

Small bowel capsule endoscopy vs conventional techniques in patients with symptoms highly compatible with Crohn's Disease

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Abstract

Background & aims: The diagnostic role of Small Bowel Capsule Endoscopy (SBCE) in Crohn's Disease (CD) is under investigation. In a prospective study we investigated the diagnostic role of SBCE in patients with symptoms highly compatible with CD and undefined diagnosis after conventional techniques.

Methods: From September 2005 to May 2009, all patients with clinically suspected CD and not conclusive diagnosis after Ileocolonoscopy (IC), Small Bowel Follow Through (SBFT) and Small Intestine Contrast Ultrasonography (SICUS) were enrolled. Findings compatible with CD included: bowel wall thickness (BWT) >3 mm (for SICUS), ulcers, stenosis/strictures, fistulae (for SICUS, SBFT); >5 aphthoid ulcers, deep ulcers and/or strictures (for SBCE).

Results: Conventional techniques did not lead to a conclusive diagnosis in 30 patients (19 F, median age 31 years, range 8–57), showing chronic diarrhoea (n=27), abdominal pain (n=23), weight loss (n=5), fever (n=5), Iron Deficiency Anaemia (IDA) (n=5) and/or perianal disease (n=4). Findings compatible but not diagnostic for small bowel CD were detected in 19 (63%) by IC in 12 (40%) by SICUS and in 15 (50%) by SBFT. SBCE showed ileal lesions in 15 (50%) patients, including findings compatible with CD in 12 (40%). SBCE retention requiring surgery was observed in 1 patient. A significant concordance was observed between SBCE and IC $k=0.33$ $C(k)=$

Abbreviations: CD, Crohn's Disease; SBCE, Small Bowel Capsule Endoscopy; SBFT, Small Bowel Follow Through; SICUS, Small Intestine Contrast Ultrasonography; IDA, Iron Deficiency Anaemia; BWT, Bowel Wall Thickness; IC, Ileocolonoscopy; CI, Confidence Interval; SBE, Small Bowel Enteroclysis; MRE, Magnetic Resonance Enteroclysis; CTE, CT Enterography; NSAIDs, Non Steroidal Anti-Inflammatory Drugs; CRP, C Reactive Protein; Hb, Haemoglobin.

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[0.25;0.42], but not between SBCE and SICUS $k=0.13$ $IC(k)=[0.045;0.22]$ and between SBCE and SBFT $k=0$ $IC(k)=[-0.089;0.089]$.

Conclusions: SBCE may detect lesions compatible with small bowel CD in almost one third of patients with symptoms highly compatible with CD and not conclusive diagnosis by using conventional techniques.

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1. Introduction

Small bowel involvement is observed in almost two-third of Crohn's Disease (CD) patients.^{1,2} Diagnostic procedures for assessing small bowel lesions in CD traditionally included small bowel follow through (SBFT) or small bowel enteroclysis (SBE).³ More recently, CT-enterography (CTE) and MR-enterography (MRE) provide accurate assessment of small bowel lesions in CD, thus representing the current standards for assessing small bowel lesions.⁴ As an alternative non-invasive technique, ultrasound examination using oral contrast (Small Intestine Contrast Ultrasonography, SICUS) showed a high sensitivity and specificity for assessing small bowel lesions in CD, when performed by an experienced ultrasonographer.^{5–9} Major limits of these techniques include the high radiation exposure (SBFT, SBE, CTE), the need of a nasogastric tube, bowel preparation and/or an experienced operator and a low availability (MRE, SICUS). Ileocolonoscopy (IC) still represents the gold standard technique for assessing CD lesions involving the colon and/or the distal ileum.⁴ However, this procedure may either not visualize the ileum ($\leq 5\%$ incomplete colonoscopy)⁴ or visualize only a few cm of the distal ileum, thus not providing a conclusive diagnosis of CD in subgroups of patients.

More recently, several independent studies concordantly reported Small Bowel Capsule Endoscopy (SBCE) as a non-invasive technique able to visualize small bowel lesions. SBCE showed a high sensitivity and specificity in the diagnosis of CD.^{10–16} At this purpose, a metaanalysis showed an incremental diagnostic yield vs SBFT of 40% (63% vs 23%; $p<0.001$; 95% CI 28–51%), vs ileocolonoscopy of 15% (61 vs 46%, $p=0.02$; 95% CI 2–27%), vs CTE of 38% (69% vs 30%, $p=0.001$; 95% CI 15–60%) and vs push enteroscopy of 38% (46% vs 8%, $p<0.001$; 95% CI =26–50%).¹⁷ In patients with an established diagnosis of CD, SBCE was reported to visualize superficial lesions (i.e. erosions, aphthoid ulcers) better than conventional techniques, thus allowing a more detailed definition of the extent of the lesions. Nevertheless, the clinical relevance of superficial upper SB lesions detected by SBCE in patients with an established diagnosis of CD is undefined. Although the diagnostic role of SBCE in patients with suspected CD has been investigated, the role of this technique vs not only IC and SBFT, but also vs SICUS is not defined. Recently, a growing number of imaging techniques able to visualize the small intestine has been developed and a higher frequency of patients with clinically suspected CD is being observed. These observations prompted us to assess, in a prospective study, the possible role of SBCE for detecting small bowel lesions compatible with CD in patients with symptoms highly compatible for CD and not conclusive findings by using conventional IC, SBFT and SICUS.

2. Materials and methods

2.1. Study population

In a prospective longitudinal study, all consecutive patients referring to our GI Unit from May 2004 to May 2009, with symptoms highly compatible with CD not confirmed by conventional techniques, including ileocolonoscopy, SICUS and SBFT were enrolled.

Inclusion criteria were: 1) Age 18–75 years; 2) Signs and symptoms compatible with clinically suspected CD of the small bowel defined as the presence of at least one the followings: chronic diarrhoea and/or abdominal pain, weight loss, fever, abdominal mass, iron-deficient anaemia (IDA), perianal disease; 3) Conventional techniques (IC, SBFT, SICUS) showing findings not conclusive for CD; 4) Absence of clinical and/or radiological evidence of stenoses/strictures; 5) Absence of known conditions contraindicating SBCE.¹¹

2.2. Study design

In each patient with clinically suspected CD according to the above mentioned criteria, the following parameters were recorded: medical history, laboratory tests (CBC, haemoglobin, serum iron, serum ferritin, CRP, ESR, serologic tests for celiac disease, foecal tests), use of Non Steroidal Anti-Inflammatory Drugs (NSAIDs) or other drugs not related to CD. NSAIDs users were not excluded from the study. NSAIDs have indeed been suggested as possible risk factors for the onset of IBD and not only as potentially harmful drugs inducing small bowel lesions similar to CD.⁴ Additional risk factors for IBD considered in the analysis included smoking habits, previous appendectomy and a family history of IBD. After clinical assessment, compliant patients were enrolled. All 30 patients underwent IC, SBFT and SICUS followed by SBCE (with the exclusion of one patient performing SICUS after SBCE). The presence of strictures/stenoses and the extent of SB lesions were assessed by conventional radiological techniques (SBFT/SICUS).

2.3. Ileocolonoscopy

All endoscopies were performed by the same gastroenterologist and endoscopic findings were documented in all patients by photographic verification.

2.4. SICUS

SICUS was performed after ingestion of 375 ml (range 250–500 ml) polyethylene glycol (PEG) solution.^{5,9} SICUS was

performed with a convex transducer (frequency 3.5–5 MHz) and then with a high frequency linear-array transducer (5–12 MHz) (Hitachi, EUB 6500, Japan). All the ultrasonographic procedures were performed by the same expert gastroenterologist (EC) (>2000 examinations). Positive findings compatible with CD were considered at SICUS^{11,12}: bowel wall thickness (BWT) (≥ 3 mm), “stiff loop” identified as a SB loop with BWT not distended by contrast solution, SB dilation (lumen diameter >2.5 cm); bowel stricture (lumen diameter <1 cm, measured at the level of maximally distended loop, with or without pre-stenotic dilation). The presence of fistulas or abscesses was also considered as described elsewhere.^{5–9}

2.5. SBFT

SBFT examinations were performed according to standard protocols³ and the presence of radiological findings compatible with small bowel CD was reported. Findings considered at SBFT included not only defined lesions (i.e. ulcers, strictures/stenoses), but also any minor changes of the small bowel (i.e. oedema, mild lumen narrowing with no overt stenosis/ulcers, fold thickening, delayed transit time), reported as “doubtful findings”.

2.6. SBCE

SBCE examination was performed by using the Given Pillcam SB capsule system (Given Imaging Limited, Yoqneam, Israel),^{8,10,16,18} After 3 days of a fiber free diet, the evening before SBCE examination, patients underwent bowel preparation by using PEG solution (2 L). All SBCE procedures were performed after an overnight fast. After SBCE procedure, the video images were reviewed by one single experienced gastroenterologist. In the CD group, SBCE findings were reviewed by the same gastroenterologist unaware of results from SICUS, SBFT and ileocolonoscopy. Any small bowel lesion visualized by SBCE was reported, including: erosions (yes/no), aphthoid or deep ulcers (yes/no). As no standardized definition is currently available by using SBCE, the following findings were considered compatible with SB lesions related to CD: aphthoid ulcers (>3), deep ulcers, strictures or stenoses. Erosions, villous dropouts and mucosal breaks were also reported, although these isolated findings were not considered conclusive for a diagnosis of CD. Any other lesion detected by SBCE was also reported.

Planar X-ray of the abdomen was performed after SBCE in patients not reporting capsule excretion after 48–72 h. Retention was defined as a SBCE persistence after 14 days, confirmed by planar X-ray. Possible abdominal symptoms during the retention period were recorded. Incomplete studies were defined when SBCE did not reach the cecum. Adverse events during and after each SBCE procedure, in particular the retention rate were recorded.

2.7. Comparison between findings at SBCE and conventional techniques

In order to compare the presence and severity of small bowel lesions compatible with CD as assessed by SBCE and SICUS, the following parameters were considered: presence (yes/no) and

severity of the lesions (erosions, deep ulcers, aphthoid ulcers, stenosis/stricture) as detected by SBCE vs presence (yes/no) and site (upper vs distal small bowel) of a BWT ≥ 3 (vs <3 mm) or strictures/stenosis as detected by SICUS. Comparison was also made between findings at SBCE (above reported) and at SBFT, including presence, site and type of lesions (aphthoid or deep ulcers, stenosis/strictures). Possible correlations between SBCE findings compatible with upper small bowel lesions and clinical parameters including age, smoking habits, epigastric pain and IDA were also investigated.

2.8. Statistical analysis

Data were expressed as median and range. Results were expressed in terms of presence or absence of small bowel lesions when using each of the 4 tested techniques (IC, SBFT, SICUS, SBCE). Characteristics of the lesions visualized by each imaging technique have been reported. Concordance test was performed in order to compare positive or negative findings (presence or absence of small bowel lesions) when using IC, SBFT, SICUS or SBCE. The concordance between SBCE and IC, SBFT and SICUS was assessed by calculating the kappa index and relative 95% confidence interval (CI 95% (k)).^{19,20}

3. Results

3.1. Study population

During the study period, conventional techniques did not lead to a conclusive diagnosis in 30 patients with symptoms highly compatible with CD (19 F, median age 31 years, range 18–57). Patients were studied within a 12 months time interval, by using 4 different techniques including IC, SICUS and SBFT followed by SBCE. Symptoms referred by each of the 30 patients included at least one of the followings: chronic diarrhoea in 27 (90%; with macroscopic blood in 1 patient), recurrent abdominal pain in 23 (77%), weight loss in 5 (16%), fever in 5 (16%), IDA in 5 (16%) and/or perianal disease in 4 (13%) patients. Among the risk factors for CD, 14 out 30 (47%) patients were smokers, 11 (37%) had previous appendectomy, 5 (16%) a familial history of IBD and 6 (20%) were NSAIDs users at time of the study.

3.2. Ileocolonoscopy

All patients underwent ileocolonoscopy before SBCE, with a median time interval between the 2 techniques of 180 days (range 10–360). All the 30 colonoscopies were completed and the operator visualized the coecum and the ileo-cecal valve. Findings at ileoscopy, SICUS and SBFT in each of the 30 patients grouped according the presence or absence of lesions at SBCE are summarized in [Tables 1 and 2](#), respectively. The distal ileum was visualized by IC in 27 out of the 30 (90%) examinations, while in 3 patients the ileum was not visualized in the absence of overt ileo-cecal valve stenosis (low compliance in 1 or difficult intubation in 2). Findings compatible but not diagnostic for CD were detected by ileocolonoscopy in 19 out of the 30 (63%) patients. Ileal lesions included erosions (n=5 patients, with perianal disease in 1), rare (<5) aphthoid ulcers (n=11 patients), ≤ 3

Table 1 Small bowel findings at ileocolonoscopy, SICUS, SBFT in the 15 patients showing lesions at SBCE (considered not compatible with CD in 3, indicated in bold).

Pt.	Ileocolonoscopy	SICUS (BWT) ^a	SBFT	SBCE
1.FR	Few (n=3) ulcers	4 mm	Normal	Multiple aphthoid ulcers
2.ML	Aphthoid ulcers	Normal	Doubtful findings	Erosions, aphthoid ulcers
3.SC	Erosions	4 mm	Doubtful findings	Deep, aphthoid ulcers
4.PG	Aphthoid ulcers	5 mm	Doubtful findings	Multiple aphthoid ulcers
5.IV	≤ 5 Aphthoid ulcers	Normal	Normal	Multiple aphthoid ulcers
6.TG	Few (n=3) ulcers	4.5 mm	Doubtful findings	Multiple aphthoid ulcers
7.RG	Aphthoid ulcers	Normal	Normal	Multiple aphthoid ulcers
8.LD	Erosions	3.5 mm	Mild lumen narrowing	Multiple aphthoid ulcers
9.VM	Aphthoid ulcers	Normal	Mild lumen narrowing	Multiple aphthoid ulcers
10.CE	Normal ^b	Normal but stenosis ^c	Normal	Ulcerated stenosis ^c
11.CM	Aphthoid ulcers	3.5 mm	Normal	Erosions, aphthoid ulcers
12.BI	Normal	Normal	Mild lumen narrowing	Multiple aphthoid ulcers
13.MM	Aphthoid ulcers	Normal	Normal	2 Erosions
14.FM	Normal	Normal	Doubtful findings	Few erosions
15.MB	Aphthoid ulcers	Normal	Normal	1 Aphthoid ulcer

Minor small bowel lesions at SBCE not considered compatible with CD reported in bold.

Abbreviations: Pt = patient; SICUS = Small Intestine Contrast Ultrasonography; SBFT = Small Bowel Follow Through; SBCE = Small Bowel Capsule Endoscopy; BWT = Bowel Wall Thickness.

^a Bowel wall thickness: n.v. <3 mm.

^b Up to the ileo-cecal valve; ileum not visualized.

^c SICUS after SBCE retention requiring surgical removal.

deep ulcers (n=2 patients), and perianal disease only (n=1 patient, associated in erosions in 1) (Tables 1 and 2).

3.3. SICUS

SICUS was performed in all 30 patients, with a median time interval between the 2 techniques of 150 days (range 15–360). Among these 30 patients, SICUS showed findings compatible with small bowel CD in 12 (40%), represented by an increased BWT in 11 patients (associated with mild lumen narrowing in 3)

and by a stricture with a normal BWT in one patient (Table 1). In this patient, SBCE retention was observed, requiring surgical removal, as detailed below (Fig. 1, panels a–d). In the remaining 17 patients SICUS was normal. No patients showed fistulae or abscesses.

3.4. SBFT findings

All patients were also studied by SBFT, with a median time interval from SBCE of 165 days (range 30–360). In 15 out of

Table 2 Small bowel findings at ileocolonoscopy, SICUS, SBFT and SBCE in the 15 out of the 30 patients showing no lesions at SBCE.

Pt.	Ileocolonoscopy	SICUS (BWT) ^a	SBFT	SBCE
1.MML	Aphthoid ulcers	Normal	Normal	Normal
2. RL	Aphthoid ulcers	Normal	Normal	Normal
3.CA	Normal	5 mm	Doubtful findings	Normal
4.CE	Normal	5–7 mm	Doubtful findings	Normal
5.GG	Erosions	Normal	Normal	Normal
6.TS	Aphthoid ulcers	Normal	Normal	Normal
7.GC	Normal	4.5 mm	Doubtful findings	Normal
8.RA	Erosions	Normal	Normal	Normal
9.FL	Normal	Normal	Doubtful findings	Normal
10.CE	Normal	3.5 mm	Normal	Normal
11.AA	Normal	4 mm	Doubtful findings	Normal
12.MR	Normal	Normal	Doubtful findings	Normal
13.CB	Normal	Normal	Doubtful findings	Normal
14.TA	Erosions, perianal ^b	Normal	Normal	Normal
15.BS	Normal, perianal ^b	Normal	Normal	Normal

Abbreviations: Pt = patient; SICUS = Small Intestine Contrast Ultrasonography; SBFT = Small Bowel Follow Through; SBCE = Small Bowel Capsule Endoscopy; BWT = Bowel Wall Thickness.

^a Bowel wall thickness: n.v. <3 mm.

^b Up to the ileo-cecal valve; ileum not visualized, perianal disease; PA = perianal disease.

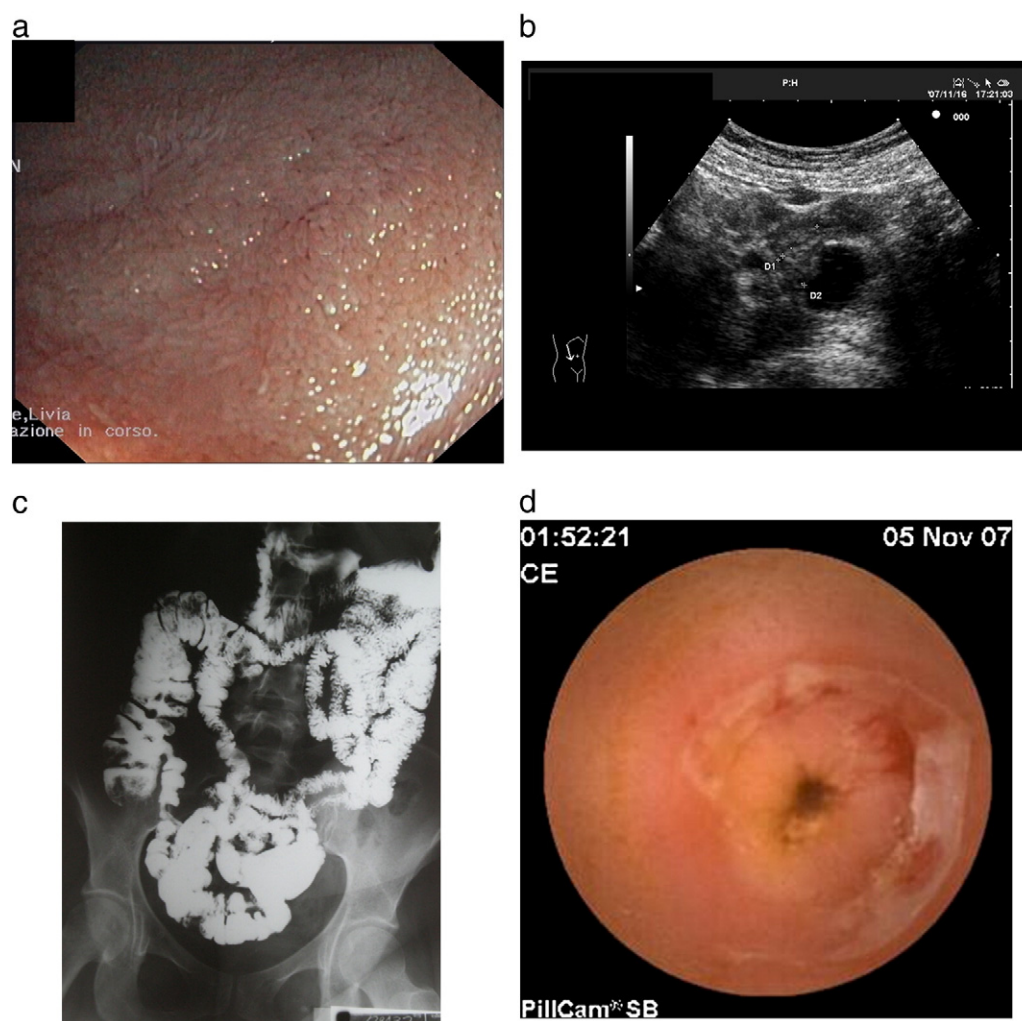


Figure 1 (panels a–d). Small bowel images from one patient (CE) showing IDA of unknown origin. Panel a. Ileocolonoscopy shows no lesions in the distal ileum; Panel b. SICUS performed after SBCE shows a stenosis with a normal BWT; Panel c. SBFT shows no small bowel lesions; Panel d. SBCE stopped at the level of one ulcerated stenosis in the middle small bowel. SBCE retention required surgical removal in the absence of overt symptoms.

these 30 (50%) patients SBFT showed findings suspected but not conclusive for CD, including a mild narrowing with no overt ulcers or stenosis in 3 and other aspecific findings in 12 patients (including fold thickening, delayed transit time and/or, aphthous lesions reported as “doubtful findings”). SBFT was normal in the remaining 15 patients (Tables 1 and 2). None of the 30 patients showed small bowel strictures or stenosis, thus contraindicating SBCE.

3.5. SBCE findings

Findings by using IC, SICUS, SBFT and SBCE in each of the 30 patients, were grouped according to the presence or not of small bowel lesions as assessed by SBCE (Tables 1 and 2, respectively). As shown, SBCE showed small bowel lesions in 15 out of the 30 patients (50%), including findings compatible with CD in 12. Among these 30 patients, lesions detected by using SBCE included multiple aphthoid ulcers with or without associated erosions in 10, one single deep ulcer in 1, one single ulcerated stenosis in 1, and minor changes considered

not compatible with CD in 3 patients (erosions in 2, one single aphthoid ulcer in 1). In the remaining 15 patients, SBCE showed no small bowel lesions.

Among the whole group of 30 patients enrolled for symptoms highly compatible with CD and no conclusive findings by using conventional techniques, SBCE therefore detected small bowel lesions considered compatible with CD in 12 (40%) patients. In one out of these 12 patients (VM), a second IC was performed after SBCE (>1 year interval from the first IC), showed multiple or deep ulcers in the distal ileum, compatible with a diagnosis of CD (Fig. 2, panels a–d).

Capsule retention was observed in 1 patient (3%) (F, 35 years) with a family history of CD and an indication for SBCE represented by IDA of unknown origin. IC and SBFT performed before SBCE showed no abnormalities, in particular no strictures/stenoses (Fig. 1, panels a,c). SBCE images clearly revealed that SBCE stopped at the level of an ulcerated stenosis of the small bowel, with no further progression of the capsule (Fig. 1, panel d). SBCE was retained in the small bowel for up to 5 days, as confirmed by repeated plain film of the abdomen. The patient showed no abdominal symptoms. Nevertheless,

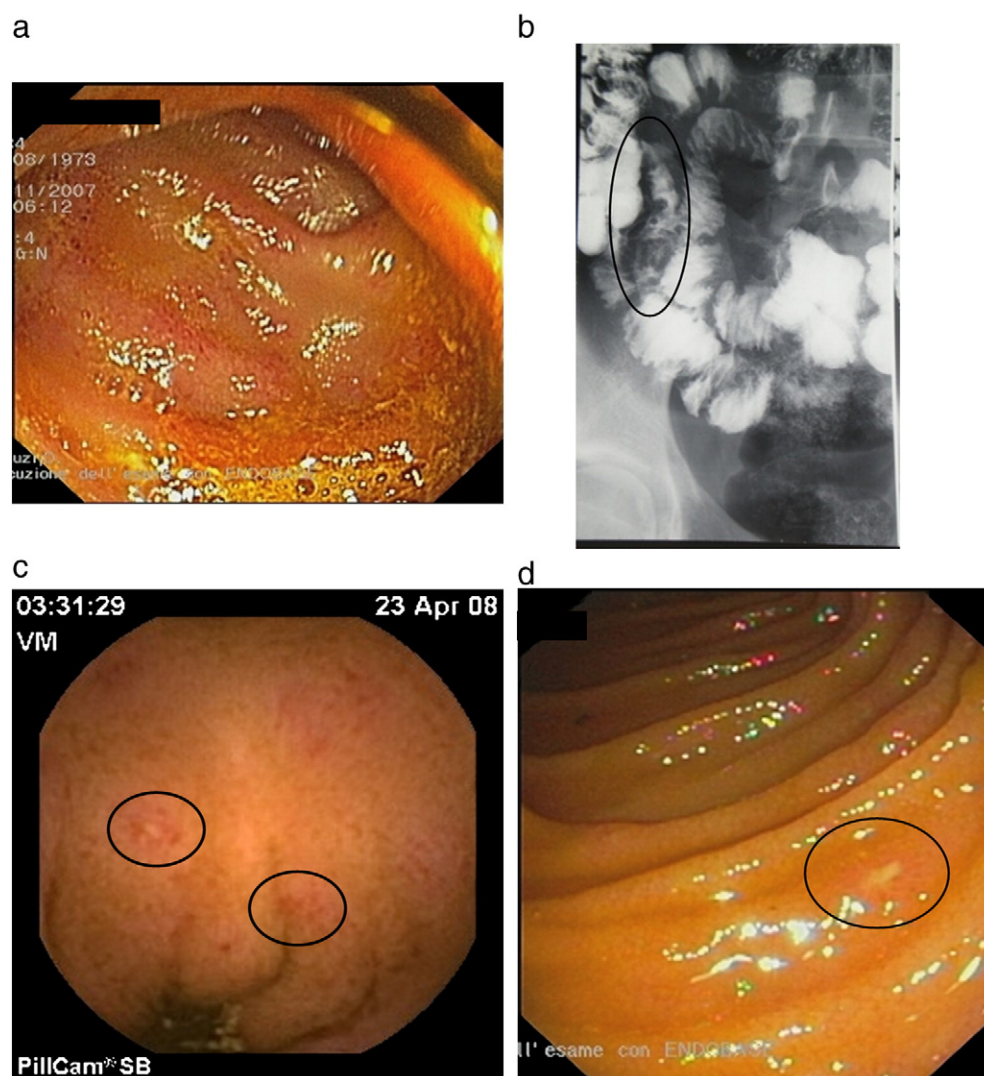


Figure 2 (panels a–d). Small bowel images from one patient (VM) showing chronic diarrhoea, abdominal pain, and weight loss highly compatible with CD. Panel a. Ileocolonoscopy shows few (≤ 5) aphthoid ulcers not conclusive for a diagnosis of CD; Panel b. SBFT shows doubtful findings, including a suspected mild lumen narrowing with no bowel dilation or mucosal alterations. SICUS showed a normal BWT (not shown); Panel c. SBCE shows multiple aphthoid ulcers along the entire small bowel. Panel d. A second IC performed after 12 months, revealed multiple aphthoid and deep ulcers in the distal ileum, confirming a diagnosis of small bowel CD.

surgical indication was given due to the occurrence of SBCE impact at the level of an ulcerated small bowel stenosis of unknown origin, not reachable by the endoscope. SICUS confirmed the presence of a limited small bowel stricture. At surgery, SBCE retention was observed in the middle small bowel, at the level of 2 ulcerated strictures between macroscopically normal mucosa. SBCE was removed, followed by a limited ileal resection and ileo–ileal anastomosis. Histology showed a chronic inflammatory infiltrate at the level of the 2 strictures, compatible with CD. The patient completely recovered and she is currently in follow up.

3.6. Comparison between findings at IC, SICUS, SBFT and SBCE

Among the 30 patients studied by using all the 4 techniques, the numbers of patients showing small bowel lesions were:

19 as detected by ileoscopy, 12 as detected by SICUS, 15 as detected by SBFT and 15 as detected by SBCE. As shown in [Tables 1 and 2](#), discrepant findings were observed by using these techniques. In particular, [Table 1](#) summarizes results from ileocolonoscopy, SICUS, SBFT and SBCE in the 15 patients showing lesions at SBCE. As indicated, among these 15 patients ileocolonoscopy detected ileal lesions in 12, SICUS detected an increased BWT in 7 and SBFT showed lesions not conclusive for CD in 8 patients. Among the 3 patients showing a normal ileum at colonoscopy but lesions at SBCE (compatible with CD in 2), in 2 patients SICUS was negative and SBFT showed doubtful findings. Differently, in one patient (CE) with SBCE retention requiring surgery, both ileoscopy and SBFT were negative while SICUS showed one ileal stenosis. In this patient only SBCE did not reach the cecum, due to the impact.

As shown in [Table 1](#), when comparing the 4 techniques, among the 15 patients showing small bowel lesions at SBCE,

lesions were concordantly detected also by IC, SICUS and SBFT in 4, by IC and SICUS but not by SBFT in 2, by IC and SBFT but not by SICUS in 2; only by IC but not by SICUS and SBFT in 4, or only by SBFT and not by IC and SICUS in 2, and only by SICUS and not by IC and SBFT in 1 patient.

Table 2 summarizes results from ileoscopy, SICUS, SBFT and SBCE in the 15 patients showing no lesions at SBCE. Among these 15 patients, ileoscopy detected ileal lesions in 7, SICUS detected an increased BWT in 5 and SBFT showed lesions not conclusive for CD in 7 patients. When comparing the 4 techniques among the 15 patients showing no small bowel lesions at SBCE, the presence of lesions were detected only by IC in (n=7), by both SICUS and SBFT but not by IC (n=4), by SBFT but not by IC or SBFT (n=3), and by SICUS but not by IC or SBFT (n=1).

When considering all the 30 patients and comparing results in patients showing small bowel lesions by using conventional techniques vs SBCE, findings included: lesions detected by ileoscopy in 19 (confirmed by SBCE in 15, considered compatible with CD in 12), by SICUS in 12 (confirmed by SBCE in 7, considered compatible with CD in all 7) and by SBFT in 15 (confirmed by SBCE in 8, compatible with CD in 7) (Tables 1 and 2).

Findings by using the 4 procedures were quite comparable in the 3 patients performing SBCE almost 1 year after either IC (n=1), SICUS (n=1), or SBFT (n=1), (Table 1, patient 4 PG; Table 2: patient 13 CB and patient 14, TA).

A significant concordance was observed only between small bowel findings using SBCE and IC $k=0.33$ IC(k)=[0.25;0.42], but not between findings using either SBCE and SICUS $k=0.13$ IC(k)=[0.045;0.22] or SBCE and SBFT $k=0$ IC(k)=[-0.089;0.089].

4. Discussion

SBCE is able to visualize small bowel lesions, missed by conventional procedures (SBFT, small bowel enema, SBE, CTE/MRE).^{15,16,21-26} The use of SBCE for the diagnosis of CD is limited by the retention risk related to possible stenosis/strictures and by the low specificity of the findings.^{4,10,27,28} Minor small bowel lesions (i.e. mucosal breaks, erosions) may indeed be visualized by SBCE not only in association with NSAIDs use, but also in almost 10% of normal subjects.^{4,29} Due to these observations, SBCE has a limited use in patients with an established diagnosis of CD, while this imaging technique has been suggested for patients with symptoms highly compatible with CD despite negative endoscopic and radiologic examinations.⁴ A recent meta-analysis including 12 trials (428 patients) further supports this concept, indicating that SBCE is superior to small bowel radiology ($p<0.0001$), CTE ($p<0.00001$), and IC ($p=0.009$) in the evaluation of suspected CD.³⁰

Although the role of SBCE in patients with known or suspected CD has been investigated by several independent studies,^{16,21-26} including comparison with both CTE and MRE,¹⁵ by our knowledge no studies has compared the role of SBCE vs not only IC and SBFT, but also vs SICUS at this purpose. In experienced hands, SICUS indeed shows a high sensitivity and specificity for detecting small bowel lesions, including CD.⁵⁻⁹ Differently from SBCE, SICUS is a non-invasive technique associated with no potential risks. As the

optimal use of the growing techniques able to visualize the small bowel is under debate, in the present study we aimed to assess the role of SBCE for detecting lesions compatible with CD in patients with compatible symptoms and not conclusive findings after conventional IC and SBFT and SICUS.

In our study population, SBCE detected small bowel lesions compatible with CD in almost half of the patients. Although the limited number of tested patients does not allow conclusive statements, present findings further support the role of SBCE for detecting superficial small bowel lesions missed by conventional procedures. Our results also support that in patients with clinically suspected CD and not conclusive findings by using standard imaging, SBCE is a technique able to visualize superficial small bowel lesions not reached by IC and missed by SBFT and/or SICUS. The OMED-ECCO consensus on the role of SBCE in the management of inflammatory bowel disease (IBD), reports that the absence of lesions by using SBCE shows a high negative predictive value for a diagnosis of CD.³¹ This observation supports the diagnostic relevance of the absence of small bowel lesions detected by SBCE in half of our symptomatic study population, thus allowing to exclude a diagnosis of small bowel CD in these patients.

The present study therefore supports that the use of SBCE represents a useful tool for the diagnosis of CD in symptomatic patients. These findings however apply only for patients with symptoms highly compatible with CD, as assessed by tertiary IBD centers, while the worldwide use of SBCE in unselected population of patients is discouraged. This in relation to both the retention risk and to the lack of specificity of small bowel findings detected by SBCE, a technique not providing histological assessment of the lesions. Several non-CD-related conditions may indeed provide small bowel lesions similar to those observed in CD (i.e. NSAIDs use, ischemic enteritis, radiation enteritis). Moreover, almost 10-13% of normal subjects showed small bowel lesions of unknown origin at SBCE.³² Nevertheless, in our study NSAIDs users were not excluded from the analysis, as NSAIDs may not only induce small bowel lesions similar to CD,²⁹ but they have also been suggested as potential risk factors for CD.⁴ Supporting this observation, in our study population IC, SICUS, SBFT and SBCE detected findings compatible with CD in 3 out of the 6 patients with a history of NSAIDs use.

As the diagnosis of CD requires compatible clinical, endoscopic, radiological, histological and biochemical findings, compatible findings at SBCE need to be supported by these conventional criteria. Nevertheless, as SBCE provides the internal view of the entire small bowel, superficial or few lesions in the distal ileum visualized by IC, or minor small bowel changes detected by SICUS or SBFT may show a wider extent or severity when using SBCE, thus supporting a diagnosis of CD. This is in agreement with our findings, showing that among the 15 patients with symptoms compatible with CD and small bowel lesions at SBCE, at least one of the 3 conventional procedures showed either no lesions or not conclusive findings. In 3 patients with clinically suspected CD, doubtful findings by using IC, SBCE and SICUS but small bowel lesions at SBCE, a subsequent second IC showed diffuse aphthoid and/or deep ulcers in the distal ileum, supporting the diagnosis of CD previously suggested by SBCE.

The sensitivity of SBCE for detecting previously unknown small bowel lesions is also supported by our previous study showing a high frequency of asymptomatic upper small bowel lesions in patients with known CD involving the distal ileum.³²

Present findings also support a higher concordance in terms of detection of superficial small bowel lesions between SBCE and IC when compared with both SBFT and SICUS. In particular, among the 15 patients showing lesions at SBCE, small bowel lesions were already detected by IC in 12, SICUS in 7 and SBFT in 8 patients. These findings are in agreement with the observation that SICUS shows a high sensitivity and specificity for detecting established small bowel lesions (i.e. increased BWT, lumen narrowing, strictures, fistulae, abscesses), while its role for detecting superficial mucosal lesions (i.e. erosions, mucosal breaks, aphthoid ulcers) appears less relevant. Superficial small bowel lesions may also be missed by SBFT, showing a lower sensitivity than CTE and MRE, even in experienced hands.^{4,33} In our study population, among the 15 patients showing no lesions at SBCE, conventional techniques detected minor small bowel changes (erosions or few aphthoid ulcers at IC in 6 patients; a BWT ≤ 5 mm in 5 patients at SICUS, doubtful findings in 7 patients by SBFT). Although the absence of lesions by using SBCE shows a high negative predictive value for a diagnosis of CD,³¹ clinical follow up of these patients is recommended. In the 3 patients performing SBCE almost 1 year after either IC (n=1), SICUS (n=1), or SBFT (n=1), findings by using IC, SICUS, SBFT and SBCE were quite comparable. This observation supports that the time interval between the 4 procedures did not significantly influence our findings. It should also be considered that a proper time interval increased the patients' compliance to the study protocol, including 4 procedures (3 quite invasive: IC, SBFT, SBCE) in patients with relatively mild symptoms (although requiring medical advice). This issue may also account for the absence of previous studies, by our knowledge, comparing the usefulness of these 4 diagnostic techniques (IC, SICUS, SBFT vs SBCE) in patients with symptoms compatible with CD.

In our study, a high proportion (50%) of patients showed not conclusive findings when using SBFT, although the examination was performed by experienced radiologists. This finding may be related to characteristics of our study population, showing either absence of few/superficial lesions in the small bowel. SBCE retention was observed in one out of 30 patients (3%), as expected.^{27,28} Although SBCE determined the need of surgery, this procedure allowed a diagnosis of stricturing CD of the middle ileum, missed by conventional techniques, in a young woman with IDA of unknown origin. In this patient, both IC and SBFT were indeed negative, while SICUS showed a small bowel stricture.

In our study, conventional techniques (IC, SBFT, SICUS) showed a high frequency of discrepant findings, thus contributing to a not conclusive diagnosis in patients with clinically suspected CD. This observation should be kept in mind in clinical practice before performing invasive procedures as IC and SBFT, particularly in young patients. The present study also suggests that, in experience hands and when available, SICUS should be preferred to SBFT in patients with symptoms highly compatible with small bowel CD. Our findings also strongly support the need of a careful and appropriate selection of symptomatic patients requiring

sequential diagnostic procedures aimed to confirm a diagnosis of small bowel CD. This is in order to avoid useless, expensive and potentially invasive techniques, associated with possible complications including intestinal perforation (for IC), high radiation exposure (for SBFT), time consuming (for SICUS and SBFT) or retention/impact leading to surgery (for SBCE). Present findings also further support the need to perform conventional procedures, including endoscopic, ultrasonographic and/or radiological procedures before using SBCE aimed to confirm a suspected diagnosis of CD.

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Statement of authorship. The author CP carried out the study and data analyses; SO, GC, MA, and FZ recruited and followed up the enrolled patients; EC performed all SICUS examinations; SZ performed the statistical analysis of the data; FP participated in the study design and revised the manuscript, LB performed all colonoscopies, conceived the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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