Accepted Manuscript online: 2022-11-14 Article published online: 2023-01-04

Endoscopic severity and classification of lesions with pan-enteric capsule endoscopy and ileocolonoscopy in ileocolonic Crohn's disease

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submitted 20.6.2022
accepted after revision 11.11.2022
published online 14.11.2022

Bibliography
Endosc Int Open 2023; 11: E32–E38
DOI 10.1055/a-1978-6586
ISSN 2364-3722

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

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ABSTRACT

Background and study aims Recent evidence supports the use of pan-enteric capsule endoscopy (CE) for the diagnosis and follow-up of Crohn's disease (CD). The aim of this study was to examine the agreement between CE and ileocolonoscopy (IC) for determining the severity and classification of lesions in ileocolonic CD.

Patients and methods In a prospective blinded multicenter study, patients with suspected CD were examined with CE and IC within 2 weeks. Ninety-nine participants with a full IC and CE were included in the analysis. The ileocolonic disease severity was assessed with the Simple Endoscopic Score for Crohn's Disease (SES-CD).

Results CD was diagnosed in 30 patients with IC and CE. The mean SES-CD was 9.8 (CI 7.9–11.8) and 10.6 (CI 8.2–13.1), respectively ($P = 0.69$). There was a substantial agreement (ICC 0.83, CI 0.68–0.92) and a strong correlation between SES-CD assessed with IC and CE ($r_s = 0.78$, $P < 0.001$). 55 bowel segments had ulcerations with both modalities (terminal ileum 24, right colon 12, transverse colon eight, left colon eight and rectum three). Mean sub-scores for ulcer size, area of ulcerated surface and area of affected surface did not differ between modalities. The inter-modality agreement (κ) was 0.46, 0.34 and 0.43, respectively ($P < 0.001$).

Conclusions There is a strong correlation between IC and CE for the severity of ileocolonic CD. The agreement for SES-CD sub-scores is fair to moderate. CE could be an alternative to IC for the assessment of endoscopic severity in selected patients with suspected CD.

Introduction

Ileocolonoscopy (IC) with segmental biopsies is the preferred modality for the initial diagnosis and follow-up of ileocolonic

Crohn's disease (CD) [1]. However, the examination is invasive, associated with patient discomfort and a small risk of colonic perforation (<1 per 1,000 colonoscopies), and conscious sedation is often required [2, 3].

Since its FDA approval in 2001, capsule endoscopy (CE) has revolutionized gastrointestinal imaging. CE is highly sensitive, patient friendly [4], less invasive and compared to cross sectional imaging, CE allows a direct and detailed evaluation of the gastrointestinal mucosa with detection of the earliest lesions of CD [1, 5]. Pan-enteric CE is now available, allowing a detailed evaluation of the entire gastrointestinal tract in one procedure, and there is an increasing amount of evidence to support the utility of CE for the diagnosis and follow-up of CD [6–8]. The Lewis score and Capsule Endoscopy Crohn's Disease Activity Index (CECDAI or Niv score) are validated scores for the severity of small bowel CD with CE [9, 10]. The CECDAI was subsequently modified to include the colon [11]. However, the ability of CE to reliably determine the disease activity in ileocolonic CD has not been sufficiently validated against the existing reference standard.

The Crohn's Disease Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score for Crohn's Disease (SES-CD) were developed for IC. Both can determine the luminal disease activity in ileocolonic CD, are highly reproducible, prospectively validated and accepted as reference standard for endoscopic severity in ileocolonic CD [12–15]. The SES-CD was developed as a more user-friendly alternative to CDEIS, and it is used in clinical practice and trials to determine the disease activity and response to treatment. Recently, a modified SES-CD was developed (MM-SES-CD) to better predict endoscopic remission while on active treatment [16]. The MM-SES-CD is based on the same endoscopic parameters and anatomical locations as the SES-CD but assigns multipliers based on the number of ulcerated segments and the different prognostic value of each parameter in each segment. Previous studies found a moderate correlation between the Pillcam Colon 2 and IC and a tendency to underestimate SES-CD with CE [6, 17]. However, additional studies are warranted to clarify the ability of CE to determine the disease activity in ileocolonic CD.

The aim of this prospective blinded study was to examine the agreement between CE and IC for determining the severity of CD, ulcer size and the area of ulcerated surface in patients examined for ileocolonic CD.

Patients and methods

Patients with suspected CD were recruited from three centers in the Region of Southern Denmark managing adult patients with inflammatory bowel diseases. All patients were prospectively enrolled in a clinical trial examining non-invasive modalities for diagnosing suspected CD (http://ClinicalTrials.gov identifier NCT03134586) [4]. Participants who completed a full IC and pan-enteric CE were selected for this analysis.

CD was clinically suspected in patients with diarrhea and/or abdominal pain for more than 1 month (or repeated episodes of diarrhea and/or abdominal pain) associated with a fecal calprotectin > 50 mg/kg and at least one additional finding suggesting CD: elevated inflammatory markers, anemia, fever, weight loss, perianal abscess or fistula, a family history of inflammatory bowel disease, or suspicion of CD after sigmoidoscopy. Use of NSAID's was an exclusion criterion. All patients had a standardized work-up including medical history, physical examination, blood and stool samples, IC, pan-enteric CE, magnetic resonance imaging enterocolonography, and bowel ultrasound within a 2-week period. All examinations were interpreted by specialists blinded to the results of the other imaging modalities, and findings were reported in a standardized fashion. CE was performed before IC to avoid misinterpretation from biopsies, and none of the patients received medical treatment between examinations.

Capsule endoscopy regimen

CE was performed with the PillCam Colon-2 (n = 33) and once commercially available with the PillCam Crohn's capsule (n = 66) (Medtronic, Dublin, Ireland) after the following bowel preparation previously described by ESGE [18]:

- Two days before CE: 10 mg bisacodyl orally at bedtime.
- The day before CE: Clear liquid diet throughout the day. 2 L of PEG ingested in the evening.
- The day of CE: 2 L of PEG ingested before attending the gastroenterology outpatient clinic. First boost: 30 mL of sodium phosphate solution. Second boost: 25 mL of sodium phosphate solution. 10 mg bisacodyl suppository 2 hours after second boost.

Images were reviewed with the PillCam software v9, and findings were reported in a standardized fashion according to the Capsule Endoscopy Standard Terminology (CEST) [19]. A capsule expelled from the rectum defined a complete CE procedure.

Ileocolonoscopy

IC was performed according to standard clinical practice after bowel preparation with sodium picosulfate (Picoprep, Ferring Pharmaceuticals, Saint-Prex, Switzerland). If IC was performed in direct extension of CE (n = 87), patients remained on a clear liquid diet and received no further bowel preparation. A complete IC was documented by intubation of the terminal ileum, and the length of terminal ileum intubation was estimated visually.

Colon cleansing

The colon cleansing was graded on a 4-point scale [20]: Poor (1): Large amount of fecal residue precludes a complete examination. Fair (2): Enough feces or turbid fluid to prevent a reliable examination. Good (3): Small amount of feces or turbid fluid not interfering with examination. Excellent (4): No more than small bits of adherent feces.

Diagnostic criterion and assessment of endoscopic activity

CD was diagnosed with CE and IC by the presence of more than three aphthous ulcerations, irregular ulcers / fissures, or luminal narrowing caused by fibrosis or inflammation. The ileocolo-

Variable	0	1	2	3
Size of ulcers	None	Aphtours ulcers (0.1–0.5 cm)	Large ulcers (0.5–2 cm)	Very large ulcers (>2 cm)
Ulcerated Surface	None	<10%	10–30%	>30%
Affected surface	Unaffected	<50%	50–75%	>75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

▶ **Fig. 1** The Simple Endoscopic Score for Crohn's Disease (SES-CD) [13]. The score is calculated for each of the segments – terminal ileum, right colon, transverse colon, left colon and rectum – and the sum of each segmental score produces the total SES-CD.

nic disease severity was assessed with the Simple Endoscopic Score for Crohn's Disease (SES-CD) (▶ **Fig. 1**) [13]. For each of the segments – terminal ileum, right colon, transverse colon, left colon and rectum – ulcerations were classified as none (0), aphthous 0.1 to 0.5 cm (1), large 0.5 to 2 cm (2) or very large >2 cm (3). The ulcerated surface was rated none (0), <10% (1), 10% to 30% (2) or >30% (3). The affected surface was rated as unaffected (0), <50% (1), 50–75% (2) or >75% (3). The total SES-CD was calculated as the sum of each segmental score. The endoscopic disease severity was defined as inactive (0–2), mild (3–6), moderate (7–15) or severe inflammation (≥16) [21]. The MM-SES-CD was calculated from SES-CD as described elsewhere [16]. With CE, the small bowel disease activity was assessed with the Lewis score [9].

Statistics

Demographic data were analyzed using descriptive statistics. The Wilcoxon rank-sum test was used to compare continuous data in patient subgroups. Differences in diagnostic yields were tested for statistical significance with a logistic regression model examining the effect of modality (IC vs. CE) for the binary outcome CD. Different observers analyzed IC and CE, and modalities were independently assessed. $P<0.05$ was considered significant. Correlation was assessed with Spearman's rank correlation coefficient (r_s), and the inter-modality agreement was assessed with the intraclass correlation coefficient (ICC) and Cohen's kappa (κ). Kappa values were interpreted the following way: absence of agreement 0, slight agreement ≤0.20, fair agreement 0.21–0.40, moderate agreement 0.41–0.60, substantial agreement 0.61–0.80, and almost perfect agreement ≥0.81 as proposed by Landis and Koch [22].

Ethics

The study was approved by the Local Ethics Committee of Southern Denmark (S-20150189) and the Danish Data Protection Agency (journal number 16/10457) and conducted in accordance with the principles of the Helsinki declaration [4]. All patients gave informed consent before participation.

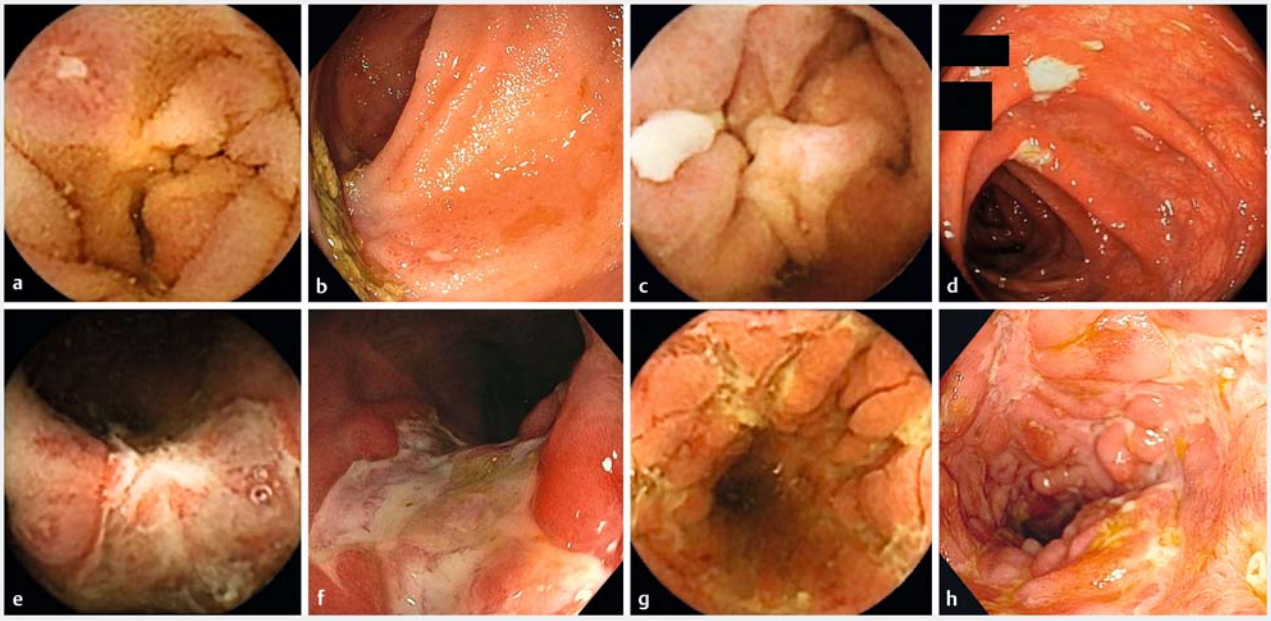
Role of funding sources

The study was initiated, planned and undertaken by the investigators without funding from pharmaceutical companies or the capsule endoscope manufacturer.

▶ **Table 1** Characteristics of 99 patients with suspected Crohn's disease included in the study.

Age (years)	
▪ Mean	30.6
▪ Range	17–68
Gender	
▪ Male	28 (28%)
▪ Female	71 (72%)
Abdominal pain (n)	97 (98%)
No. of bowel movements	
▪ Mean	4.2
▪ Range	every 3rd day–17
Family history of IBD (n)	33 (33%)
Smokers (n)	27 (27%)
Height (cm)	
▪ Mean	172
▪ Range	152–190
Weight (kg)	
▪ Mean	78.8
▪ Range	52–150
BMI	
▪ Mean	26.6
▪ Range	18.9–57.2
C-reactive protein (mg/L)	
▪ Mean	14.7
▪ Range	0.6–122
Fecal calprotectin (mg/kg)	
▪ Mean	828.7
▪ Range	51–6000
Bowel resection prior to inclusion in the study (n)	0

IBD, inflammatory bowel disease; BMI, body mass index.



▶ **Fig. 2** Ulcers of different size with capsule endoscopy and ileocolonoscopy according to the Simple Endoscopic Score for Crohn's Disease. **a** Capsule endoscopy with an aphthous ulceration in the small bowel. **b** Ileocolonoscopy with an aphthous ulceration in the small bowel. **c** Large ulcer in the colon with capsule endoscopy. **d** Large ulcer in the colon with ileocolonoscopy. **e** Very large ulcer in the colon with capsule endoscopy. **f** Very large ulcer in the colon with ileocolonoscopy. **g** Very large longitudinal ulcers with capsule endoscopy. **h** Very large longitudinal ulcers with ileocolonoscopy.

Results

A total of 153 patients were included in the original diagnostic study [4]. CE and IC were performed in 133 and 152 patients, respectively, of which 109 and 130 were complete. Ninety-nine patients had a complete CE and IC, and these patients were included in this analysis. Patient characteristics are shown in ▶ **Table 1**. The bowel preparation quality was rated excellent or good in 48 % of ICs compared to 82 % of CE procedures, and the mean bowel cleansing score was 2.6 and 3.2, respectively (P < 0.001).

Ulcerations were detected with a substantial inter-modality agreement (κ = 0.71, P < 0.001). CD was diagnosed in 33 patients (33.3 %) with IC compared to 39 (39.4 %) detected with CE (P = 0.08). With IC, 64 segments contained CD lesions (terminal ileum 25, right colon 16, transverse colon 11, left colon 12 and rectum 10) compared to 74 segments with CE (terminal ileum 34, right colon 20, transverse colon 11, left colon 10 and rectum six). In 30 patients, both modalities were consistent with CD.

Endoscopic disease severity

IC was consistent with mild, moderate or severe CD in 10 (30.3%), 16 (48.5 %) and seven patients (21.2 %), respectively. Corresponding numbers with CE were 16 (41.0 %), 17 (43.6 %) and six (15.4 %) (▶ **Fig. 2**). In 30 patients with CD detected with both modalities, the mean total SES-CD was 9.8 (CI 7.9–11.8) and 10.6 (CI 8.2–13.1), respectively (P = 0.69). There was a substantial agreement and a strong correlation between the total SES-CD score assessed with IC and CE (ICC 0.83, CI 0.68–0.92; r_s = 0.78, P < 0.001), ▶ **Fig. 3a**. For the terminal ileum, the mean Lewis score was 1250 (CI 872–1628). There was an almost perfect correlation between the Lewis score and the corresponding segmental SES-CD score with IC (r_s = 0.80, P < 0.001).

MM-SES-CD

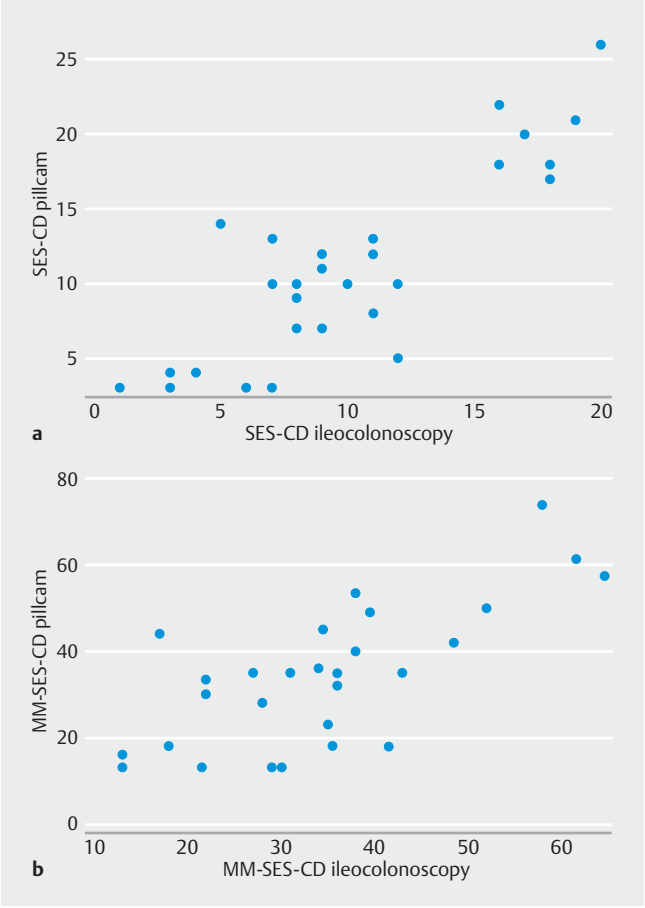
In 30 patients with CD detected with both modalities, the mean total MM-SES-CD 33.1 (27.9–38.3) and 32.9 (CI 26.8–39.0), respectively (P = 0.87). There was a substantial agreement and a strong correlation between the total SES-CD score assessed with IC and CE (ICC 0.75; CI 0.55–0.87; r_s = 0.77, P < 0.001) (▶ **Fig. 3b**).

Lesion classification

In 495 bowel segments assessed with IC and CE, 55 had ulcerations with both modalities (terminal ileum 24, right colon 12, transverse colon eight, left colon eight and rectum three). The mean score for ulcer size was 1.49 (CI 1.32–1.66) and 1.62 (CI 1.41–1.83) with IC and CE, respectively (P = 0.64). Ulcer size was determined with a moderate inter-modality agreement (κ = 0.46, P < 0.001) (▶ **Table 2**).

The mean score for the area of ulcerated surface was 1.49 (CI 1.31–1.67) and 1.56 (CI 1.34–1.78) with IC and CE, respectively (P = 0.91). The area of ulcerated surface was determined with a fair inter-modality agreement (κ = 0.34, P < 0.001).

The mean score for the area of affected surface was 1.84 (CI 1.67–2.06) and 1.66 (CI 1.44–1.87) with IC and CE, respectively



▶ **Fig. 3** **a** The Simple Endoscopic Score for Crohn's Disease (SES-CD) rated with ileocolonoscopy and pan-enteric capsule endoscopy in 30 patients with Crohn's disease ($r_s = 0.78$, $P < 0.001$). **b** The corresponding modified multiplier-SES-CD ($r_s = 0.77$, $P < 0.001$).

($P = 0.19$). The area of affected surface was determined with a moderate inter-modality agreement ($\kappa = 0.43$, $P < 0.001$).

None of the patients had stenosis, and the inter-modality agreement for this parameter was not assessed.

Per segment analysis

The sample size was not sufficient to compare ulcer detection and classification for separate bowel segments.

Discussion

For CE to be feasible and an alternative to IC in clinical practice, it should be able to detect lesions consistent with CD with a high sensitivity and accurately determine lesion size, the area of inflamed mucosa and overall disease activity including mucosal healing. These aspects are pivotal for diagnosis, prognosis, choosing treatment and assessing the response to treatment. With the Pillcam Crohn's, pan-enteric evaluation in one procedure is now possible [6–8, 23]. Although the role of pan-enteric CE in CD is not yet established, it could play a major role in a future algorithm for a noninvasive diagnosis and monitoring of non-complicated CD. The diagnostic performance may be hampered, however, by a poor visibility in the colon affecting the diagnostic yield, lesion classification and assessment of the disease severity.

The present study examined the agreement between CE and IC for determining the disease severity and classification of lesions in ileocolonic CD. We found a strong correlation between the SES-CD assessed with IC and CE, and the mean SES-CD was equal with both modalities. Furthermore, the mean ulcer size, area of ulcerated surface and area of affected surface did not differ between IC and CE, and the inter-modality agreement for lesion classification was fair to moderate. These results suggest that not only has CE a high sensitivity for detection of CD in the colon and terminal ileum, there is also a significant agree-

▶ **Table 2** Inter-modality agreement for classification of lesions with ileocolonoscopy and pan-enteric capsule endoscopy in patients examined for suspected Crohn's disease.

Finding	Mean SES-CD sub-score, 1–3 (CI)	*P* value	Inter-modality agreement (κ)	*P* value
Ulcer size				
▪ IC	1.49 (1.32–1.66)	0.64	0.46	<0.001
▪ CE	1.62 (1.41–1.83)			
Ulcerated surface				
▪ IC	1.49 (1.31–1.67)	0.91	0.34	<0.001
▪ CE	1.56 (1.34–1.78)			
Affected surface				
▪ IC	1.84 (1.67–2.06)	0.19	0.43	<0.001
▪ CE	1.66 (1.44–1.87)			
Stenosis	N/A		N/A	

A total of 55 bowel segments had ulcerations with both modalities. Agreement is expressed as Cohens kappa. Lesions were classified according to the Simple Endoscopic Score for Crohn's Disease. No patients had stenosis.
IC, ileocolonoscopy; CE, pan-enteric capsule endoscopy

ment with IC for lesion classification, extent of ulcerated surface and the overall disease severity. These are pivotal findings for the future clinical use of pan-enteric CE.

A few studies have evaluated the ability of CE to assess the endoscopic severity of ileocolonic CD. D'Haens et al. compared the Pillcam colon 2 and IC in 40 patients with active CD [6]. The mean SES-CD score was lower with CE, and the agreement for the total score was moderate (ICC = 0.50). The score for ulcerated surface was also lower with CE, and CE systematically underestimated the severity of CD. Similarly, a study by Bruining et al. found a moderate agreement between CE and IC for the SES-CD score applied separately for the terminal ileum and colon [8]. In a recent study by Papalia et al., 47 patients with CD were evaluated with the Pillcam Colon 2 and IC [17]. There was moderate correlation between SES-CD scores ($r_s = 0.49$). The correlation was strongest for the terminal ileum ($r_s = 0.77$), decreased in the colon and was lowest for the rectum ($r_s = 0.16$). A similar trend was observed in the study by D'Haens et al., in which ICC decreased from 0.73 to 0.49 from the terminal ileum to the rectum. These findings may relate to a poorer bowel cleansing in the colon compared to the terminal ileum. Eliakim et al. developed a new score for Pillcam Crohn's [24]. The Eliakim score showed a high inter-rater reliability coefficient between two readers (0.9, $P < 0.0001$), and it is currently a recognized quantitative score for the evaluation of pan-enteric endoscopic activity with the PillCam Crohn's capsule. This score, however, was not available at the time the present study was initiated. We did not show a significant difference between IC and CE for classification of ulcers, ulcerated surface and the disease activity overall. However, we analyzed a group of patients undergoing their first diagnostic work-up for CD, and patient characteristics may differ from previous studies. Furthermore, we achieved a good or excellent bowel cleansing in the majority of CE's, which could influence results. The frequency of CD in separate colonic segments was not sufficient for a comparison of CE and IC on a segmental level.

Recently, the SES-CD score was further developed for a better ability to predict endoscopic healing while on medical treatment (MM-SES-CD) [16, 25]. The MM-SES-CD is calculated from the SES-CD score by assigning multipliers based on the number of ulcerated segments and different prognostic values for each parameter in each segment. For a correct classification, it is crucial that lesions are precisely located, which can be a major challenge with CE. Localizing lesions in the colon can be extremely difficult except for the cecum and the rectum, where landmarks are clearly visualized (the ileocecal valve and anal canal, respectively). Despite these difficulties, we found similar good results when comparing the MM-SES-CD score for IC and CE. Scores were equal and showed a strong correlation between modalities.

Strengths and limitations

In this prospective multicenter study, we included patients with clinically suspected CD. This population is appropriate for non-invasive diagnosis with CE because the majority of patients have non-complicated disease as the initial presentation. Single experienced gastroenterologists at each participating center performed the examinations. Variations between multiple observers were not accounted for in this study. The bowel preparation quality was significantly better with CE compared to IC, which could have influenced the classification of lesions and the inter-modality agreement. IC was performed the day after CE in 87 patients (88 %), and patients not complying with the fasting rules could have caused the observed difference. However, this is merely speculations.

The SES-CD was developed in patients with known CD, and it is an accepted standard for determining the endoscopic severity of ileocolonic CD with IC. In this study, we applied the SES-CD in patients undergoing their first diagnostic work-up for CD. Only patients with a firm diagnosis of CD with both modalities were included in the analysis. The sample size and prevalence of CD was not sufficient for a comparison between different bowel segments. At the time when this study was initiated, there was no available score for assessing ileocolonic CD with CE other than CDEIS and SES-CD [11]. Hence, we applied SES-CD for the ileocolon with both CE and IC, and the Lewis score for the terminal ileum with CE. Other scores of endoscopic severity were not applied.

Conclusions

In conclusion, CE is a patient friendly and minimally invasive modality with a high sensitivity for detection of CD in the small bowel and colon. The current study examined the agreement between IC and CE for classification of lesions and disease severity. Although contents of the colon can obscure visibility, we found a strong agreement between IC and CE for detection of CD lesions and determining the overall disease severity. The ulcer size, ulcerated surface and area of affected surface was not significantly different between modalities, and the agreement for SES-CD sub-scores is fair to moderate. These findings suggest that CE can be used as a patient-friendly alternative to IC for the assessment of disease severity with SES-CD in selected patients with suspected CD.

Acknowledgments

This work was supported by public grants from the Region of Southern Denmark and the Research Council Lillebaelt Hospital. The Danish Colitis and Crohn's Association granted further support.

Competing interests

The authors declare that they have no conflict of interest.

Funding

Region of Southern Denmark 16/9780 & 19/37100
The Danish Colitis and Crohn's Association
Research Council Lillebaelt Hospital

Clinical trial

ClinicalTrials.gov (http://www.clinicaltrials.gov/)
NCT03134586
TRIAL REGISTRATION: Prospective cohort study NCT03134586 at ClinicalTrials.gov (http://www.clinicaltrials.gov/)

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