Performance of Capsule Endoscopy and Cross-Sectional Techniques in Detecting Small Bowel Lesions in Patients with Crohn's Disease

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Background: Crohn's disease (CD) can be classified according to endoscopic and cross-sectional imaging characteristics. Information regarding disease extent and phenotype may be provided by advanced endoscopic and imaging techniques. In this study, we compare the ability of capsule endoscopy (CE) and cross-sectional imaging techniques (CST) (MRE/Computer Tomography Enteroscopy [CTE]) in detecting small bowel (SB) lesions.

Methods: We retrospectively analyzed 102 patients with a diagnosis of CD who underwent both CE and CST. Only patients with at least a 12-month follow-up after CE were included.

Results: Sensitivity and specificity for the detection of SB lesions were, respectively, 100% and 83.3% for CE, 55.1% and 80% for CTE, and 60% and 82.3% for MRE. CE detected proximal CD lesions in 73% of patients, whereas MRE and CTE detected proximal lesions in 41% and 16% of patients, respectively ($P < 0.001$). Positive findings on CE led to management changes in all patients, in a median follow-up period of 58.7 months. During the follow-up period, 26.5% of patients underwent surgery. Multivariate analysis revealed that moderate-to-severe disease at CE was independently correlated with surgery ($P = 0.03$).

Conclusions: CE has a superior sensitivity for detecting CD lesions in the proximal and medium SB compared with CST. In the terminal ileum, MRE and CTE displayed similar performance to CE.

Lay summary

Crohn's disease is a heterogeneous entity including a variety of complex phenotypes, and there is no single procedure for diagnosis. Capsule endoscopy demonstrated superior sensitivity in the proximal-medium small bowel while extra-luminal complications were detected more accurately by cross-sectional techniques.

INTRODUCTION

Risk stratification and stage-adjustment treatment in Crohn's disease (CD) require the evaluation of disease location, extension, and severity. The Montreal classification is used to assess CD phenotype and location.[1] Although any area of the gastrointestinal system may be affected by CD, the most common site of the chronic inflammatory process is the ileocecal region. Lesions in the proximal region of the small intestine occur in half of the patients with terminal ileal and colonic disease, and one third of patients present isolated small bowel (SB) lesions. Furthermore, a wide number of studies showed that SB disease is associated with more nonspecific symptoms[2] and early complications (ie, strictures, fistulae, and abscesses) that may require surgery,[3] justifying the need for an early and accurate diagnosis of SB-CD.

Standard endoscopy is the preferred method for initial diagnosis and assessment of the extent of terminal ileal and colonic disease, while capsule endoscopy (CE) and cross-sectional techniques (CST) such as magnetic resonance enterography (MRE) and Computer tomography enteroscopy (CTE) are commonly employed for detecting SB involvement.[4]

Extensive consensus has established that, while CST can be used to accurately detect strictures and extra-luminal complications, CE can also assess the severity and the extent of CD mucosal lesions.[5–10]

Based on this background, we retrospectively studied the accuracy of CE and CST in the detection of SB lesions in a cohort of patients with CD. In addition, we evaluated whether CE results correlated with changes in patient management.

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MATERIALS AND METHODS

Patient Selection Criteria

The study was carried out at the IBD-Unit Referral Centre in Bologna. We retrospectively analyzed patients with a diagnosis of CD referred to our center from January 2010 to December 2015, who underwent both CE and at least one CST (in the last 4 months). Only patients with a minimum of 12 months follow-up after the procedure were included.

Clinical data collected included patient demographics, CD duration, previous bowel resections, previous CST and ileocolonoscopy.

Exclusion criteria: any documentation of nonsteroidal anti-inflammatory drug use in the 2 months prior to SB examination; any patient with <6 months of follow-up postprocedure; any patient without a previous ileocolonoscopy and histology (biopsies or surgical specimen); and patients presenting suspected obstructive symptoms (ie, abdominal distention, nausea, vomiting, and episodes of recurrent bowel obstruction).

For each patient, disease severity was assessed via Harvey–Bradshaw Index on the day when CE was proposed to the patient, and Montreal classification of disease phenotype was determined by a blinded physician (S.M.) based on data extracted from patients' medical records. A revised Montreal classification was established by a second blinded physician (G.P.), according to the CST and CE results.

SB was divided in to three main segments: proximal, medial, and distal.[11] Each investigator performing CE or any CST analyzed the severity of the lesions and the segment involved.

Readers were blinded to the patients' clinical information and to other tests results. At the end of the study, the results were compared and discrepancy was discussed reaching a consensus on each segment. Nineteen patients investigated for occult gastrointestinal bleeding were used as a control group.

The study protocol was approved by the *Comitato Etico Indipendente dell'AOU di Bologna* (n°173/2017/O/OssN) and the study was conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

CE Procedures

All patients performed CE after performing CST. The procedures for performing the CE study are described in Supplementary File.

The Lewis score (LS) was used to quantify mucosal inflammation.[12] The SB was divided into equal tertiles by the software application used to calculate the LS. SB lesions were considered as proximally located when detected in the upper two tertiles of the SB with an LS of ≥135. SB inflammatory activity was classified as either mild (135 ≤ LS < 790) or moderate to severe (LS ≥ 790).

Gastric and SB transit time were recorded from the CE studies. In the event of an incomplete study, SB transit time was calculated as gastric transit time minus 480 min. CE studies were defined as complete when the capsule reached the cecum. SB cleanliness was scored from 1 to 3 (1 = free of stool and debris, 2 = some stool and debris, and 3 = full of stool and debris).

The capsule videos were read by two board-certified gastroenterologists (C.C., R.F.) blinded and individually. Capsule retention was defined in accordance with the international consensus on CE[13].

Cross-Sectional Imaging Technique

The procedures for performing the CST study are described in Supplemental File.

At the time of the examination, MRE/CTE was interpreted by 2 radiologists experienced in gastrointestinal imaging (D.M., C.A.), blinded to each other's results. CST readers identified findings indicating active CD: segmental mural hyperenhancement, mural stratification, increased perienteric fat density, sinus tract, or fistula. Fibrofatty proliferation and luminal narrowing in the absence of hyperenhancement were considered as representing inactive CD. Small bowel distension was scored as either sufficient (≥50%, score = 1), or poor (<50%, score = 0) for each examined segment. Image quality was scored as good (diagnostic images without artifacts, score = 3), sufficient (diagnostic images with artifacts, score = 2), or poor (non-diagnostic images, score = 1). A bowel wall measuring ≥4mm was considered as thickened. Small bowel stenosis was defined as a reduction in bowel caliber with dilatation of the proximal segment >2.5 cm and/or a collapse of the distal segment.

Statistical Analysis

The baseline quantitative data are presented as mean ± SD. For discrete variables, Fisher's exact test or the χ^2 test was used as appropriate. Student's *t*-test was used for quantitative variables with normal distribution. Sensitivities and specificities were obtained from 2 × 2 contingency tables and were compared for statistical significance in a clustered exact logistic regression model. Differences in diagnostic yields were tested for statistical significance in a clustered logistic regression model, and modalities were compared with linear combinations of estimators. The statistical tests were defined as having a confidence interval of 95%.

Area under curve (AUC) was calculated plotting the ROC curve. The AUC represents the accuracy, ranges from 0 to 1 and is classified as poor (AUC < 0.5), low (0.5 ≥ AUC < 0.7), moderate (0.7 ≥ AUC < 0.9), or high (0.9 ≥ AUC = 1).[14]

Multivariate analysis was carried out using binary backward stepwise logistic regressions. The risk of surgery was estimated as OR with 95% confidence intervals (CIs). Two-tailed *P*-value < 0.05 was considered statistically significant. All statistical analyses were performed with a statistical software package (SPSS-20).

TABLE 1. Demographics and Clinical Data of the Study CD Patients

Total no. patients	102
Mean age ± SD (years)	40.82 ± 12.8
Males/females	66/55
Disease location	
Ileal	57
Ileocolonic	45
Previous ileal resection	71
Disease duration (years)	9.1 ± 4.3
Medications prior to capsule	
5-ASA	19 (18.8%)
Antibiotics	19 (18.8%)
Infliximab	16 (15.8%)
Adalimumab	3 (3%)
Thiopurines	28 (27.8%)
Budesonide	16 (15.8%)
Harvey–Bradshaw Index (mean ± SD)	11.1 ± 2.3
Total Lewis score (mean ± SD)	1410 ± 527
Gastric transit time (min) (mean ± SD)	35.2 ± 44.1
Small bowel transit time calculated (min) (mean ± SD)	341 ± 51
Non-arrival to cecum	2

RESULTS

Patient Population

The study included a total of 102 CD patients (Table 1). Nineteen patients studied for occult gastrointestinal bleeding were used as a control group. 64 patients underwent CTE, 97 patients underwent MRE and 40 patients underwent both techniques. The most common indication for CST was restaging of disease, while for CE the most common indications were unexplained iron deficiency, obscure GI bleeding, or unexplained symptoms.

Median time between CST and CE was 73.5 ± 10.7 days (range 50–85). Forty-nine patients received a patency capsule prior to CE. Active inflammation in the SB was detected by MRE in 48/94 patients (51%) and by CTE in 27/61 (44.3%) patients. At CE, active inflammation evaluated by LS was 1410 ± 527.

Change in Disease Classification and Location

The majority of patients (56%) had isolated terminal ileal disease. According to CE findings the original Montreal classification had to be revised in 45 patients (44%). In 39 of these cases, a previously unknown proximal SB involvement (L4) was identified. CST were able to confirm this change in the Montreal classification only in 12 out of the 45 patients identified by CE ($P < 0.01$).

Diagnostic Accuracy

In the detection of SB lesions, sensitivity and specificity were 100% and 83.3% for CE, 55.1% and 80% for CTE, and 60% and 82.3% for MRE, respectively (Table 2).

CE demonstrated a significantly higher sensitivity than both CTE ($P < 0.001$) and MRE ($P < 0.001$). Specificities were comparable ($P < 0.5$). Positive predictive values of all examinations were above 90%. Negative predictive values of CE, CTE, and MRE were 100%, 35.3%, and 30.4%, respectively. Diagnostic accuracy (AUC) of CE, CTE, and MRE was 0.921 (±0.04; CI95%: 0.837–1), 0.675 (±0.06; CI95%: 0.549–0.802), 0.712 (±0.06; CI95%: 0.603–0.820), respectively (Fig. 1). Overall intermodality agreement was very weak ($k = 0.195$).

In the detection of lesions in the proximal ileum, sensitivity and specificity were 100% and 94% for CE, 16% and 100% for CTE, and 41% and 100% for MRE, respectively. CE showed a significantly higher sensitivity than both CTE ($P < 0.001$), and MRE ($P < 0.001$). Specificities were comparable ($P < 0.5$). Positive predictive values of CE, CTE, and MRE were 91%, 90%, and 94%, respectively (Table 3).

In the detection of lesions in the medium ileum, sensitivity, and specificity were 100% and 94% for CE, 38% and 82% for MRE, and 17% and 100% for CTE, respectively (Table 3).

Finally, in the detection of lesions in the distal ileum, sensitivity and specificity were 100% and 100% for CE, 88% and 83% for MRE, and 90% and 80% for CTE, respectively (Table 3).

Involvement of the jejunum, proximal ileum, and distal ileum was found in 73%, 44%, and 81% of cases, respectively. Lesions were observed in multiple regions of the SB in 78% of CE procedures. Nearly, all patients with proximal SB involvement also showed involvement in the distal ileum.

Ulcers in the SB were detected by CE in 70/102 (68.6%) of patients: 27 in the proximal SB and 43 in the distal SB. CST detected ulcers in 24 patients (sensitivity 34%), 3 in the proximal SB and 3 in the distal SB. Overall, intermodality agreement was very weak ($k = 0.12$).

Strictures were detected by MRE and CTE in 23 patients (2 in the proximal SB, 4 in medium SB ad 17 in distal SB). CE demonstrated strictures in only 9 (8.8%) patients (2 in the proximal SB, 2 in the medium SB, and 5 in the distal SB).

Interobserver Agreement

Overall interobserver agreement was moderate ($k = 0.49$). For SB lesions, the CE interobserver agreement kappa values ranged between 0.91 (jejunum) and 0.97 (distal ileum), with an overall value of 0.93. The area under the receiver operating characteristic curves for SB lesions ranged from 0.95 (jejunum) to 1.000 (distal ileum).

For SB lesions, the radiologists' interobserver agreement kappa values ranged between 0.77 (jejunum) and 0.94 (distal ileum), with an overall value of 0.83. The area under the receiver operating characteristic curves for SB lesions ranged from 0.92 (jejunum) to 1.000 (distal ileum). Full concordance between the two observers was reached for all cases of perianal disease and other complications.

Bowel Preparation

Bowel preparation with PEG solution was considered excellent in 40 patients (39%), good in 52 patients (51%), fair in 9 patients (9%), and poor in 1 patient (1%) by the capsule reader, indicating an adequate bowel preparation in 92% of cases.

Safety

The CE procedure was well tolerated by all patients. There were no reports of capsule retention or CE-associated complications in our patient cohort. One patient reported an episode of severe abdominal pain and one patient presented nausea and vomiting following the ingestion of methylcellulose double-contrast small bowel enema for MRE.

TABLE 2. Sensitivity and Specificity of CE, MRE, and CTE for the diagnosis of CD in the SB with histology as Gold Standard

	CE (*n = 121*)	CTE (*n = 64*)	MRE (*n = 97*)
Sensitivity % (CI)	100 (96–100)	55 (40–69)	60 (48–71)
Specificity % (CI)	84 (60–97)	80 (52–96)	82 (57–96)
PPV % (CI)	97.1 (91–99)	90 (72–97)	94.1 (82–98)
NPV % (CI)	100 (75–100)	35.3 (20–53)	30.4 (18–45)
AUC	0.92 (0.84–1)	0.67 (0.55–0.80)	0.71 (0.60–0.82)

SB, small bowel; CE, capsule endoscopy; MRE, magnetic resonance enteroscopy; CTE, Computer Tomography Enteroscopy; CD, Crohn's disease.

Follow-up

Positive findings at CE led to a change in medical management (ie, initiation or discontinuation of any IBD-specific medication) in all patients in which these were recorded. During the follow-up period (58.7 months, SD±17.7 months), the most commonly initiated medications were thiopurines and/or biologic agents (91%) (Fig. 2).

In the follow-up period, a total of 27 patients (26.5%) underwent surgery. In particular, 18.6% and 7.8% of patients underwent SB resection or stricturoplasty, respectively. The following risk factors for surgery were identified by univariate analysis: the presence of severe inflammatory activity ($P < 0.001$), and the therapy carried out before ($P = 0.06$) and after CE ($P = 0.01$). In a binary logistic regression analysis considering these variables, the presence of severe inflammation and the type of therapy carried out after CE remained independent risk factors for surgery, with $P = 0.039$ and $P = 0.002$ (95% CI 1.81–16.43), respectively (Table 4).

The number of patients that initiated treatment with either thiopurines or biologics after CE was significantly higher among patients with proximal SB lesions ($P < 0.01$). However, the number of bowel resections during the follow-up period was not different in patients with and without proximal SB lesions.

DISCUSSION

CD is a heterogeneous entity including a variety of complex phenotypes. As there is no single procedure to diagnose CD, diagnosis is currently established through a nonstrictly defined combination of clinical features, endoscopic appearance,

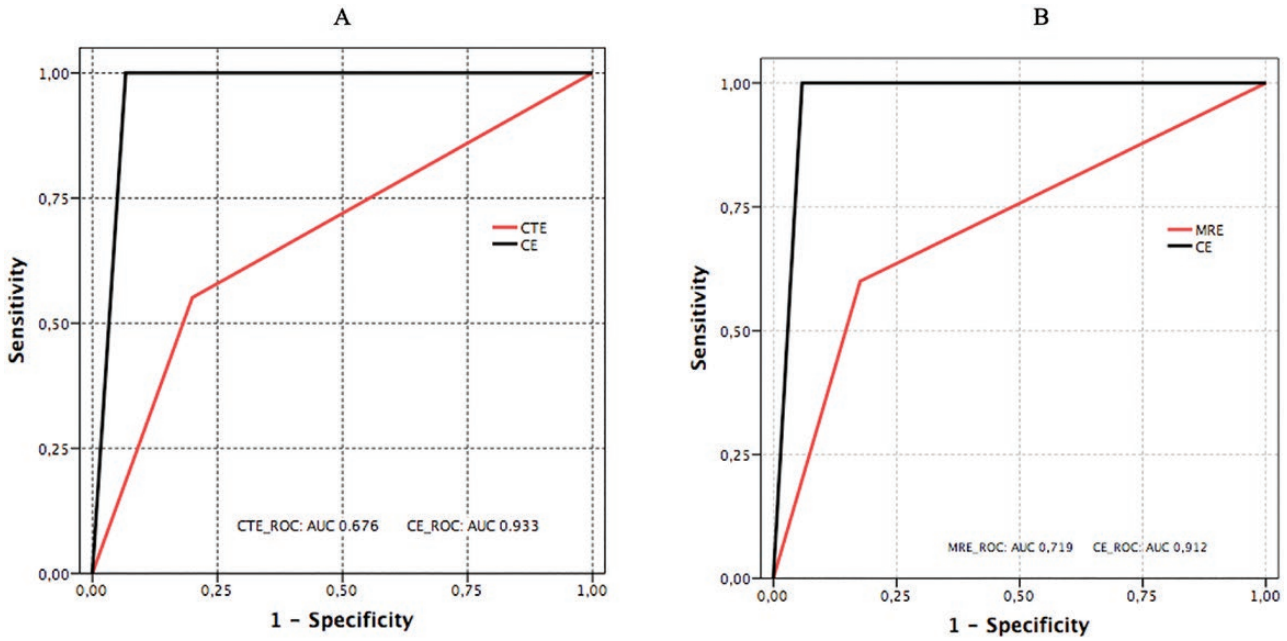

FIGURE 1. ROC curves, graphs show ROC curves for all sites SB lesions, CTE vs CE (A) and MRE vs CE (B).

TABLE 3. Sensitivity and Specificity of CE, MRE, and CTE for the Diagnosis of CD in the Proximal, Middle and Terminal SB

	Sensitivity % (CI)	Specificity % (CI)	PPV % (CI)	NPV % (CI)	AUC (CI)
Proximal					
CE (n = 55)	100 (88–100)	94.1 (66–99)	97.4 (84–99)	100 (76–100)	0.82 (0.71–0.93)
CTE (n = 53)	16.2 (6–32)	100 (75–100)	100 (51–100)	34 (21–49)	0.56 (0.51–0.61)
MRE (n = 53)	41.7 (26–59)	100 (77–100)	100 (74–100)	44.7 (29–61)	0.63 (0.58–0.68)
Middle					
CE (n = 56)	100 (88–100)	94.7 (66–99)	97.5 (80–99)	100 (75–100)	0.72 (0.63–0.79)
CTE (n = 33)	16.7 (4–42)	100 (74–100)	100 (30–100)	50 (31–68)	0.56 (0.51–0.61)
MRE (n = 56)	38.4 (23–55)	82.3 (55–95)	83.3 (57–95)	36.8 (45–77)	0.63 (0.58–0.68)
Distal					
CE (n = 86)	100 (93–100)	100 (77–99)	100 (93–99)	100 (77–100)	0.93 (0.89–0.97)
CTE (n = 45)	90 (72–97)	80 (51–94)	90 (72–97)	80 (51–94)	0.68 (0.55–0.80)
MRE (n = 86)	88.2 (77–94)	83.3 (55–95)	95.2 (85–98)	65.2 (42–82)	0.81 (0.70–0.91)

SB, small bowel; CE, capsule endoscopy; MRE, magnetic resonance enteroscopy; CTE, Computer Tomography Enteroscopy; CD, Crohn's disease.

radiological, histological and surgical findings and serological markers.

The international guidelines suggest the use of endoscopy and CST in order to assess the location and extent of CD[4,5]. CST have a high sensitivity in detecting transmural inflammation and complications[2,15,16], but a low sensitivity in the detection of proximal SB mucosal lesions.[2,9] Furthermore, CST have several limitations such as radiation exposure, limited availability, radiologists' expertise, and patient tolerance of oral contrast material. CE is generally safe[17]; its main complication is capsule retention, which can be avoided by excluding patients with obstructive symptoms or by testing with a patency capsule.[12] CE has demonstrated improved detection of proximal SB lesions compared with CST, whereas the diagnostic yield appears to be similar when lesions are limited to the terminal ileum.[9,15,18-20]

Our study compared the diagnostic accuracy of CE and CST in detecting SB lesions in a large series of patients with active CD. We found that CE was able to identify proximal SB lesions not previously diagnosed by CST in 73% of patients. On the other hand, CST were superior in identifying CD complications such as strictures and fistulae. These results are consistent with prior studies reporting comparable detection rates of active proximal disease by CE.[2,15,16,21–26]

Research has shown that the location of CD typically remains stable following diagnosis, whereas disease behavior tends to progress from an inflammatory phenotype to a more severe stricturing or penetrating disease.[27] Several studies have attempted to determine clinical predictors of severe CD at diagnosis in order to identify patients in which to consider early introduction of disease-modifying treatment (thiopurines or biologics).[28–30] Beaugerie et al[28] have shown that perianal disease, younger age at diagnosis and upper gastrointestinal tract disease are associated with a poor prognosis. The severity of mucosal damage has also demonstrated prognostic relevance in patients before and after surgery. As previously shown in studies by Flamant et al[2] and Dias De Castro et al,[31] we also observed an association between the detection of proximal lesions with CE and the initiation of treatment with immunosuppressants or biologics. The STRIDE initiative suggests endoscopic and/or CST remission as treatment targets in the management of CD.[32] To this end, in patients with documented bowel patency, CE can offer a precise, safe and quantitative assessment of inflammatory lesions, particularly in proximal SB disease.[33,34] The LS, recently validated in established CD,[31] can be used to accurately quantify inflammatory activity and to define mucosal healing.

Our study used the LS to objectively quantify inflammatory activity, and multivariate analysis revealed that only moderate-to-severe inflammatory activity on CE was able to independently predict any type of surgery.

The present study suffers some limits. One of the major drawbacks is that the data concerning the initial assessment of patients is retrospective in nature, as our study population involved patients who in most instances were diagnosed several years prior to entering the study. In addition, the patient population at an IBD tertiary care center such as the one in which this study was conducted may differ from the population in a

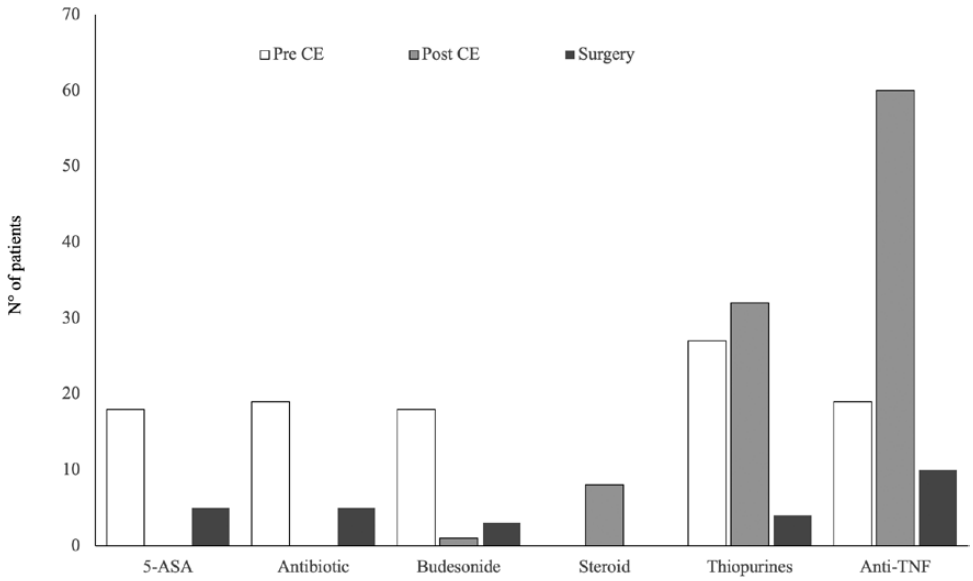

FIGURE 2. Change in treatment management after capsule endoscopy (CE), stratified by therapy.

TABLE 4: Risk Factors for Surgery During Follow-up at Univariate and Multivariate Analysis

	Univariate			Multivariate		
Patient characteristics	OR	95% CI	*P*	OR	95% CI	*P*
Sex (male vs female)	1.19	0.3–3.4	0.997	1.28	0.48–3.42	0.52
Age at CE	0.99	0.9–1	0.678	0.994	0.96–1.03	0.97
Lewis score >790	*		0.001	*		0.03
Proximal SB lesions at CE	1.002	0.3–3.4	0.627	1.061	0.32–3.49	0.63
Therapy before CE	1.55	0.4–5.7	0.06	1.10	0.58–2.09	0.12
Therapy after CE	*		0.01	5.45	1.81–16.43	0.002

* Impossible to calculate.

community practice, potentially rendering the results not generalizable to such a setting.

In conclusion, CE demonstrated superior sensitivity for detecting CD in the proximal and medium SB compared with CST. MRE and CTE showed comparable performance to CE in the terminal ileum. Extra-luminal complications were detected more accurately by CST compared with CE.

CE could become the new gold standard and first-line modality for the detection of SB-CD in patients with suspected or newly diagnosed CD. Early CE could help to more accurately assess the extent and the severity of the disease, leading to important changes in management. The results of this study demonstrated that CE is feasible and safe for monitoring SB mucosal lesions, even in patients with active CD. Furthermore, we found that the information provided by CE had significant implications in patient management during the follow-up period. Cross-sectional imaging and trans-abdominal ultrasonography are complementary to endoscopy in the evaluation of disease activity and complications. While further prospective studies are necessary, our data emphasizes the important role of CE in the management and prognosis of patients with SB-CD.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *Crohn's & Colitis 360* online.

DISCLOSURE STATEMENT

None of the authors have a financial relationship with a commercial entity that produces relevant healthcare products and/or services relevant to this article.

DATA AVAILABILITY

This article provides an analysis of endoscopic records with sensitive data associated. Original data will not be available since it would be not possible to guarantee patients' privacy. Capsule endoscopy: PillCam™ SB 3, Medtronic Parkway, Minneapolis, MN (55432–5604 USA)

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