare CE vs DBE regarding identification of multifocality of SBNETs	SBNETs have a high incidence of multifocality. DBE can be used in the preoperative assessment to detect

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			associated outcomes.	which 23 patients (82.1%) had the lesions confirmed as NET on pathology of biopsied specimens. In 10.6% of patients that underwent capsule endoscopy, carcinoid tumours were identified in only 2 of 11 patients. Twenty-one patients (75%) who had additional lesions on DBE had a primary tumour in the ileum		multifocal NET.
Goyal et al 2015	prospective	73 patients with obscure gastrointestinal bleeding were referred to our center for DBE after undergoing SBCE elsewhere	the degree of concordance between CE and DBE	12 patients were referred for a mass identified on CE and the finding was confirmed in 2, while DBE revealed another mass in a patient with a previous normal CE.	uncontrolled, nonrandomized prospective study referral bias i	The κ-coefficient for SBCE and DBE was calculated to be 0.28, suggesting poor agreement between the two tests. Especially for SB masses
Han et al 2015	retrospective	79 patients with histologically proven SBT	to evaluate the efficacy of various diagnostic tools such as computerized tomography (CT), small bowel follow-through (SBFT), and capsule endoscopy (CE) in diagnosing small bowel tumours (SBTs)	CT detected 55.8% of proven SBTs; SBFT, 46.1%; and CE, 83.3%. The sensitivity for detecting SBTs was 40.4% for CT, 43.9% for SBFT, and 79.6% for CE. Two patients with nondiagnostic but suspicious findings on CE and seven patients with negative findings on CE were eventually found to have SBT.	retrospective design. The study included only patients with proven SBTs so the specificity of each diagnostic method could not be analyzed. There are limitations to measure accurate sensitivity or miss rate of CE because the patients with negative CE results were more likely not to undergo DBE or surgery.	the miss rate of CE for SBTs was 16.5%. Missed tumours were most commonly located in the proximal jejunum (55.6%).
Limsrivilai et al	Prospective	52 consecutive patients with	To compare the efficacy of	The diagnostic yields and sensitivities of SBCE and CTE	First, we could not use the findings at surgery or balloon-	The sensitivity of

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2017		potential SB bleeding. All underwent SBCE and CTE within a 1-week interval.	video capsule endoscopy (SBCE) with computed tomography enterography (CTE) in potential small bowel (SB) bleeding, and to identify factors predictive of a high diagnostic yield for CTE.	were 59.6% and 30.8% (P = 0.004), and 72.2% and 44.4% (P = 0.052), respectively. The combined sensitivity of SBCE and CTE (88.9%) was significantly greater than SBCE (P = 0.03) or CTE (P < 0.01) alone. SBCE was better for ulcers, enteritis, and angiodysplasia, whereas CTE was better for tumours and Meckel diverticula. Age below 40 years and severe bleeding were associated with a higher diagnostic yield for CTE [odds ratios (95% confidence interval) =7.3 (1.04-51.4), P = 0.046 and 6.1 (1.4-25.5), P = 0.014, respectively].	assisted enteroscopy as the reference standard in all cases. This might have led to bias and overestimated the sensitivity of SBCE. Selection bias toward more complex cases. Clinical review bias	CE for SB tumours was 66.67% vs 100% for CTE. Both investigations complement each other in the diagnosis of potential SB bleeding. CTE should be considered when SBCE is negative. Age below 40 years and severe bleeding were independent predictors of a higher diagnostic yield for CTE.
Kakiya et al 2017	Retrospective	223 patients with SSBB	to compare, in terms of diagnostic yield, the efficacy of DBE with that of CE in patients with previous SSBB.	The diagnostic yields were 41.9% in DBE group and 11.6% in CE group, respectively (p < .01). On logistic regression analysis, DBE was significantly superior to CE after matching (Odds ratio [OR], 4.25; 95% confidence interval [CI], 1.43–12.6; p < .01), even after adjustment for propensity score (OR, 5.65; 95% CI, 1.56–20.5; p < .01). Especially for SB tumours there was no difference between CE and DBE, both exhibiting a diagnostic yield of 4.7%.	small sample, retrospective study Patients that underwent CE did not receive bowel prep.	For SB tumours DBE and SBCE had the same diagnostic yield

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Kalra et al 2015	retrospective	116 patients were included in the study.	To compare and correlate sequential CE and DBE findings in a large series of patients at two tertiary level hospitals in Wisconsin	Although there was overall good agreement (kappa value of 0.396 with $P< 0.001$), regarding SB tumours there was no concordance between CE and DBE. Two lesions identified on CE as tumours were not confirmed by a normal subsequent DBE whereas 2 lesions found on DBE where characterized as AVM on CE.	retrospective nature of the study and the discrepancy between AVMs and any other findings	good overall agreement between DBE and CE especially for angioectasias but not for SB tumours
Kim et al 2020	retrospective, observationalreview	178 patients diagnosed with SBNENs from 1996 to 2016	to determine the (1) incidence of SBNEN first diagnosed at our institution over the last 20 years by various imaging modalities, (2) the impact of CTE and endoscopy on the diagnosis of SBNEN, and (3) the impact of CTE and endoscopy on the rates of disease-free survival and incidence of liver and local metastases.	of the 178 patients, 55 received CT enterography (CTE) or multiphase-CTE (mpCTE) imaging, with 94.5% (n = 52) of these imaging reports identifying a small bowel mass and 90.9% (n = 50) specifically mentioning SBNEN as the diagnosis. In contrast, 85 of these patients underwent routine abdominopelvic CT, with only 44.6% (n = 37) of these clinical reports identifying a small bowel mass and 34.9% (n = 29) specifying that SBNEN as a potential diagnosis See for MRI	retrospective observational study. There may be over- estimation of the relative performance of CTE compared to routine abdominopelvic CT as CTE exams were interpreted by subspecialized GI radiologists.	SBNEN detection and correct identification are more frequent with CTE/mpCTE compared to routine abdominopelvic CT SB endoscopy not included
Li et al 2016	Retrospective	853 patients that underwent CE for SSBB. Patients were divided into two groups: those 65 years of age and older (n=287) and those younger than	to evaluate the diagnostic efficacy of CE and to determine the subsequent impacts on the treatment of the	SB tumours were identified in 5.2% in □65 years old and in 9% of patients <65 years old	Retrospective No follow-up	There were no significant differences between the two groups with respect to the incidence of

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		65 years of age (n=566).	SSBB episode in older individuals.			small bowel tumours
Ma et al 2016	retrospective	700 patients undergoing CE, SBE or both for SSBB	To evaluate diagnostic yields of capsule endoscopy (CE) and/or single-balloon enteroscopy (SBE) in patients with suspected small bowel diseases.	The overall diagnostic yield for the CE group was 57.6%. The overall diagnostic yield of SBE was 69.7% For the 47 patients that had both tests, the diagnostic yield of SBE with positive findings on prior CE was 93.3%.The detection rate for SB tumours was 10.4% for CE and 10.6 for SBE. For the 47 patients that underwent both, there was concordance of the findings in 3 cases but in 1 case with positive CE, the finding was not conformed by SBE	retrospective	SBE abd CE had similar detection rate for SB tumours
Murino et al 2016	retrospective	30 patients with suspected SB tumours	to determine the effectiveness of this technique for characterization and management of sub mucosal tumours in a large cohort of patients.	DBE-EUS successfully characterized 19/30 (63%) SMT Endoscopic biopsies were taken during 23/30 (77%) DBE-EUS providing a correct diagnose of 16 SMT (53%) Out of 30 SMT, 12 (40%) were characterized only by DBE-EUS while SBCE performed in 14 cases missed 6 lesions and mischaracterized 2. DBE- EUS failed to establish the nature of 11/30 (37%) SMT, nine of which were correctly identified by endoscopic biopsies and the other 2 by surgery.	retrospective single- centre study involving potential bias for data collection and a small number of cases. In addition, endosonographicinformationwere missing in 7 cases.	Endoscopic Ultrasonography performed during Double Balloon Enteroscopy is a safe and useful technique for submucosal tumours characterization
Nishimura et al 2018	retrospective	13 patients with metastatic SB tumours	to investigate the role of DBE in the diagnosis and surgical treatment of metastatic small bowel tumours.	Computed to- mography (CT) was performed in all 13 patients, and lesions suspected of being SBTs were identified in 9 (69%). In the 4 patients with negative CT findings of SBTs, SBTs were suspected by SBCE in two, fluoroscopic enteroclysis in one, and positron	Retrospective. Small sample	DBE is a useful and safe procedure for making a definitive diagnosis of metastatic

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				emission tomography with 2-deoxy-2- [fluorine-18] fluoro-D-glucose integrated with computed tomography (^{18}F-FDG PET/CT) in one. SBCE was performed in four patients (two patients with negative and two with positive CT findings), and the test detected the SBT in all. DBE confirmed the metastatic SBTs, and biopsy specimens at DBE yielded a definite pathological diagnosis in all 11 patients whose condition permitted a biopsy. In addition, DBE detected unexpected SBTs that had not been recognized with any of other examinations in four patients. In two patients, metastatic SBTs were detected by DBE at the time of the diagnosis of the primary cancer.		SBTs. DBE can aid in the selection of the appropriate operation and, through the ability to tattoo lesions, help surgeons locate tumours for resection.
Otani et al 2018	retrospective	89 patients with negative CE for SSBB that underwent repeat CE (n=41) or DBE (n=48)	to determine whether CE or DBE DBE should be performed after negative CE.	5 tumours were identified on repeat CE (16.7%) And another 5 on DBE (26.3%)	retrospective it is unknown whether small erosions could be the true source of bleeding. it is difficult to identify the accurate date on which bleeding occurred, especially in occult SSBB cases, and the period from bleeding to examination varies. As the effectiveness of earlier CE was reported previously,[27,28] the interval between the bleeding episode and CE examination may have affected our results.	The rate of positive findings in the repeat CE group was significantly higher than that in the DBE group (73.2% vs. 39.6%; p 1⁄4 0.001). SB tumours were detected almost equally in the repeat CE group and the DBE group.

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Ooka et al 2016	retrospective	CE and SBE were performed in 103 and 91 patients, respectively, and 26 patients underwent both examinations.	comparing the diagnostic performances of CE and BE for detecting the source of the SSBB	CE identified 3 tumours (6.1%) whereas SBE identified 2 (3%)	Retrospective/small	The rate of positive findings was significantly higher with SBE (73.6%) than with CE (47.5%, p<0.01). There was no significant difference in the detection rate of SB tumours between CE and SBE performed in the context of SSBB
Pérez-Cuadrado Robles et al 2015	retrospective	332 patients that underwent CE and DBE for SSBB	to characterize the degree of agreement between both techniques with focus on the type of lesion in a large cohort of patients	Both procedures were carried out in 332 patients and they have a similar diagnosis yield (70.5% vs. 69.6%, p = 0.9). Overall enteroscopy diagnosis yield was higher within patients with a previous positive capsule endoscopy (79.3% vs. 27.9%, p < 0.001). The degree of agreement was very good for polyps (0.89 [95% CI: 0.78-0.99]), good for vascular lesions (0.66 [95% CI: 0.55-0.77]) and tumours (0.66 [95% CI: 0.55-0.76]) and moderate for ulcers (0.56 [95% CI: 0.46-0.67]). Diverticula (0.39 [95% CI: 0.29-0.5]) achieved a fair agreement. The results of CE and DBE differed in 73 patients (22%).	retrospective study with a referral bias The interobserver variability, the elapsed time between CE and DBE and the different cleansing regimens previously administered to retrograde DBE may also have influenced the results. the possibility to detect many different types of lesions in one of the procedures, while the other procedure fails to detect the lesion with the highest bleeding potential. This may decrease the degree of agreement between both even if they have detected at least one of the lesions.	CE and DBE detected equally tumours (Diagnostic Yield) (7.2% *vs.* 6.9%) and polyps (4.8% *vs*. 3.9%) Regarding tumours, the CE and DBE had 7 and 8 false negatives respectively (30.4% *vs*. 33.3%, *p* = 0.8). The degree of agreement

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						was very good for polyps (0.89 [95% CI: 0.78-0.99]) and good for tumours (0.66 [95% CI: 0.55-0.76])
Pérez-Cuadrado Robles et al 2018	restrospective	2311 patients undergoing CE. 648 were in the older group (□75 years old) and 1663 in the younger group (<75 years old)	to assess the usefulness of capsule endoscopy in older patients.	The diagnostic yield of CE on SB tumours did not differ between the two age groups 6.13% for □75 years old vs 5.62 for <75) (p=0.650)	the retrospective and single-center nature of the study, the lack of data regarding comorbid conditions for patients under-going CE, patient hospitalization status, and the extensive period of study. Referralbiasalsomayhaveinfluenced the results.	The diagnostic yield of CE on SB tumours did not differ between the two age groups 6.13% for □75 years old vs 5.62 for <75) (p=0.650)
Pérez-Cuadrado Robles et al 2015	Single – center retrospective descriptive study	Consecutive patients who underwent a DBE with final diagnosis of a malignant neoplasm from 2004 to 2014 (n=28) (out of the 89 patients that were diagnosed with SB tumours in general) They were diagnosed by DBE biopsy (n = 18, 64.3%), histological	To assess the double-balloon enteroscopy) role in malignant small bowel tumours (MSBT).	DBE was indicated following CE in 17 cases (60.7%) and this procedure confirmed the MSBT in 14 cases (82.4%). The capsule was retained in 4 cases due to SB stenosis identifying the tumour in two of them and retrieved by DBE in all patients. CT scan (*n* = 8, 28.6%) and other radiological studies (*n* = 2, 7.1%) were previously performed and a suspected mass was identified in 6 cases (21.4%). CT scan also detected a SB complete stenosis in four cases and DBE clarified that only in three of them there was a complete stenosis without overpassing it with the endoscope.	retrospective design and potential referral bias.	DBE is critical in the management of MSBT and may have an impact delaying or avoiding emergency surgery. This procedure clarifies the tumour location and characteristics allowing tattoo injection to

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		analysis of surgical specimen (n = 7, 25%) and unequivocal endoscopic findings (n = 2, 7.1%)		Among patients with obstructive symptoms, radiological imaging was the first SB study in 6 (75%) cases and direct DBE was performed in 2 (25%) patients. DBE modified outcome in 7 cases (25%), delaying or avoiding emergency surgery (n = 3), modifying surgery approach (n = 2) and indicating emergency SB partial resection instead of elective approach (n = 2).		guide a possible surgery and provides additional information to other procedures that may be decisive in the clinical course of these patients. DBE allowed histopathological diagnosis in most patients (71.4%), except in GI stromal tumours. DBE allowed histopathological diagnosis in most patients (71.4%), except in GI stromal tumours. The histological detection rate in GIST was low (57.4%) but higher than reported by other authors

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Rossi et al 2021	Single center prospective study	6 patients with a suspected sbNEN selected for diagnostic DBE between 2011 and 2016	DBE efficacy in the detection of sbNENs	DBE showed a sensitivity of 60% and, in absence of false-positive results, a specificity of 100%. Accuracy resulted in 67%. Five out of 6 of our patients had previous conventional radiological examinations within normal limits Moreover, 4 out of the 6 included patients underwent CE prior to DBE, and the findings were identical in 3 out of the 4 patients.	small sample size, (given the rarity of NENs) the small sample size has possibly affected the specificity that we observed (100%); of note, such high specificity cannot be owed to any work-up bias as all the included patients had undergone a subsequent reference standard, which was either surgical intervention or clinical follow-up.	DBE is a safe and effective procedure in the diagnosis of sbNENs, and compared with radiological examinations had no false positive results)
Sheba et al 2017	prospective	patients that underwent DBE for SSBB	to assess the role of DBE in the diag- nosis and management of patients with SSBB.	the potential source of SSBB was defined as the small intestine in 18 of 26 patients (69.2%), and negative DBE findings were noted in eight patients (30.8%)	Small number	DBE diagnosed the source of bleeding in 18 of 26 patients (69.2%) and identifed 8 SB tumours (30.8%)
Shiani et al 2016	retrospective	95 patients that underwent SBE originally after a positive CE result for the evaluation for SSBB.	to evaluate the diagnostic correlation between these two modalities after an initial positive CE finding.	Masses and polyps made up a small per- centage of findings on CE (2.1%, 6.3%) and SBE (1.1%, 7.4%) The degree of concordance was not significant for the diagnosis of masses and polyps	retrospective	The degree of concordance between CE and SBE was not significant for the diagnosis of masses and polyps
Singeap et al 2020	retrospective	224 SBCE examinations for SSBB, of which 148 were for overt SSBB, and 76 for unexplained IDA.	to evaluate the diagnostic yield (DY) of SBCE in overt and occult SSBB	Positive findings were found in 139 patients, resulting in an overall DY for SSBB of 62%, higher in overt SSBB (75%) compared to IDA (37%). SB tumours were identified in 18(16.2%) patients with overt SSBB and in one (3.6%) with occult SSBB.	single-center study and the lack of long-term follow up for all patients.	SBCE showed a good diagnostic performance for diagnosing small bowel tumours

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Singeap et al 2019	retrospective	14 patients with SBTs, evaluated by SBCE and furthermore explored, for which a final histopathological diagnosis was made, either on biopsy tissue samples, or on surgical specimens, using routine techniques and immunohistochemistry.	To assess if structured visual description of SBTs detected by SBCE correlates with the histological type.	the calculated frequency of SBTs at SBCE for all indications was 5.2% All SBTs presented as protruding lesions. Features as size, color, type, shape, discoloration, presence of mucosa ulceration, bleeding stigmata or potential, contributed outlining a prototype. SBCE was accurate in terms of localization and suspected diagnosis	Retrospective Small Non-standarised terminology	Even if SBCE is a purely visual technique, thorough examination and rigorous analysis of macroscopic features, as well as adoption of a structured terminology, may successfully predict the final diagnosis
Stone et al 2020	retrospective	1351 patients that underwent CE	to examine the yield of CE in diagnosing the cause of IDA and to define clinical parameters that predict higher diagnostic yields.	We report a 33.9% positive yield, with 65.8% of patients undergoing further workup as a result of CE and 12.7% requiring therapeutic intervention. 2 definitive SB masses were identified on CE in this study, with 1 being confirmed as malignant on the follow-up study and the remaining lost to follow-up	retrospective analysis, single-center experience, and limitations inherent to post hoc surveys, including respondent bias, missing data, and patients lost to follow-up. Another limitation for the survey of physicians as to their approaches to the CE findings is the lack of uniform approach and the lack of local availability of an important intervention such as balloon endoscopy	2 definitive SB masses were identified on CE in this study, with 1 being confirmed as malignant on the follow-up study and the remaining lost to follow-up
Sidhu et al 2015	retrospective	971 patients referred for CE for recurrent IDA	We aim to assess its utility of capsule endoscopy (CE) in the <50 years of age patients with iron	SB tumours were found in 1.7% of our cohort with recurrent IDA. In the <50 years of age patients cohort, SB tumours were found in 3% of patients	retrospective nature, all referrals made were taken at face value, and we did not revisit the history to scrutinise any previous investigation undertaken. In addition, we did not have the menopausal status for all the females <50 years of age and our	SB tumours were equally common in both groups (<50 years old and □50 years old

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			deficiency anaemia (IDA)		study lacked the long-term follow-up data on patients which would have helped to strengthen this study.	
Tseng et al 2017	retrospective	71 patients including 25 patients with positive CTA findings and 46 patients with negative CTA findings in the setting of acute overt SSBB	to evaluate the impact of CTA before enteroscopy for acute overt SSBB.	All 25 patients with positive CTA findings were confirmed to have mid GI lesions, a significantly higher proportion than among patients with negative CTA findings (100% vs. 52.2%, respectively; P <0.001). CTA had a higher diagnostic yield for bleeding from tumour origin than from non-tumour origin (80.0% vs. 23.7%, respectively; P <0.001). The diagnostic yield of CTA and enteroscopy was 35.2% and 73.2%, respectively. The lesions could be identified by the initial route of enteroscopy in more patients with positive CTA findings than in those with negative CTA findings (92.0% vs. 47.8%, respectively; P <0.001). Lesions could be identified in seven of the 25 patients (28.0%) with positive CTA findings by using only push enteroscopy instead of single-balloon enteroscopy (SBE), but all 46 patients with negative CTA findings needed SBE for deep small-bowel examination.	not all patients with positive CTA findings underwent subsequent enteroscopy. the risk of con-trast nephropathy may limit the use of CTA, especially in patients with renal insufficiency. In the present study, CTA was not performed in 12 of 83 patients (14.4%) because of renal insuffi- ciency. Therefore, these results did not necessarily apply to all patients with acute overt SSBB.	Sixteen of the 20 patients (80%) with confirmed diagnosis of tumours as the cause of overt SSBB were identified by CTA, 15 as small bowel tumours and one as thickened bowel wall. the diagnostic yield of CTA for small bowel neoplasms was 80%,
Unno et al 2021	Retrospective cohort study	Patients that underwent small bowel examination (CTE, CE, or DAE) for gastrointestinal bleeding between April 2008 and March 2019. 71	To investigate the diagnostic ability of CTE and long-term prognosis after CTE in Japan.	The 43 patients (60.6%) with a definite and suspicious source of bleeding in the small bowel were detected by CTE. When the 31 patients with a definite source of bleeding in the small bowel were analyzed, the sensitivity of CTE was 19/31 (61.3%) and that of CE was 24/31 (77.4%), thus indicating	Single-center, retrospective study, and the number of cases was small. The study targeted patients who underwent both CTE and CE, but there may have been some selection bias because CTE is not performed in many patients with	When the 31 patients with a definite source of bleeding in the small bowel were analyzed, the sensitivity of

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		patients were finally included that underwent CTE & CE within 30 days. These patients were divided into 3 diagnosis groups: 43 (60.6%) in the small bowel bleeding group, 14 (19.7%) in the non-small bowel bleeding group, and 14 in (19.7%) in the SSBB group		no significant difference (p=0.332). However, the sensitivity when CTE and CE were used in combination was 30/31 (96.8%), which was significantly higher than that of CE alone (p=0.0412). No rebleeding was observed in the CTE and CE negative group (p=0.0965).	kidney dysfunction, and CTA is often performed for overt ongoing bleeding. As this study includes both CT enteroclysis and CT enterography, it may include the effects of these two different diagnostic abilities. The study period was long, and the performance of CE and CT scanners may have improved during that time.	CTE was 19/31 (61.3%) and that of CE was 24/31 (77.4%), thus indicating no significant difference (p=0.332). However, the sensitivity when CTE and CE were used in combination was 30/31 (96.8%), which was significantly higher than that of CE alone (p=0.0412). Among these 31 patients, 6 cases were positive by CTE and negative by CE. The final diagnosis of these cases consisted of 3 cases of GIST, 1 case of metastatic tumour, and 2 cases of NSAIDs ulcer. The

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						CTE findings of these cases were a tumour in 3 cases, stenosis in 1 case, and contrast enhancement of the intestinal wall in 2 cases. In the cases of tumour/polyp by CTE, polypoid (or protruded) lesions were actually detected in the lesions for which a final diagnosis could be made (9/11, 81.8%). Therefore, CTE was accurate in raising the suspicion of SB tumours
Urgesi et al 2015	retrospective study	1008 consecutive patients who underwent capsule endoscopy for various indications. (Group A: <50 years; Group B: 50–69	To assess the Pillcam diagnostic yield, clinically significant findings and post-treatment outcomes	SB tumours were identified more often in groups A (n=14, 8.9%) and B (n=15, 9.4%)compared to group C (n=8, 2.6%)	its retrospective nature and the evaluation of patients from a single institution,	There was no significant difference on the detection of SB tumours between the

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		years; Group C: >70 years)	between groups.			three age groups.
Van de Bruaene et al 2016	retrospective	211 patients with negative CE for SSBB	to investigate the long-term outcome of patients with a negative CE.	There were 19 (9%) cases of false negative CE where the source of bleeding was finally identified in the SB. Out of the missed lesions there were 3 cases of SB malignancy	retrospective, single-center study. the number of FN CEs remained relatively small (n=19). heterogeneity in the patient population	In the case of false negative capsules there were 3 cases of SB malignancies, therefore negative CEs in patients with SSBB do not reassure the treating physician, but warrant close monitoring and alternative diagnostic modalities in suspicious cases.
Wang et al 2020	Retrospective	877 patients that underwent DBE procedures. Patients were divided in two groups adults (18–64 years old) and elderly (≥65 years old).	to compare the diagnostic yields and safety of DBE between adults and elderly with obscure gastrointestinal bleeding and incomplete small bowel obstruction	The diagnostic yield of DBE for SB tumours in the SSBB setting were similar between the groups. On the other hand, in case of incomplete SB obstruction, a higher rate of adenocarcinoma was identified in the elderly group (19.4% vs. 7.1%, P = 0.038)	retrospective Elderly were defined as individuals aged ≥65 years and did not subdivide the elderly into additional groups for evaluation.	The diagnostic yield of DBE for SB tumours in the SSBB setting were similar between the groups. On the other hand, in case of incomplete SB obstruction, a higher rate of adenocarcino

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						ma was identified in the elderly group (19.4% vs. 7.1%, P = 0.038) DBE has high a diagnostic yield in small bowel disorders with slightly different disease spectrum between the adults and elderly
Yoo et al 2021	retrospective	28 patients with SB tumours that underwent DBE and CE	to investigate the clinicopathological features of small bowel malignant tumours diagnosed by SBCE and DBE in a single tertiary center.	28 of 438 patients who underwent SBCE or DBE were diagnosed with small bowel malignancy, 27 of the 28 patients (96.4%) who were diagnosed with small bowel malignancy had positive CT findings, including heterogeneous wall thickening or masses (in all cases of GIST, adenocarcinoma, and metastatic cancer). The only case that was missed by CT was a case of lymphoma.	retrospective- small number	Approximately 6% of the patients who underwent either SBCE or DBE were diagnosed with small bowel malignancy CT prior to SB investigations revealed the lesions in all but one case.
Zhang et al 2015	Single – center prospective descriptive study	From June 2009 to December 2014, 88 patients were included in this study that underwent both CE and DBE.	To compare the roles of capsule endoscopy (CE) and DBE in the diagnosis of obscure small bowel diseases	This study revealed no obvious differences in the detection rates (DR) of CE (60.0%, 53/88) and DBE (59.1%, 52/88). However, the etiological diagnostic yield (DY) difference was apparent. The CE diagnostic yield was 42.0%	retrospective nature of the study with selection bias, a heterogeneous clinical population, and a heterogeneous reference standard, probably due to the wide spectrum of diagnoses that cause GI	DBE was superior to CE for larger tumours (P = 0.018, Fisher's test)

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		70/88patients for SSBB		(37/88), and the DBE diagnostic yield was 51.1% (45/88).	bleeding.	
Pei-You et al 2015	retrospective	(n=30) patients who were diagnosed with small bowel disease from July 2012 to February 2014 and underwent both CTE & MRE. Pathological diagnosis of postoperative results by operation or biopsy results by small intestinal endoscopy were used as the gold standard.	compare the efficacy of computed tomography enterography and magnetic resonance enterography in diagnosing small intestinal diseases.	the clinical diagnostic accuracy of computed tomography enterography and magnetic resonance enterography was 24(80%) and 21(70%) cases respectively (p>0.05). CTE had a sensitivity, specificity, PPV & NPV of 80% each, whereas for MRE it was 78%, 73%, 70% and 80%, respectively.	Retrospective Small number	Out of the 30 patients included in the study, 11(36.6%) cases were diagnosed with small bowel tumour lesions by both CTE and MRE, with a consistent, accurate diagnosis both CTE and MRE provided a panoramic view of small intestine cavity, wall, mesentery, lymph nodes, blood vessels, and adjacent organs.
Zhang et al 2020	retrospective	1102 patients with 1140 procedures completed in total.	To determine the characteristics of small bowel tumours (SBTs) in patients underwent double balloon endoscopy (DBE) and to compare the clinical value of	99/1102 patients (9.0%) had SBT (See table)	Retrospectivel. Furthermore, not everyone who underwent the DBE had produced the other imaging ex- amination. Moreover, the study cannot represent all pa- tients with SBTs because the study did not take patients who did not receive DBE into consideration.	Small bowel tumour is mainly located in jejunum and with SSBB and abdominal pain as major complaints. DBE had better

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			DBE with other diagnostic tools.			sensitivity (89.2%), specificity (95.2%), positive predictive value (PPV) (90.0%), and negative predictive value (NPV) (94.8%) than other tools for suspected SBTs. Concerning the other diagnostic tools, CTE had high specificities and PPV (92.2% and 93.5%, respectively) whereas CE was a better choice as a screening method with 90.0% NPV. Of SBTs, 33 were not found by CTE while DBE had positive findings. Using CTE and MRI, nine

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						malignant SBTs and three benign polyps were diagnosed, whereas DBE and CE had negative findings.
Author, year	**P**atients	**I**nterventio n	**C**omparis on	**O**utcome		**Comment**
Al-Bawardy et a 2015	All the patients that underwent CE from January 2002 through January 2013 at Mayo Clinic in Rochester, Minnesota (n= 5593)	CE		There were a total of 17 CE retentions (0.3%) in 15 patients. Only 2 cases with SB tumours: A submucosal mass in the proximal SB in the context of SSBB and an adenocarcinoma of the jejunum in the context of coeliac disease		Imaging findings that could possibly be predictive of CE retention are SB anastomoses and partial small bowel obstruction.
Assadsangabi et al 2015	All patients who were referred for PC prior to CE from April 2010 to September 2012. (n= 400 consecutive patients)	Patency capsule (PC)	radiologic al imaging to confirm luminal patency after PC	In a study of the confidence with which radiologists could localize the PC on plain films, radiologists preferred abdominal CT to localize PCs identified on plain films in 74% of cases. In a protocol based on the use of a PC and targeted, limited CT scan to confirm small bowel patency in those failing to excrete the PC 30 h post-ingestion, the sensitivity, specificity, positive, and negative predictive value were 99.4%, 90.0%, 99.7%, and 81.0%, respectively. Crohn's diseasewas the onlystatisticallysignificant predictor		Crohn's disease was the only statistically significant predictor associated with higher risk of luminal stricture (P = 0.001) in post-hoc analysis. No distinction was made regarding SB tumours There was relatively small number of patients with stricturing disease (n = 10).

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Kopylov et al 2016	Out of all patients that underwent patency capsule examinations (n=1615), those that developed symptomatic patency capsule retention (n=20)	patency capsule		In total, 20 cases of symptomatic patency capsule retention were identified (1.2 %). In one patient, the patency capsule was retained in the esophagus, while in the rest, it was retained in the small bowel. The patency capsule examination was performed in 19 patients for suspected (6/20, 30%) or established (13/20, 65%) CD, and in one patient for a suspected mesenteric ischemic event. Six patients (30%) had a previous history of abdominal surgery; 7 (35%) had previous episodes of small-bowel obstruction (SBO); 2 (10%) patients had used nonsteroidal anti-inflammatory drugs (NSAIDs) at least once within the preceding 12 months. Two (10%) of the patientshadundergonepreviousradiotherapy.	Symptomatic patency capsule retention is a very rare adverse event that resolves without surgical or endoscopic intervention in the vast majority of cases Almost all cases were patients with suspected or established CD. No cases of SB tumours
Ormeci et al 2016	359 CE outpatient procedures	CE (All patients had CT prior to CE)		The capsule retention rate was 11/359 (3.1%); it was retained in a malignant lesion area (adenocarcinoma or melanoma) in two patients (18.2%), in the small bowel in an ulcerated area in five patients (45.5%), and in the	In two patients, capsules were retained in areas of tumour lesions. These patients had no symptoms of obstruction but underwent surgery because of the underlying disease based on the CE findings. Melanoma was

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				oesophagus/stomach in four patients (36.4%) due to dysmotility.	detected in one of these patients and small bowel adenocarcinoma in the other. No distinctive information regarding history and/or symptoms prior to CE
Calabrese et al 2015	849 consecutive patients that underwent CE for occult gastrointestinal bleeding	CE.		SB tumours were detected in 75 patients (8.8%). The most frequent tumours were adenocarcinomas (n=14; 18.7 %), gastrointestinal stromal tumours (GIST) (n=9; 12 %), and lymphoma (n=5; 6.7 %) Benign neoplasms included dysplastic adenomatous polyps (n=27; 36 %). Non-neoplastic lesion included an inflammatory polyp (n=1) and hyperplastic polyps (n=19; 25.3 %).	Capsule retention occurred in four patients (5.3%) with SB tumours. In particular, all these patients had an adenocarcinoma-related stenosis, and in these patients the retained capsule was retrieved during surgery. The prevalence of SB tumours found by CE in only SSBB patients is 6.5%, and is similar to those studies that include a population with the same clinical characteristics No distinctive information regarding history and/or symptoms prior to CE No assessment of SB patency
Lim et al 2015	A total of 2,914 CE examinations in the capsule registry	(CE) Capsule Endoscopy		The overall capsule retention rate was 3% (90/2,914). The rate was high in patients with small bowel tumours (5.7%) and Crohn's disease (3.4%)	In the present study, small bowel tumours were identified as high-risk factors for capsule retention (5.7%). Nevertheless previous history, symptoms of SB obstruction, previous imaging and assessment of SB patency are not mentioned.
Rezapour et al 2017	systematic review of 33 studies consisting of 8,513 patients undergoing video capsule endoscopy	SBCE		Small-bowel neoplasms were present in 17 (17%) of cases and were due to neuroendocrine tumour in 1 (6%) case, lymphoma in 2 (11.8%) cases, metastases from endometrial cancer in 1 (6%) case,	SBCE retention rates varied from 0-7%. Using a random effects model, the pooled retention rate was 2.1% (95% CI 1.5-2.8%, p=0.000)

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				and adenocarcinoma in 7 (41%) cases.	
Mitsui et al 2016	12 consecutive patients with small bowel stricture where retrieval of entrapped SBCE was attempted using DBE	double-balloon endoscopy (DBE) for small bowel capsule endoscopy (SBCE) retrieval		Diagnoses were Crohn's disease, NSAIDs–induced enteropathy, ischemic enteritis, and carcinoma in 8, 2, 1, and 1 patients, respectively. SBCE was successfully retrieved in 11 of the 12 patients (92%). No complications were recorded. Nine of the 12 patients (75%) did not undergo surgical treatment for the stricture where SBCE was entrapped through the follow-up period (mean, 1675 ± 847 d)	DBE was useful not only to remove the entrapped SBCE, but also to evaluate the lesion of stricture for indication of surgery. Furthermore, DBE was useful to treat the stenosis by balloon dilation in Crohn's disease, which was the most common disease in the study. Only one case of SB tumour was included and the patient was referred to surgery after DBE.
Fernández-Urién 2015	5428 procedures performed at 12 institutions between August 2001 and January 2012	CE		The incidence of capsule retention was significantly higher in patients suffering from inflammatory bowel disease (IBD) than in obscure GI bleeding (SSBB) (3.3% vs. 1.5%; $p < 0.05$) and in patients with the combination of nausea/vomiting, abdominal pain and distension. Capsule retention after a negative GI patency test procedure was significantly more frequent after small bowel follow through (SBFT) and abdominal CT-scan than after Patency© capsule and MRI-enterography: 1.9% for Patency© capsule, 0% for MRI, 21.5% for CT-scan and 34.3% for SBFT ($p < 0.05$). The incidence of capsule retention in the small bowel was significantly higher when the following combinations were observed before CE procedures: Abdominal pain and abdominal distension (13.1%), abdominal pain and nausea/vomiting (5.7%), abdominal distension and nausea/vomiting	CR was significantly higher in patients with IBD than SSBB. Patency assessment using the PC or MRE was more reliable than SBFT or CT. CR was observed more often when abdominal distention, abdominal pain and nausea/vomiting were recorded pre-CE

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				(8.3%) and abdominal pain, abdominal distension and nausea/ vomiting (33.3%).	
Kim et al 2020	4650 CEs	CE		the capsule retention rate was 3% and 0.7% when CE was performed for SB tumours. Compared to other factors for CR, SB tumours had an OR of 0.213 (95%CI 0.030-1.533, p<0.124)	SB tumours were not a risk factor for CR
Gao et al 2020				The estimated pooled successful retrieval rate was 86.5% (95% confidence interval, 75.6–95.1%). Anterograde approach and capsules retained in the jejunum or trapped by malignant strictures were associated with a higher successful retrieval rate than the retrograde approach (62/83 [74.7%] vs. 10/38 [26.3%], p < .001) and capsules retained in the ileum (41/41 [100.0%] vs. 43/58 [74.1%], p < .001) or trapped by benign strictures (21/21 [100.0%] vs. 65/83 [78.3%], p 1⁄4 .043). Endoscopic balloon dilation was performed in 38.8% (95% confidence interval, 22.3–56.3%) of patients with benign strictures. Two perforations (1.3%) were reported as severe adverse events after DBE. A significantly lower surgery rate was found among cases with successful video capsule removal compared with unsuccessful cases (7.2% vs. 38.5%, p 1⁄4 .002).	DBE capsule retrieval could decrease the need for surgery in patients with benign diseases and facilitate subsequent surgery in patients with malignancies. Given its high success rate and multiple potential clinical benefits, DBE might be a reasonable choice for most cases of small- bowel capsule retention unless there are contradictions to endoscopy or emergency surgery is required
Author	**P**atients	**I**nterventio n	**C**omparis on	**O**utcome	**C**omment
Unno et al 2021	71 patients that underwent CTE & CE within 30 days for small bowel bleeding. 31 patients in the small bowel bleeding group with definite lesions	CTE	CE	When the 31 patients with a definite source of bleeding in the small bowel were analyzed, the sensitivity of CTE was 19/31 (61.3%) and that	Therefore, CTE was accurate in raising the suspicion of SB tumours as among the 11 patients diagnosed as having tumour/polyp

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				of CE was 24/31 (77.4%), thus indicating no significant difference (p=0.332). However, the sensitivity when CTE and CE were used in combination was 30/31 (96.8%), which was significantly higher than that of CE alone (p=0.0412). Among these 31 patients, 6 cases were positive by CTE and negative by CE. The final diagnosis of these cases consisted of 3 cases of GIST, 1 case of metastatic tumour, and 2 cases of NSAIDs ulcer. The CTE findings of these cases were a tumour in 3 cases, stenosis in 1 case, and contrast enhancement of the intestinal wall in 2 cases. In the cases of tumour/polyp by CTE, polypoid (or protruded) lesions were actuallydetected in the lesions for which a final diagnosis could be made (9/11, 81.8%).	lesions by CTE, tumour/polyp was confirmed in 9 (81.8%) indicating a high-positive rate.
Limsrivilai et al 2017	52 patients were included in the analysis, 41 with overt potential SB bleeding and 11 with occult potential SB bleeding. All underwent SBCE and CTE within 1 week.	video capsule endoscopy (SBCE)	computed tomography enterography (CTE	The diagnostic yields and sensitivities of SBCE and CTE were 59.6% and 30.8% (P = 0.004), and 72.2% and 44.4% (P = 0.052), respectively. The combined sensitivity of SBCE and CTE (88.9%) was significantly greater than SBCE (P = 0.03) or CTE (P < 0.01) alone. SBCE was better for ulcers, enteritis, and angiodysplasia, whereas CTE was better for tumours and Meckel diverticula. Age below 40 years and severe bleeding were associated with a higher diagnostic yield for CTE [odds ratios (95% confidence interval)=7.3 (1.04- 51.4), P = 0.046 and 6.1 (1.4-25.5), P = 0.014, respectively].	SBCE had a higher diagnostic yield and sensitivity than CTE in patients with potential SB bleeding, but CTE and SBCE can complement each other. SBCE was superior for mucosal lesions, whereas CTE was better for mural lesions. CTE is capable of making definitive diagnoses in patients with negative SBCE as the combination of both tests increased the diagnostic sensitivity. Age below 40 years and presentation with severe bleeding were independent predictors of positive diagnosis by CTE.

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					* Specific to mass lesions, CTE demonstrated a sensitivity of 100% as compared with 66.7% for SBCE. 4 tumours missed by SBCE included a jejunal GIST 1.9x1.6cm, a proximal jejunal GIST 2x2.2cm, a distal ileal GIST 4x1.5cm and an appendiceal neuroendocrine tumour 1.6cm in diameter.
Chu et al 2016	121 patients who underwent capsule endoscopy, DBE and/or CTE before or after CE with the indication of SSBB. CE was performed in all patients; CTE and DBE were performed in 100 (82.6%) and 46 (38.0%) of the patients, respectively.	CE	CTE	Specifically, regarding SB tumours, CE detected tumours in 15/27 cases (sensitivity 55.6%, 95% confidence interval [CI] 35.3%–74.5%; specificity 100%, 95% CI 96.2%–100%) CTE was positive in 15/21 cases (sensitivity 71.4%, 95% CI 47.8%–88.7%; specificity 97.5%, 95% CI 91.2%–99.7%).	The diagnostic yields of CE and DBE were comparable in patients with SSBB, (73.9% versus 60.9%) which were significantly higher than the yield of CTE (87% versus 25%, $p< 0.001$). CE proved to be superior in the detection of angiodysplasia. The three approaches showed comparable performances in the identification of small bowel tumours. DBE and CTE identified small bowel diseases undetected or undetermined by CE. Conversely, CE improved

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			DBE	DBE identified tumours in 15/17 cases (sensitivity 88.2%, 95% CI 63.6%–98.5%; specificity 100%, 95% CI 88.1%–100%).	diagnosis in the cases with negative CTE and DBE, and positive findings at initial CE directed further diagnosis made by DBE. Combination of the three diagnostic platforms in a properly integrated manner based on individual patient conditions provides complementary value in the diagnosis of SSBB. Twenty-five patients received all three examinations in this study, and SBT was diagnosed in 12 of them. CE and CTE each detected 6/12 tumours (sensitivity 50%; 95% CI 21.1%–78.9%), and DBE found 9/12 tumours(sensitivity 75%; 95% CI 42.8%–94.5%).
Deepak et al 2019	Patients with suspected small bowel bleeding that underwent mpCTE (n=1087)	mpCTE		A definitive diagnosis of small bowel bleeding was established in 340 patients (31.3%) through surgical, endoscopic, angio-graphic, or pathologic findings. In this cohort, 165 patients had their definitive cause of small bowel bleeding identified on mpCTE, 56 had indeterminate findings, and 119 did not have the lesion identified at mpCTE, resulting in an overall sensitivity of 58.1% (165 of 284; 95% CI, 50.0%-66.0%). For patients who had a positive finding on mpCTE as well as a definitive diagnosis, the overall PPV was 88.2% (165 of 187; 95% CI, 83.0%- 92.0%).	Overall sensitivity and PPV of mpCTE in the setting of suspected SB bleeding were 58.1% (165/284) and 88.2% (165/187) respectively. The highest sensitivity and positive predictive value of CTE were for small bowel masses (90.2% [55 of 61] and 98.2% [55 of 56], respectively)

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				The highest sensitivity and positive predictive value of CTE were for small bowel masses (90.2% [55 of 61] and 98.2% [55 of 56], respectively) *especially for age <40 years old	
Pérez-Cuadrado Robles et al 2015	Consecutive patients who underwent a DBE with final diagnosis of a malignant neoplasm from 2004 to 2014 (n=28) (out of the 89 patients that were diagnosed with SB tumours in general) They were diagnosed by DBE biopsy (n = 18, 64.3%), histological analysis of surgical specimen (n = 7, 25%) and unequivocal endoscopic findings (n = 2, 7.1%)	DBE	SBCE	DBE was indicated following CE in 17 cases (60.7%) and this procedure confirmed the malignant small bowel tumour (MSBT) in 14 cases (82.4%). The capsule was retained in 4 cases due to SB stenosis identifying the tumour in two of them and retrieved by DBE in all patients.	Among patients with obstructive symptoms, radiological imaging was the first SB study in 6 (75%) cases and direct DBE was performed in 2 (25%) patients. DBE modified outcome in 7 cases (25%), delaying or avoiding emergency surgery (n = 3), modifying surgery approach (n = 2) and indicating emergency SB partial resection instead of elective approach (n = 2). DBE is critical in the management of MSBT and may have an impact delaying or avoiding emergency surgery. This procedure clarifies the tumour location and characteristics allowing tattoo injection to guide a possible surgery and provides additional information to other procedures that may be decisive in the clinical course of these patients. DBE allowed histopathological diagnosis in most patients (71.4%), except in GI stromal tumours. The histological detection rate in GIST was low (57.4%) but higher than reported by other authors%
			CT scan (*n* = 8, 28.6%) and other radiological studies (*n* = 2, 7.1%)	A suspected mass was identified in 6 cases (21.4%). CT scan also detected a SB complete stenosis in four cases and DBE clarified that only in three of them there was a complete stenosis without overpassing it with the endoscope.	

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Zhang et al 2015	88 patients that underwent both CE and DBE. 70/88patients for SSBB	capsule endoscopy (CE)	DBE	Regarding SB tumours DBE was superior to CE identifying 17/18 lesions, compared to 10/18 for CE. (P = 0.018, Fisher's test)	This study revealed no obvious differences in the detection rates (DR) of CE (60.0%, 53/88) and DBE (59.1%, 52/88). However, the etiological diagnostic yield (DY) difference was apparent. The CE diagnostic yield was 42.0% (37/88), and the DBE diagnostic yield was 51.1% (45/88). DBE was superior to CE for larger tumours (P = 0.018, Fisher's test)
Pei-You et al 2015	(n=30) patients who were diagnosed with small bowel disease and underwent both CTE & MRE. Pathological diagnosis of postoperative results by operation or biopsy results by small intestinal endoscopy were used as the gold standard.	computed tomography enterography (CTE)	magnetic resonance enterography (MRE)	the clinical diagnostic accuracy of computed tomography enterography and magnetic resonance enterography was 24(80%) and 21(70%) cases respectively (p>0.05). CTE had a sensitivity, specificity, PPV & NPV of 80% each, whereas for MRE it was 78%, 73%, 70% and 80%, respectively.	Out of the 30 patients included in the study, 11(36.6%) cases were diagnosed with small bowel tumour lesions by both CTE and MRE, with a consistent, accurate diagnosis. Both CTE and MRE provided a panoramic view of small intestine cavity, wall, mesentery, lymph nodes, blood vessels, and adjacent organs.

Author, year	**P**atients	**I**ntervention	**C**omparison	**O**utcome	**Comment**
Faggiano et al 2016	67 patients with a clinical suspicion of intestinal neoplasia	MR enteroclysis		Sensitivity of MR enteroclysis in the diagnosis of small-bowel neoplasms in the sample data was 87.5% and 91.6%, while specificity was 93 and	MR enteroclysis is an accurate modality for detecting small-bowel neoplasm.

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				97.6%, respectively, for readers 1 and 2	
Min et al 2019	34 patients that were found to have a SB protruding lesion on SBCE	Evaluation of the mucosal protrusion angle in differentiating between true submucosal masses and bulges of the small bowel on video capsule endoscopy		small-bowel protruding lesions with a protrusion angle >90° are more likely to represent bulges and may not warrant any additional workup, whereas lesions with angle <90° are more likely to be true masses that should be evaluated for malignancy with enteroscopic or surgical interventions	Acute angle of protrusion accurately discriminated between true submucosal masses and extrinsic compression bulges on Fisher's exact test (p = 0.0001)
Nakano et al 2019	25 patients who underwent DBE and were diagnosed with GISTs. A CT scan preceded DBE	double-balloon endoscopy (DBE) +/- Biopsy		This study showed the diagnostic results of performing biopsies in DBE and that was 46.7% in the patients who obtained biopsy	Low accuracy of biopsy samples in addition to increased risk of post-biopsy bleeding.
Vasconcelos et al 2017	111 patients with histologically proven GISTs in the small bowel	CT	CTE	Diagnosis of GIST in 82% (32/39) of CTE, but in only 30% (13/43) of abdominopelvic CT	CTE superior to CT
		CT	SBCE	CT identified 13/14 tumours while capsule endoscopy identified 5/14, including the one missed by CT.	CT superior to SBCE
Wang et al 2016	190 patients with suspected small bowel diseases were examined with MDCTE and DBE.	Multidetector CT enterography (MDCTE)	DBE	The overall detection rates of DBE and MDCTE were 92.6% and 55.8%, respectively ($P < 0.05$), while the overall diagnostic yields were 83.2% and 33.7%,	The diagnostic value of DBE for small bowel diseases is better than that of MDCTE as a whole, but if gastrointestinal tumours are suspected, MDCTE is also needed to

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				respectively ($P< 0.05$). The sensitivity, specificity, positive predictive value, and negative predictive value of DBE were all higher than those of MDCTE. DBE had a higher diagnostic yield for SSBB (87.3% versus 20.9%, $P< 0.05$). The diagnostic yields of DBE were statistically significantly higher than those of MDCTE for inflammatory diseases, angioma/angiodysplasia, and diverticulums, while being not for gastrointestinal tumours/polyps. (56.1% for MDCTE vs 75.6% for DBE, p=0.096)	gain a comprehensive and accurate diagnosis. In case of small bowel tumours there is no statistically significant difference between MDCTE and DBE, (56.1% for MDCTE vs 75.6% for DBE, p=0.096), regarding diagnostic yield
Zhou et al 2018	32 patients diagnosed with primary GIST of the small bowel	Imaging (computed tomography (CT)/computed tomography angiography (CTA))	DBE	DBE was performed in nine patients (28.1%). Review of the imaging findings of these cases showed that DBE located the lesion in the small bowel in eight out of nine cases (88.9%) of small bowel GIST. DBE did not show the ninth lesion as it was with exophytic growth but a protrusion was identified in the upper part of the jejunum.	The exophytic nature of these lesions may challenge successful endoscopic identification Retrospective review of the imaging detection rates included ultrasound (0%), magnetic resonance imaging (0%), computed tomography (54.8%), computed tomography angiography (71.4%), and DBE (88.9%).

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Dohan et al 2016	19 patients with 27 pathologically confirmed NETSB	MR-enterography (MRE)		On a per-patient basis, MRE had an overall sensitivity of 95% (18/19; 95%CI: 74-100%). On a per-lesion basis, overall sensitivity was 74% (20/27; 95%CI: 54-89%). Regarding detection of NET ≥10 mm, sensitivity was 94% (15/16; 95%CI: 70%-100%). Regarding detection of NET < 10 mm, sensitivity was 45% (5/11: 95%CI: 17%-77%). 7 NETs in 3 patients were not visible on MRE; mean diameter 5.2 mm ± 2.5 (SD) [range: 3 - 15 mm].	MR-enterography shows highly suggestive features for the diagnosis of NETSB and has high degrees of sensitivity for the diagnosis of NETSB on a per-patient basis. Significantly lower sensitivity for lesions <10mm
Gangi et al 2018	178 patients with SBNET	Double balloon Enteroscopy (DBE) to rule out multifocal disease	SBCE to rule out multifocal disease	Preoperatively, 11 patients (10.6%) underwent capsule endoscopy and 45 (53%) patients had a DBE (retrograde and antegrade) performed. Of the patients who underwent DBE, 28 (62.2%) had additional lesions identified, of which 23 patients (82.1%) had the lesions confirmed as NET on pathology of biopsied specimens. In 10.6% of patients that underwent capsule endoscopy, carcinoid tumours were identified in only 2 of	SBNETs have a high incidence of multifocality. DBE can be used in the preoperative assessment to detect multifocal NET. Small number of patients that underwent CE, therefore not enough evidence to compare CE vs DBE regarding identification of multifocality of SBNETs

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				11 patients. Twenty-one patients (75%) who had additional lesions on DBE had a primary tumour in the ileum	
Kim et al 2020	178 patients diagnosed with SBNENs	CT enterography (CTE) or multiphase-CTE (mpCTE) imaging,	Routine abdominopelvic CT	Of the 178 patients, 55 received CT enterography (CTE) or multiphase-CTE (mpCTE) imaging, with 94.5% (n = 52) of these imaging reports identifying a small bowel mass and 90.9% (n = 50) specifically mentioning SBNEN as the diagnosis. In contrast, 85 of these patients underwent routine abdominopelvic CT, with only 44.6% (n = 37) of these clinical reports identifying a small bowel mass and 34.9% (n = 29) specifying that SBNEN as a potential diagnosis	SBNEN detection and correct identification are more frequent with CTE/mpCTE compared to routine abdominopelvic CT SB endoscopy not included Small number of MRI (n=3) but detected 2/3 tumours (66.67%)
Manguso et al 2018	85 patients with primary SBNET who underwent imaging, endoscopy and surgery	DBE (n=41, 39.3%)	Imaging CT (n=72, 67.3%), MRI (n=47, 46.7%), SRI (n=44, 46.7%)	The sensitivity of each in identifying the NET was CT: 59.7% MRI: 54% SRI: 56% DBE: 88.1% Eighteen (21.2%) patients had primary tumours not identified on imaging. Of these 18, 13 underwent DBE, and 12 of 13 (92.3%) DBEs	DBE was significantly better at identifying the primary NET than CT, MRI or SRI (P = 0.004, 0.007, and 0.012). Comparison between CT, MRI, and SRI showed no significant differences in identifying additional small bowel lesions. DBE was found to be significantly better at detecting multifocal disease when compared to

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				identified the primary lesion.	CT (P = 0.010) and SRI (P = 0.004) but not MRI (0.10) Most SBNETs are identified with a combination of imaging modalities. In those with unidentified primary tumours after imaging, DBE should be considered as it may provide valuable information as to the location of the primary tumour.
Rossi et al 2021	6 patients with a suspected sbNEN selected for diagnostic DBE	DBE	Conventional radiological investigations (including CT, MRE and in others not specified)	Five out of 6 of our patients had previous conventional radiological examinations within normal limits whereas DBE identified the tumours in 3 of these patients	DBE showed a sensitivity of 60% and, in absence of false-positive results, a specificity of 100%. Accuracy resulted in 67%. DBE is a safe and effective procedure in the diagnosis of sbNENs, and compared with radiological examinations had no false positive results
			SBCE	4 out of the 6 included patients underwent CE prior to DBE, and the findings were identical in 3 out of the 4 patients.	
Tomba et al 2016	24 CD patients that underwent DBE	DBE in complicated CD.	SBCE (n=22)	Two jejunal adenocarcinomas and an ileal neuroendocrine tumour were detected in	This is the largest international study on the outcomes of DBE in CD demonstrating its usefulness to

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			CTE (n=9) MRE (n=5)	presence of iron-deficiency anaemia. Neuroendocrine tumour was identified at SBCE and DBE in the terminal ileum but was missed by CTE. One case of adenocarcinoma was initially diagnosed on CE and the other on MRE and both then confirmed by DBE	exclude/confirm malignant or premalignant conditions, associated with even minor lesions.
Baheti et al 2015	102 patients with histopathologically confirmed GIST	MDCT		22/41 (54%) tumours were exophytic, 16/41 (39%) had both exophytic and intraluminal components and 3/41 (7%) were intraluminal. The exophytic component was greater than 50% in all except one of the 16 tumours having both the components	Predominant exophytic component of GISTs
Pérez-Cuadrado Robles et al 2015	Consecutive patients who underwent a DBE with final diagnosis of a malignant neoplasm from 2004 to 2014 (n=28) (out of the 89 patients that were diagnosed with SB tumours in general) They were diagnosed by DBE biopsy (n = 18,	DBE	SBCE	DBE was indicated following CE in 17 cases (60.7%) and this procedure confirmed the malignant small bowel tumour (MSBT) in 14 cases (82.4%). The capsule was retained in 4 cases due to SB stenosis identifying the tumour in two of them and retrieved by DBE in all patients.	Among patients with obstructive symptoms, radiological imaging was the first SB study in 6 (75%) cases and direct DBE was performed in 2 (25%) patients. DBE modified outcome in 7 cases (25%), delaying or avoiding emergency surgery (n = 3), modifying surgery approach (n = 2) and indicating emergency SB partial resection instead of elective approach (n = 2).

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	64.3%), histological analysis of surgical specimen (n = 7, 25%) and unequivocal endoscopic findings (n = 2, 7.1%)				DBE is critical in the management of MSBT and may have an impact delaying or avoiding emergency surgery. This procedure clarifies the tumour location and characteristics allowing tattoo injection to guide a possible surgery and provides additional information to other procedures that may be decisive in the clinical course of these patients. DBE allowed histopathological diagnosis in most patients (71.4%), except in GI stromal tumours. The histological detection rate in GIST was low (57.4%) but higher than reported by other authors

Author, year	**P**	**I**	**C**	**O**	**Design**
Zhou et al 2018	32 pts. with surgically resecte4d SB GIST (R0)	Clinical follow-up	none	No endoluminal recurrence during follow-up (3 -54 months, mean 30 months)	Retrospective, single center

Author, year	**P**	**I**	**C**	**O**	**Design**
Nakahara et al 2015	3 cases with malignant SB stenosis 7 months – 4 years after surgery for bilio-pancreatic cancer	SEMS Through the overtube (TTO) after removal of with single balloon enteroscope		successful for survival (1-14 months)	Case reports

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Tsuboi et al 2016	3 cases with malignant SB stenosis	SEMS TTS (n=1) or TTO (n=2),		100% clinical and technical success, survival 29d, 76d, 109 d after stenting	Case reports
Nishimura et al 2018	13 pts. with SB metastasis on imaging or SBCE	DBE with biopsy and ink mark for palliative resection (n=7)	No resection (n=6)	Survival after surgery 47 weeks, without 8.8 weeks	Retrospective, single center
Zhang et al 2017	34 Malignant SB strictures from distal duodenum to deep jejunum	21 SEMS	12 medical treatment	21/22 technically feasible, 19/22 clinical success. Gastric outlet obstruction scoring system (GOOSS) increase ≥ 1. Medical treatment: no increase	single-center comparative clinical observation based on Patient choice

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Task force 4 **Coeliac disease**
Sanders **(Leader)**, Elli

Author, year	Study Objective	Participants/ Setting	Intervention	Comparisons	Outcome	Study Type	Results	Conclusion
Wang et al 2020	Use of image elaboration to diagnose CeD	Outpatients NA	Image elaboration	Histology	Sens, spec	NA	Overall, the accuracy, sensitivity and specificity of the 10-time 10-fold cross-validation were 95.94%, 97.20% and 95.63%, respectively	A novel deep learning recalibration module, with global response and local salient factors is proposed, and it has a high potential for utilizing deep learning networks to diagnose coeliac disease using VCE images.
Vicnesh et al 2019	the use of DAISY descriptors to project two-dimensional images onto one-dimensional vectors	Outpatients Coeliacpatients	Image elaboration	Histology	Sens, spec	Bowel cleansing, measured by Ottawa Bowel Preparation Scale (OBPS), patient satisfaction, acceptance and hunger	The accuracy, positive predictive value, sensitivity and specificity obtained in distinguishing coeliac versus control video capsule images were 89.82%, 89.17%, 94.35% and 83.20% respectively	the computer-aided detection system presented herein can render diagnostic information, and thus may provide clinicians with an important tool to validate a diagnosis of coeliac disease.
Zhou et al 2017	Computer-aided quantitative analysis by a deep learning method helps in alleviating the workload during analysis of the retrospective videos	Outpatients N=6/5	Image elaboration	NA	Quality of bowel preparation assessed by the Boston Bowel	Case control	GoogLeNet achieved 100% sensitivity and specificity for the testing set	A deep convolutional neural network was established for quantitative measurement of the existence and

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					Preparation Scale, patient satisfaction, rate of deviation from the diet, side effects			degree of pathology throughout the small intestine
Branchi et al 2020	To compare sens for villous of axial view capsule vs frontal vew	Outpatients Coeliacpatiens n=25	Axialvew capsule	Forntal view capsule and histology	sensibility	Clinical trial	Twenty-five CD patients were enrolled (four males, age at CE 51.2 ± 16.6 years, age at CD diagnosis 41.7 ± 20.6, years on a gluten-free diet [GFD] 9.6 ± 9.4). Indications at CE were refractory CD in nine cases, non-responsiveness to GFD in 10 and GFD non-compliance in six. A positive finding was evidenced in 15 (60%) and 13 (52%) cases by CapsoCam and PillCam respectively (not significant). Atrophy was detected by both capsules. Considering the percentage of the small-bowel	Lateral/panoramic view CE is effective in the detection of small-bowel atrophy in CD and presents good sensitivity and specificity when compared to histology

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							mucosa presenting atrophy signs, mean values were 22% ± 35 and 20% ± 29 for lateral/panoramic and axial systems, respectively (not significant). Compared to duodenal histology, PillCam correctly identified 80% of patients with SB atrophy, whereas CapsoCam identified 73% of cases.	

Author, publicationyear	Study Objective	Participants/ Setting	Intervention	Comparisons	Outcome	Study Type	Results	Conclusion
Zammit et al 2020	Evaluation of CeD severity with CE	Outpatients Coeliacpatients	capsule	Histology	Clinical data	Case-control	There was substantial agreement in the kappa coefficient for the detection of CD features between reviewers (0.67). Agreement for extent of affected small bowel (SB) mucosa was high (0.97). On multiple regression analysis, several features of CD	The good correlation of CD scores between expert reviewers confirms the validity of features of CD on SBCE. An objective score of CD features in the SB is useful in the follow up of patients with CD and serology

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							correlated with extent of affected SB mucosa for both reviewers. The odds ratios derived from this analysis were then used to score features of CD, enabling scores of severity to be calculated for each patient. The median overall scores for patients increased significantly according to the independent classification of severity by the capsule reviewers: mild (20, 0–79), moderate (45, 25–123), and severe (89, 65–130) (P = 0.0001).	negative villous atrophy
Zammit et al 2021	Evaluation of small bowel injury and BMD two-dimensional images onto one-dimensional vectors	Outpatients Coeliacpatients	Capsule and DXA	NA	BMD % of damaged mucosa	Case series	BMD correlates with the extension of intestinal damage	CE could be useful in CeD monitoring

Author, year	Study Objective	Participants/ Setting	Intervention	Comparisons	Outcome	Study Type	Results	Conclusion

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Zammit et al 2020	Evaluation of uncertainCeD	Outpatients Equivocal Coeliac patients (n=177)	capsule	NA	Finaldiagnosis, atrophy extension	Case series	Overall, 56 patients (31.6%) had a positive SBCE. Thirty-three patients (58.9%) had disease affecting the proximal third of the small bowel (SB). The diagnostic yield of SBCE was 40.0% (22 patients), 51.4% (18 patients), 27.0% (10 patients), and 14.0% (7 patients) in patients with an unknown cause for SNVA (SNVA-UO), patients with SNVA who responded to a gluten-free diet (SNVA-CD), patients with a known cause for SNVA, and patients with railed IELs ± crypt hyperplasia, respectively. In SNVA-UO, SBCE at diagnosis was more likely to be positive in patients with persistent SNVA (10, 90.9%) and persistent SNVA with lymphoproliferative features (4, 80.4%) than patients with spontaneous resolution of SNVA (8, 20.5%) (P = .0001). All patients in the SNVA-CD group who eventually developed adverse events had a positive SBCE (P = .022). They also had more extensive SB disease than those without adverse events (50% vs 1% P = .002). More extensive SB disease on SBCE correlated with a higher SNVA-related mortality in patients with SNVA-UO and SNVA-CD (P = .019). Severity of histologydidnot correlate with mortality (P = .793).	A positive SBCE at diagnosis predicts a worse outcome. More importantly, more extensive disease in these patients is associated with poor survival. Targeting patients with extensive disease at diagnosis with more aggressive therapy can help to improve prognosis.
Luján-Sanchis et al 2017	Capsule endoscoy in equivocal cases of coeliac disease	Outpatients Equivocal Coeliac patients (n=163)	Capsule	NA	Final diagnosis and capsule findings	Case series	The overall DY was 54% and the final diagnosis was villous atrophy (*n* = 65, 39.9%), complicated CD (*n* = 12, 7.4%) and other enteropathies (*n* = 11, 6.8%; 8 Crohn's). DY for groups I to IV was 73.7%, 69.2%, 50% and 44.4%,	CE has a high DY in cases of suspicion of CD and it leads to changes in the clinical course of the disease. CE is safe procedure with a high degree of

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							respectively. Atrophy was located in duodenum in 24 cases (36.9%), diffuse in 19 (29.2%), jejunal in 11 (16.9%), and patchy in 10 cases (15.4%). Factors associated with a greater DY were positive serology (68.3% *vs* 49.2%, $P = 0.034$) and older age ($P = 0.008$). On the other hand, neither sex nor clinical presentation, family background, positive histology or HLA status were associated with DY. CE results changed the therapeutic approach in 71.8% of the cases. Atrophy was associated with a greater TI (92.3% *vs* 45.3%, $P < 0.001$) and 81.9% of the patients responded to diet. There was one case of capsule retention (0.6%). Agreement between CE findings and subsequent histology was 100% for diagnosing normal/other conditions, 70% for suspected CD and 50% for complicated CD	concordance with histology and it helps in the differential diagnosis of CD

Author, year	Study Objective	Participants/ Setting	Intervention	Comparisons	Outcome	Study Type	Results	Conclusion
Zammit et al 2021	Evaluation of RCeD	Outpatients refractory Coeliac patients (n=60)	capsule	NA	Capsule findings	Case series	O Sixty patients with RCD were included. The percentage extent of the affected small bowel (SB) mucosa improved on repeating a second SBCE in 26 patients (49.1%) (median 27.6% vs. 18.1%, P=0.007). Patients with RCD type II had more extensive disease than those with RCD type I on first (41.4% vs. 19.2%,	SBCE can be a useful tool for monitoring the effects of treatment, primarily following its initiation. Patients with RCD type II have more extensive SB disease, equating to a more

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							P=0.004) and second (29.8% vs. 12.0%, P=0.016) SBCE. Patients with RCD type I tended to show a greater improvement in percentage of abnormal SB involved on repeat SBCE compared to those with RCD type II (P=0.049). Nine patients (15%) had RCD-related complications. Five patients developed ulcerative jejunoileitis, 3 patients developed enteropathy-associated T-cell lymphoma, and 1 patient developed cutaneous T-cell lymphoma	aggressive disease pattern.
Ferretti et al 2020	Capsule endoscoy in complicated coeliac disease	Outpatients Equivocal Coeliac patients (n=163)	Capsule	NA	Final diagnosis and capsule findings And mortality	Case series	In total, 130 patients (97 women; age, 49 ± 16 y) underwent 151 CEs and 23 DBEs. The DY of CE was 46%. Patients older than age 50 years (at CE examination or at CD diagnosis) with a CD duration shorter than 5 years were at higher risk of positive CE (relative risk, 1.6 and 1.7 in case of enrollement or CD diagnosis after 50 years of age, and 1.5 in case of short CD duration; P < .05) than their counterparts. Up to 40% of SB lesions were unreachable by upper	In case of suspected CCD, CE should be the first-line approach to detect complications and to identify patients deserving DBE. Older and symptomatic patients with suspected CCD deserve a careful evaluation of the SB, especially during the first years after diagnosis

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							endoscopy. At the end of the diagnostic work-up, 25 patients with premalignant/malignant lesions were identified: 12 type 1 refractory CD (RCD-1), 7 type 2 RCD (RCD-2), and 6 enteropathy-associated T-cell lymphoma (EATL). Six patients died: 2 patients with RCD-2 and 4 patients with EATL.	
Zammit et al 2019	Evaluation of RCeD	Outpatients refractory Coeliac patients (n=48)	capsule	NA	Capsule findings	Case series	Patients with RCD had a greater extent of mucosal involvement on SBCE than patients with uncomplicated CD (42.4+/-34.1% vs 9.7+/-21.7%, p=0.0001). Following treatment with steroids and / or immunosuppressants, patients with RCD had an improvement in the extent of affected small bowel mucosa (42.4+/-34.1% vs 26.4+/-28.9% p=0.012). There was no statistical difference in histology and serology taken at the time of the first and second SBCE in patients with RCD	Our study suggests that SBCE is valuable in documenting the extent of mucosal involvement in patients with RCD. This is the first study that delineates the value of a second look SBCE to assess improvement in the extent of disease in the small bowel following treatment.
Perez-Cuadrado-Robles et al 2018	Evaluation of VCE in non responsiveCeD	Outpatients Non responsive Coeliac patients (n=119)	capsule	NA	Capsule findings	Multicenter case series	Capsule endoscopy was completed in 95.2% of patients (small bowel transit time: 270.5 ± 100.2 min). Global DY was 67.2%, detecting atrophic mucosa (n = 92, 48.7%),	Capsule endoscopy may be a moderately helpful and safe diagnostic tool in the suspicion of complicated CD,

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							ulcerative jejunoileitis (n = 21, 11.1%), intestinal lymphoma (n = 7, 3.7%) and other enteropathies (n = 7, 3.7%, six Crohn's disease cases and one neuroendocrine tumour). The DY of CE was significantly higher in patients presenting with non-responsive disease compared to patients with alarm symptoms (73.8% vs 59.3%, P = 0.035)	modifying the clinical course of these patients
Elli et al 2017	DY of capsule and DAE	RCeD	Capsule enteroscopy or DAE	NA	Enteroscopy findings	Meta analysis	Of the 529 titles initially resulting from the search, 10 studies on capsule enteroscopy (CE) and 3 on double-balloon or push enteroscopy met the inclusion criteria. Overall, 439 and 76 patients were enrolled in these studies using CE and enteroscopy, respectively. Twelve tumours and 47 UJs were found by CE versus 8 tumours and 13 UJs detected by wired enteroscopy. For malignancies the CE yield was 1.9% (95% CI, .5%-3.8%) and wired enteroscopy yield 8.7% (95% CI, 0%-21.2%); similarly, for UJ the DYs were 8.4% (95% CI, 2.1%-17.7%) and 16.7% (95% CI, 8.7%-26.3%); for either UJ or neoplasia the DYs were 13.0%	Enteroscopy is a powerful and efficient diagnostic tool for the detection of SB malignancies in complicated CD.

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							(95% CI, 5.6%-22.5%) and 27.7% (95% CI, 14.8%-42.6%). For RCD the DYs of all enteroscopic techniques were 1.8% (95% CI, 0%-7.7%) for neoplasia, 22.3% (95% CI, 8.2%-39.7%) for UJ, and 27.5% (95% CI, 13.1%-44.2%) for either.	
Tomba et al 2016	DAE in complicated coeliac disease	Outpatients Equivocal Coeliac patients (n=163)	DAE	Non coeliacpatients	DAE findings And mortality	Case series	Twenty-four CD cases (12 males, P=0.01 vs. controls) were reviewed. Mean age at CD diagnosis (y±SD) was 37±20 versus 27±18 and at SB evaluation 47±15 versus 38±13 (P<0.01 compared with controls). Indications for DBE were refractory CD (#9), gastrointestinal symptoms (#6), severe iron-deficiency anaemia (#6), and long standing poor dietary adherence (#3). Two jejunal adenocarcinomas and an ileal neuroendocrine tumour were detected in presence of iron-deficiency anaemia. Three type I and 3 type II refractory CD patients showed jejunal ulcerations; 2 of type II presented small white raised patches. Patchy atrophy was observed in nonadherent patients and in 2 on a gluten-free diet	This is the largest international study on the outcomes of DBE in CD demonstrating its usefulness to exclude/confirm malignant or premalignant conditions, associated with even minor lesions. Studies are needed to understand the clinical relevance of the SB endoscopic features and to optimize DBE indications.

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							for a short time. Therapy was planned in 33% of patients after DBE. No adverse events were detected at follow-up [21 mo (range, 0 to 60 mo)].	

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Task force 5 **Other indications**
Moreels **(Leader),**Perez-Cuadrado Martinez,Fuccio

DAE-ERCP

Author, year	Study Type	Patient Group	Key Outcomes	Key Results	Limitations	Conclusions
Inamdar et al 2015	Meta-analysis of 15 studies SBE-ERCP in surgically altered anatomy: RYGB, HJ, Whipple Long SBE	Patients with history of surgically altered anatomy and biliary indication for ERCP Total of 461 patients	Enteroscopy success Diagnostic success Procedural success Adverse events	Enteroscopy success: 80.9% Diagnostic success: 69.4% Procedural success: 61.7% Adverse events: 6.5% (major AE: pancreatitis, bleeding, perforation, n=1 death due to unrelated embolic stroke) 0% AE in 7/15 studies	Heterogeneity of included studies Only biliary indications Only long SBE	SBE-ERCP has high diagnostic and procedural success rates in this challenging patient population. It should be considered a first-line intervention when biliary access is required after RYGB, HJ, or Whipple.
Shao et al 2017	Meta-analysis of 10 studies DBE-ERCP in surgically altered anatomy: RYGB, HJ, Whipple Short and long DBE	Patients with history of surgically altered anatomy and biliary and/or pancreatic indication for ERCP Total of 301 patients	Enteroscopy success Diagnostic success Procedural success Adverse events	Enteroscopy success: 89.8% Diagnostic success: 79.9% Procedural success: 63.6% Adverse events: 6.3% (major AE: perforation, pancreatitis, cholangitis, bleeding, no mortality) 0% AE in 3/10 studies	Heterogeneity of included studies No long-term follow up Only DBE	Diagnostic and therapeutic DBE-ERCP is feasible in patients with altered gastrointestinal anatomy. DBE-ERCP may be considered when pancreaticobiliary diseases occur in patients undergoing Roux-en-Y reconstruction or pancreaticoduodenectomy. Short DBE may be less efficacious in patients with long surgical limbs.
Klair et al 2020	Meta-analysis of 10 studies DAE-ERCP in surgically altered anatomy: RYGB	Patients with history of RYGB and biliary and/or pancreatic indication for ERCP Total of 398 patients	Enteroscopy success Procedural success Adverse events	Enteroscopy success: 75.3% Procedural success: 64.8% Adverse events: 8.0% (major AE: pancreatitis, perforation, cholangitis, no mortality) 0% AE in 3/10 studies	Heterogeneity of included studies Publication bias of retrospective studies included in the meta-analysis	DAE-ERCP is effective and safe in RYGB patients. Among the currently available techniques, DAE-ERCP is the least invasive approach in this challenging group of patients.

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	Short and long DBE, long SBE, manual spiral enteroscope		Sub-analysis of DBE-ERCP of 4 studies	For DBE-ERCP: Enteroscopy success: 83.5% Procedural success: 72.5% Adverse events: 9.0%		
Anvari et al 2021	Meta-analysis of 24 studies DBE-ERCP in surgically altered anatomy: RY and BII reconstructions Short and long DBE	Patients with history of surgically altered anatomy and biliary and/or pancreatic indication for ERCP Total of 1523 patients	Enteroscopy success Diagnostic success Procedural success Adverse events	Enteroscopy success: 90% Diagnostic success: 94% Procedural success: 93% Adverse events: 4% (major AE: pancreatitis, perforation, cholangitis, no mortality) 0% AE in 6/24 studies	Heterogeneity of included studies Diverse range of surgically altered anatomies	Short and long DBE are safe and efficacious for facilitating ERCP in patients with surgically altered gastrointestinal anatomy.
Tanisaka et al 2021	Meta-analysis of 21 studies SBE-ERCP in surgically altered anatomy: RY and BII reconstructions Short and long SBE	Patients with history of surgically altered anatomy and biliary indication for ERCP Total of 1227 patients	Enteroscopy success Diagnostic success Procedural success Adverse events	Enteroscopy success: 86.6% Diagnostic success: 90.0% Procedural success: 75.8% Adverse events: 6.6% (major AE: pancreatitis, cholangitis, bleeding, perforation, n=1 death due to post-ERCP pancreatitis) 0% AE in 6/24 studies	Heterogeneity of included studies Publication bias of retrospective studies included in the meta-analysis Only biliary indications Diverse range of surgically altered anatomies	SBE-ERCP in patients with surgically altered anatomy on biliary interventions is effective. Although good outcomes were reported for short SBE-ERCP, these should not be directly compared to the outcomes observed for long SBE-ERCP, as they assume different backgrounds and include confounding variables.

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CHRONIC ABDOMINAL PAIN

Study Reference	Study Type	Patient Group	Key Outcomes	Key Results	Limitations	Conclusions
1. Original article Shim KN, *et al*. 2006 *Scandinavian Journal of Gastroenterology* Korean study	Retrospective multicentre study SBCE for unexplained CAP PillCam capsule	Patients with unexplained CAP Total of 110 patients	Diagnostic yield Risk factors for positive findings	Diagnostic yield: 17.3% Risk factors in multivariate analysis: Weight loss: OR 18.6	Retrospective design with possible selection bias and incomplete data on blood analysis Incomplete small bowel examination in 31% of patients	SBCE can be helpful in patients suffering from CAP that cannot be explained by established examinations, if CAP is accompanied by weight loss.
2. Original article Katsinelos P, *et al*. 2011 Greek study	Prospective multicentre study SBCE for unexplained CAP with / without diarrhea PillCam capsule	Patients with unexplained CAP Total of 72 patients	Diagnostic yield Risk factors for positive findings	Diagnostic yield: 44.4% Risk factors in multivariate analysis: Elevated ESR: OR 67.9 Elevated CRP: OR 41.5	Possible selection bias in tertiary referral centres	CAP with/without diarrhea should be accompanied by elevated inflammatory markers to be regarded as a valid indication for SBCE.

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European Journal of Internal Medicine Greek study						
3. Original article Huang L, *et al*. 2018 *Medicine* Chinesestudy	Retrospective single centre study SBCE for unexplained CAP OMOM capsule	Patients with unexplained CAP Total of 341 patients	Diagnostic yield Risk factors for positive findings	Overall diagnostic yield: 28.15% Diagnostic yield CAP with symptoms: 33.16% Diagnostic yield CAP without symptoms: 21.38% Risk factors in multivariate analysis: Weight loss: OR 2.827 Hypoalbuminemia: OR 6.142 Elevated ESR: OR 4.025 Elevated CRP: 7.539	Retrospective design based on medical files only No follow-up data available	SBCE may be helpful for CAP patients to detect small bowel diseases, half of which were inflammatory diseases. Besides, weight loss, hypoalbuminemia, elevated ESR, or increased CRP may be regarded as the indications of SBCE in CAP patients.
4. Original manuscript & Meta-analysis Kim W, *et al*.	Retrospective single centre study SBCE for unexplained CAP MiroCam capsule	Patients with unexplained CAP Total of 65 patients	Diagnostic yield Risk factors for positive findings	Diagnostic yield: 41.5% Risk factors in multivariate analysis: Elevated ESR: OR 1.06	Retrospective design based and limited number of patients	SBCE could be a frontline diagnostic modality to evaluate unexplained CAP with elevated inflammatory markers such as ESR and CRP.

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2021 *Diagnostics* Korean study	Meta-analysis of 3 studies	Meta-analysis with total of 523 patients		Meta-analysis: Diagnostic yield: 28.15% Risk factors in multivariate analysis: Elevated CRP: OR 14.09 Elevated ESR: OR 14.45	Meta-analysis of only 3 studies Heterogeneity of included studies	

DAE-ASSISTED PEJ

Study Reference	Study Type	Patient Group	Key Outcomes	Key Results	Limitations	Conclusions
1. Original article Al-Bawardy B, *et al*. 2016 *Endoscopy* USA study	Case series DBE-assisted PEJ DBE enteroscope	Patients with indication for jejunostomy Total of 94 patients	Technical success Adverse events	Technical success rate: 93% Adverse events: 9% (abdominal hematoma, gastric interposition)	Retrospective single centre case series	DBE-PEJ tube placement was technically successful in a high proportion of patients (93 %) and with a relatively low rate of significant adverse events.
2. Original article	Retrospective single centre study	Patients with indication for PEJ or PEG	Post procedural survival	Multivariate analysis of mortality risk factors after PEJ:	Retrospective single centre study	DAE-PEJ is considered a safe and feasible method of access for enteral feeding.

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Nishiwaki S, *et al*. 2021 *Gastrointestinal Endoscopy* Japanese study	Comparison of PEJ and PEG SBE enteroscope	Total of 115 PEJ and 651 PEG patients	Technical success Adverse events	>80 years of age: OR 1.30 Elevated CRP: OR 1.29 Diabetes mellitus: OR 1.57 Technical success rate: PEJ: 93.9% PEG:97.1% Adverse events: PEJ: 10.1% PEG: 9.3%	All procedures by 1 single endoscopist	
3. Original article Simoes PK, *et al*. 2018 *Journal of Parenteral and Enteral Nutrition* USA study	Retrospective single centre study PEJ using gastroscope or paediatric colonoscope	Patients with indication for PEJ Total of 452 patients	Technical success Adverse events	Technical success rate: 83% Adverse events: Total: 18% Immediate: 3% Delayed: 15%	Retrospective single centre study with incomplete data Use of push enteroscopy technique, no DAE	PEJ is a successful and safe procedure that effectively provides access for enteral nutrition support in malnourished patients and patients with postoperative upper gastrointestinal cancer.
4. Meta-analysis	Meta-analysis of 29 studies	Patients who underwent PEJ or PEG-J	Technical success	Technical success rate: PEJ: 86.6% PEG-J: 94.4%	Heterogeneity of included studies	PEJ and PEG-J are safe and effective procedures with comparable outcomes. PEJ had fewer tube malfunction and failure rates; however, it

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Deliwala SS, *et al*. 2022 *Endoscopy International Open*	Comparison of PEJ and PEG-J	Total of 1874 patients	Clinical success Adverse events	Clinical success rate: PEJ: 96.9% PEG-J: 98.7% Adverse events: Malfunction: PEJ: 11% PEG-J: 24% Major AE: PEJ: 5% PEG-J: 1% Minor AE: PEJ: 15% PEG-J: 25%	Different types of endoscopes	is technically more complex and not standardized, while PEG-J had higher placement rates. The use of DAE was found to enhance PEJ performance.

FOREIGN BODY RETRIEVAL

Study Reference	**Study Type**	**Patient Group**	**Key Outcomes**	**Key Results**	**Limitations**	**Conclusions**
1. Meta-analysis Gao Y, *et al*. 2020	Meta-analysis of 12 studies DBE retrieval of retained SBCE in the small bowel DBE enteroscope	Patients with retained SBCE in the small bowel Total of 150 patients	Retrieval rate EBD rate Adverse events	Retrieval rate: 86.5% Retrieval rate antegrade DBE: 74.7% Retrieval rate retrograde DBE: 26.3% EBD rate: 38.8% in case of benign stricture	Retrospective case series with limited sample size and heterogeneity of retrieval rates	DBE is feasible and safe for removing retained SBCE, and its use could decrease the need for surgery in patients with benign strictures and facilitate subsequent surgery in patients with malignant strictures.

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Scandinavian Journal of Gastroenterology				Adverse events: 1.3% (perforation)		
2. Original article Kim J, *et al*. 2020 *Gastroenterology Research and Practice* Korean study	Retrospective multicentre study DAE retrieval of foreign bodies in the small bowel DBE and SBE enteroscope	Patients with retained foreign body in the small bowel Total of 34 patients	Retrieval rate Risk factors for retrieval rate EBD rate Adverse events	Retrieval rate: 50.0% Risk factors in multivariate analysis: Symptomatic patients: OR 13.4 EBD rate: 17.6% Adverse events: 5.9% (acute pancreatitis, peforation)	Retrospective case series with limited sample size Different types of foreign bodies No differentiation between antegrade and retrograde retrieval rate	DAE can be the first option for foreign body removal in the small intestine. The presence of symptoms was associated with successful enteroscopic retrieval.

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Online Table 3s. DAE-ERCP

Author	Year	Endoscope	N studies	N patients	Enteroscopic success	Diagnostic success	Procedural success	Adverse events	Patient characteristics
Inamdar	2015	SBE (L)	15	461	80.9%	69.4%	61.7%	6.5%	RYGB – HJ – Whipple (B>P)
Shao	2017	DBE (S+L)	10	301	89.8%	79.9%	63.6%	6.3%	RYGB – HJ – Whipple (B>P)
Klair	2020	DBE (S+L) SBE SE	10	398	75.3%	NA	64.8%	8.0%	RYGB
Anvari	2021	DBE (S+L)	24	1523	90%	94%	93%	4.0%	RYGB – Whipple – HJ – BII (B>P)
Tanisaka	2021	SBE (S+L)	21	1227	86.6%	90.0%	75.8%	6.6%	RYGB – Whipple – HJ – RYgastrect – BII (B)

B: biliary indication; BII: Billroth II partial gastrectomy; DBE: double-balloon enteroscope; HJ: hepaticojejunostomy; L: long enteroscope; NA: not available; P: pancreatic indication; RYgastrect: Roux-en-Y gastrectomy; RYGB: Roux-en-Y gastric bypass; S: short enteroscope; SBE: single-balloon enteroscope

