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Intestinal ultrasound in patients with suspected Crohn's disease – results of a prospective evaluation by trainees

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Abstract

Background and aims: Intestinal ultrasound (IUS) performed by experts is a valuable tool for the diagnostic work-up and monitoring of Crohn's disease (CD). However, concern about insufficient training and perceived high inter-observer variability limit the adoption of IUS in CD. We examined the diagnostic accuracy of trainee-performed IUS in patients with suspected CD.

Method: Patients recruited to a prospective trial investigating the diagnostic accuracy of magnetic resonance enterocolonography (MREC) in patients with clinically suspected CD underwent IUS performed by trainees. The primary end-point was IUS per-patient sensitivity and specificity for ileocolonic CD determined by ileocolonoscopy.

Results: 129 patients with clinically suspected CD and a complete IC and IUS were included in the analysis. IUS detected signs of CD in 49 cases (small bowel 31, colon 15, small bowel, and colon 3). The sensitivity and specificity for detection of ileocolonic CD by trainee performed IUS improved during the first to the second half of the study period from 57.1% (CI 34.0-78.2) to 73.1% (CI 52.2-88.4) and 76.5% (CI 58.8-89.3) to 89.7% (CI 72.6-97.8). The overall sensitivity and specificity of diagnosing CD with IUS were 65.4% (CI 50.9-78.0) and 80.5% (CI 69.9-88.7). There was no difference in diagnostic performance between IUS and MREC for the detection of CD.

Conclusion: Trainees improved during the study, and IUS performance in disease detection corresponded to expert-evaluated MREC.

Registered at ClinicalTrials.gov (NCT03134586).

Keywords: Crohn's disease, intestinal ultrasound, magnetic resonance imaging, diagnostic imaging

Background

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) characterized by transmural inflammation, segmental distribution, and frequent recurrent episodes of intestinal inflammation.[1] A steady increase in the incidence and prevalence of CD[2] and increased focus on mucosal healing have led to an increased need for diagnostic workups and monitoring.[3] Ileocolonoscopy (IC) is the first-line exam for assessing CD, but several drawbacks exist. It is an invasive procedure that requires bowel cleansing and introduces the risk of bowel perforation. Furthermore, the terminal ileum is not reached in up to 15% of the procedures[4], and the procedure is associated with considerable patient-experienced discomfort. IC is, therefore, not ideal for frequent examinations, nor does it visualize the small bowel proximal to the terminal ileum or extra-visceral lesions, e.g., abscesses, fistulas, etc. Intestinal ultrasound (IUS) offers an excellent alternative to monitor disease activity and has significant advantages. It is non-invasive, fast, cheap, and requires no preparation. The diagnostic accuracy of IUS in patients with established CD corresponds to that of magnetic resonance enterography [5-7], and the interobserver agreement is substantial.[8, 9] Nevertheless, general concern for inter-observer variability, operator-dependent factors, and unfamiliarity with IUS indications and techniques probably limit the further implementation of IUS.[10] Consensus guidelines recommend a high level of experience, and dedicated training in bowel ultrasound is necessary and should preferably be performed following training in general abdominal ultrasound.[11] In most studies, IUS is performed by highly experienced operators with a particular interest in the field. It thus raises the question of whether gastroenterologists with limited IUS experience can achieve acceptable diagnostic accuracy.

This study aimed to evaluate the diagnostic accuracy and patients' experienced discomfort of IUS when performed by trainees compared to MREC in patients with suspected CD.

Methods

Study population

All patients were enrolled in a prospective, blinded, multicenter study from June 2016 to July 2020, where we assessed the diagnostic accuracy of pan-enteric capsule endoscopy and magnetic

resonance enterocolonography (MREC) in patients with suspected CD (ANDI-trial)[12]. As part of the work-up, patients underwent IUS.

Eligible patients were ≥16 years old with no prior IBD diagnosis but suspected clinically of CD. CD was suspected in patients with diarrhea and/or abdominal pain for more than one month (or repeated episodes of diarrhea and/or abdominal pain) associated with negative serologic markers for celiac disease, negative stool culture (or polymerase chain reaction) for pathogenic bacteria, 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. Use of NSAIDs, renal failure, known gastrointestinal disorder, drug abuse, pregnancy, acute bowel obstruction, implanted magnetic foreign bodies, or an IC performed three months before inclusion were exclusion criteria.

Patients were included from Odense University Hospital and the University Hospitals of Southern Denmark in Vejle and Esbjerg.

IUS

IUS was done before the other diagnostic examinations but on the same day as MREC. Examinations were performed using a standardized protocol following the recommendations of EFSUMB[11]. We used two ultrasound machines (Acuson S3000 or Acuson Sequoia, Siemens Medical Solutions USA, CA, USA) and two probes (abdominal convex, 1–6 MHz and linear, 4–9/5–10 MHz). Increased bowel wall thickness (BWT) was measured in the longitudinal section, and the cut-off for all segments was >3.0 mm.[13] The vascularity within the affected bowel wall areas was assessed according to the Limberg score using duplex US examination with flow settings 5–7 m/s.[14] (Example in figure 1.) Operators had to make an overall and segmental decision on whether CD was present and record: BWT, vascularity, fatty wrapping, stratification of layers, and signs of stenosis, fistula, or abscesses. The image quality was categorized into Poor, Acceptable, and Good (See supplement S1). The Simple Ultrasound Score for Crohn's Disease [SUS-CD] was used for activity assessment.[15] IUS was performed supine after 4 - 6 hours of fasting. Intravenous contrast agents were not administered.

Reference modalities

As described previously[12], MREC was conducted following an overnight fasting period using a 1.5 Tesla Philips Intera MRI unit (Eindhoven, Netherlands) equipped with a Syn-body coil. To ensure optimal visualization, 1 L of Mannitol 7.5% solution was ingested 1.5 hours before the examination. Intravenous administration of Hyoscine butylbromide 20mg was performed to minimize artifacts caused by bowel peristalsis. For post-contrast assessment, 15 ml of gadoterate meglumine (0.5 mmol/ml) (Dotarem®, Guerbet, Raleigh, North Carolina, USA) was administered intravenously. Imaging sequences included cor T2, B-FFE, T1, SPIR, axial T1w, and diffusion-weighted sequences. The diagnosis of CD involved evaluating the following findings: mucosal ulcerations, bowel wall thickening (≥ 3 mm), bowel wall hyper-enhancement, diffusion restriction, bowel stenosis, creeping fat, dilated vasa recta, and the presence of an abscess or fistula in conjunction with a diseased bowel segment.[13] The diagnosis was based on an overall evaluation of lesions consistent with CD. The severity of CD was assessed using the MaRIA score.[16]

The IC was conducted according to standard clinical practice, following bowel preparation with sodium picosulfate (Picoprep®, Ferring Pharmaceuticals, Saint-Prex, Switzerland). In cases where IC was performed the day after panenteric capsule endoscopy, patients were placed on a clear liquid diet and received no further bowel preparation. Successful IC was confirmed by intubation of the terminal ileum. CD was defined endoscopically by more than three ulcerations (aphthous lesions or ulcers), irregular ulcers/fissures, or stenosis caused by fibrosis or inflammation.[17] The severity of ileocolonic disease was assessed using the SES-CD (Simple Endoscopic Score for Crohn's Disease).

All examiners were blinded to the findings of the previous examination. MREC was used as a comparison to a cross-sectional modality. IC served as the clinical reference standard for both IUS and MREC. All exams were performed within 14 days.

Operators

Four physicians performed the IUS examinations. Two radiologists with 15 and 30 years of experience in general abdominal ultrasound, but not IUS experts, and two gastroenterologists (IUS trainees) with less than 50 IUS examinations before the study started.

Patients experienced discomfort

Patients filled in the visual analog scales for physical and psychological discomfort after the IUS examination. Both scales were 10 cm; 0 cm equals no discomfort, whereas 10 cm equals the worst imaginable discomfort.

Statistics

Only subjects with no protocol deviation, a complete IC, and IUS were eligible for study analyses. Sample size calculations for diagnostic test accuracy were based on capsule endoscopy and MREC for the ANDI-trial[12] and not separately for IUS. Continuous data were summarized using descriptive statistics, and confidence intervals (CI) levels of 95% were used. The sensitivity and specificity of IUS diagnosing CD in the terminal ileum and colon were calculated on 2 x 2 tables. The area under the receiver operator characteristic curve (AUC) was used as a measure of diagnostic performance. Comparisons to MREC included only subjects with all three exams performed. The difference in sensitivity and specificity between IUS and MREC was tested with McNemar's test [18, 19].

To evaluate whether the IUS experience acquired during the study influences the diagnostic performance, we divided the participants, based on inclusion number, into Group A (IUS performed in the first half of the study period) and Group B (IUS performed in the second half of the study period). The two groups' diagnostic performances were compared (DeLong method)[20]. This analysis is solely based on the examinations performed by the trainees. We created a combined CD and ulcerative colitis variable to adjust for misclassification, confounding the diagnostic accuracy. The Wilcoxon matched-pairs signed-ranks test was used to compare the differences in patients experienced discomfort during IC, MREC, and IUS examinations.

Statistical analyses were performed using Stata (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC).

Data management and collection

Study data were collected and managed using REDCap electronic data capture tools hosted at OPEN – Region of Southern Denmark.[21] All authors had access to the study data, reviewed and

approved the final manuscript. The trial protocol and data underlying this article will be shared on reasonable request to the corresponding author.

Ethical considerations, approvals, and registration

The study was conducted following the principles of the Helsinki Declaration and was approved by the regional ethics committee of Southern Denmark (S-20150189) and the Danish Data Protection Agency (16/10457). Before participation, patients gave informed consent, both oral and written. If the participant was 15 to 17 years of age, then both parents and the patient consented. The study was registered at ClinicalTrials.gov (NCT03134586).

Results

129 patients were eligible for analysis; see the flow chart in Figure 2 and patient characteristics in Table 1.

The image quality of IUS was rated good or adequate in 89% (n=114) of the cases. 110 (85%) IUS examinations were performed by trainees (gastroenterologists) and 19 (15%) by radiologists.

IUS detected signs of CD in 49 cases (small bowel 31, colon 15, small bowel and colon 3), with a mean and median SUS-CD score of 2.4 (standard deviation (SD) 1.1) and 2 (range 1-6).

Diagnostic performance

The trainee-obtained sensitivity and specificity for diagnosing ileocolonic CD with IUS was 66.0% (CI 50.7-79.1) and 82.5% (CI 70.9-90.9). The AUC for IUS was 0.74 (CI 0.66-0.83). Separate results for the terminal ileum and colon are available in Table 2.

The sensitivity and specificity of IUS for the detection of disease during the first half of the study period was 57.1% (CI 34.0-78.2) and 76.5% (CI 58.8-89.3) vs. 73.1% (CI 52.2-88.4) and 89.7% (CI 72.6-97.8) in the second half. The AUC increase from 0.67 to 0.81 is not significant (p=0.09). See Table 2 for further details.

IUS compared to MREC with IC as the reference standard

One patient did not have an MREC, and in a comparative analysis of 128 patients examined with both IUS and MREC, no significant differences were found in overall sensitivity (65% vs. 69%, p=0.83), specificity (80% vs. 76%, p=0.56) or AUC (0.73 vs. 0.73, p=0.99).

IUS's sensitivity and AUC were significantly superior to MREC for detecting colonic CD (37% vs. 18%, p=0.02; 0.65 vs. 0.55, p=0.02). However, there was no difference in the combined detection of CD or UC (p=0.36). Neither was there any difference in specificity.

In eight patients, CD was detected by IC and MREC, but IUS performed by trainees missed it. The CD was predominantly located in the terminal ileum (7 out of 8 cases), with a disease extent not exceeding 6cm (median 3.57cm, range 3-6). The median SESCD score was 3 (range 1-20), and the median MaRIA score was 9.8 (range 6-15). MREC and IUS failed to identify the colonic lesions in two of these cases. The eight patients had a mean BMI of 27 (SD 4.4). In general, although not statistically significant, a trend suggested reduced accuracy with increasing BMI, with an AUC of 0.75 in patients with a BMI below 25 compared to 0.65 in those with a BMI above 25 (p=0.2).

Patient experienced discomfort

93 patients (72%) completed the questionnaire. The median score on a 10-point VAS scale was 0 (range 0-9) and 0 (range 0-4.5) for physical and psychological discomfort, respectively. IUS was associated with less physical and psychological discomfort than IC and MREC ($p < 0.001$); see results in Table 3. The mean physical discomfort reported during IUS performed by trainees was 0.6 (SD 1.5), while for exams performed by radiologists, it was 1.7 (SD 2.1), p=0.01. Notably, there was no significant difference in psychological discomfort between the two operator groups, and IUS was better tolerated regardless of the operators.

Discussion

In this prospective, blinded, multicenter study including patients with suspected CD, trainees performed IUS as the first examination. IUS examinations conducted by the trainees achieved the same overall diagnostic accuracy as MREC evaluated by an expert. There was a tendency towards improvement of the trainees' diagnostic accuracy from the first to second half of the study period. IUS was associated with almost no patient discomfort and far better tolerated than IC and MREC.

The diagnostic accuracy in this study is not as high as reported in other studies[5], which may partly reflect the trainees' limited competencies, e.g., limited IUS training/experience and lack of knowledge and skills. However, there is no commonly accepted standard of IUS training. While studies by both Bhatnagar et al. and De Voogd et al. found no difference between observers with 3-15 years of experience[8, 22], other studies suggest trainees must undertake at least 150 examinations before they have the skills needed [23] to obtain a reasonable diagnostic accuracy[24]. The limited knowledge of learning curves and lack of standardization in IUS training programs greatly limit the implementation of IUS. In a recent Delphi consensus survey, experts listed 41 statements that should be basic in future training programs and evaluations of trainees[25] to ensure a high level of expertise and reduce operator dependency. In all 8 cases where MREC (and IC) documented CD missed by the trainees with IUS, the extent of disease was 6 cm or less – demonstrating the importance of a systematic IUS examination. There is an apparent learning curve in the first half of the study, as the sensitivity and specificity increased in the last 55 examinations. The improved diagnostic performance of trainees who performed IUS suggests that acceptable diagnostic performance is achievable with increasing IUS experience. This should encourage clinicians to consider using IUS in daily practice despite not being experts. In patients with established CD and known disease location, one must expect an even better IUS performance than shown in this study.

Opposite most studies, we use a population of patients with suspected CD instead of established disease, which may affect our results. Sævik et al. suggested that IUS is not always sensitive enough to detect aphthous lesions[15]. This phenomenon is likely to affect the sensitivity in this study since those diagnosed were in the early stages of CD - where the transmural inflammation is less pronounced. The phenomenon is not limited to IUS but occurs in MREC too, which performed suboptimally in our study[12]. In addition to unknown disease status, patients were not selected according to an optimal IUS setup, e.g., BMI median of 24.6 kg/m2 (range 17.1- 57.2) – and the operator had no information of disease location or phenotype as a guide to areas of interest.

Although MREC is not the optimal modality in suspected CD, it is still frequently used in the primary diagnostic work-up. It has clear benefits in assessing advanced disease and evaluating disease extent. It is striking that the AUC intervals of IUS and MREC are identical in our study. This

indicates that even inexperienced operators can reach a diagnostic level with IUS comparable to MREC regarding simple disease detection.

We found that patients experienced minimal discomfort during the IUS examination and were significantly better tolerated than MREC and IC. This is in line with the results of Buisson et al.[26] The slightly higher physical discomfort reported by patients examined by the radiologist could be attributed to the possibility that experienced radiologists applied more transducer pressure to optimize image acquisition. Although IUS may never become a stand-alone tool for evaluating patients with suspected CD, it may become the primary examination for assessing known CD and - in relation to this work - a possible add-on to IC in patients with clinical suspicion or newly discovered CD instead of MRI: For visualization of the gastrointestinal tract proximal to the reach of the colonoscope; including terminal ileum in incomplete colonoscopy. IUS is patient-friendly, requires no preparation, and is quickly done, which makes it ideal for frequent evaluations. Furthermore, an ongoing study by Madsen et al. demonstrates the ability of IUS to predict short-term disease outcomes in newly diagnosed patients and identify those at high risk of surgery[27] – an example of IUS's potential in clinical practice.

Strengths and limitations

The study was a prospective blinded, multicenter study with IC as the clinical reference standard and IUS performed before the other modalities. The four physicians participating in the study were not IUS experts – the two gastroenterologists had limited experience before the study, although one had started the IBUS training program. Due to the smaller subset of IUS examinations conducted by the two participating radiologists, we are unable to draw meaningful comparisons between the findings of the two groups. The trainees' diagnostic performance improved during the study, however, this study is not intended or powered to demonstrate operator improvement over time, and the observed improvement was not significant (p=0.09). We did not account for the lack of inter-observer variance. However, previous studies report moderate to substantial practitioner agreement with IUS[8, 28]. In this study, patients diagnosed with CD had primarily non-complicated disease; hence evaluation of complications like fistulas, abscesses, and bowel stenosis is not accounted for. Due to the low frequency of disease observed in the small bowel proximal to the terminal ileum, we cannot draw definitive conclusions regarding this area. Advanced

ultrasound techniques, e.g., contrast-enhanced ultrasound and elastography[29], might have yielded better outcomes but were not applied since trainees performed the IUS.

Conclusion

In terms of disease detection, trainees improved during the study and achieved a diagnostic performance corresponding to that of MREC evaluated by an expert. Although debatable, our results indicate that experience level should not limit or impede the usage of this patient-friendly technique. Further prospective studies to clarify the implementation and training of IUS are needed to get the best from this promising modality.

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Disclosure of interest

The authors report there are no competing interests to declare

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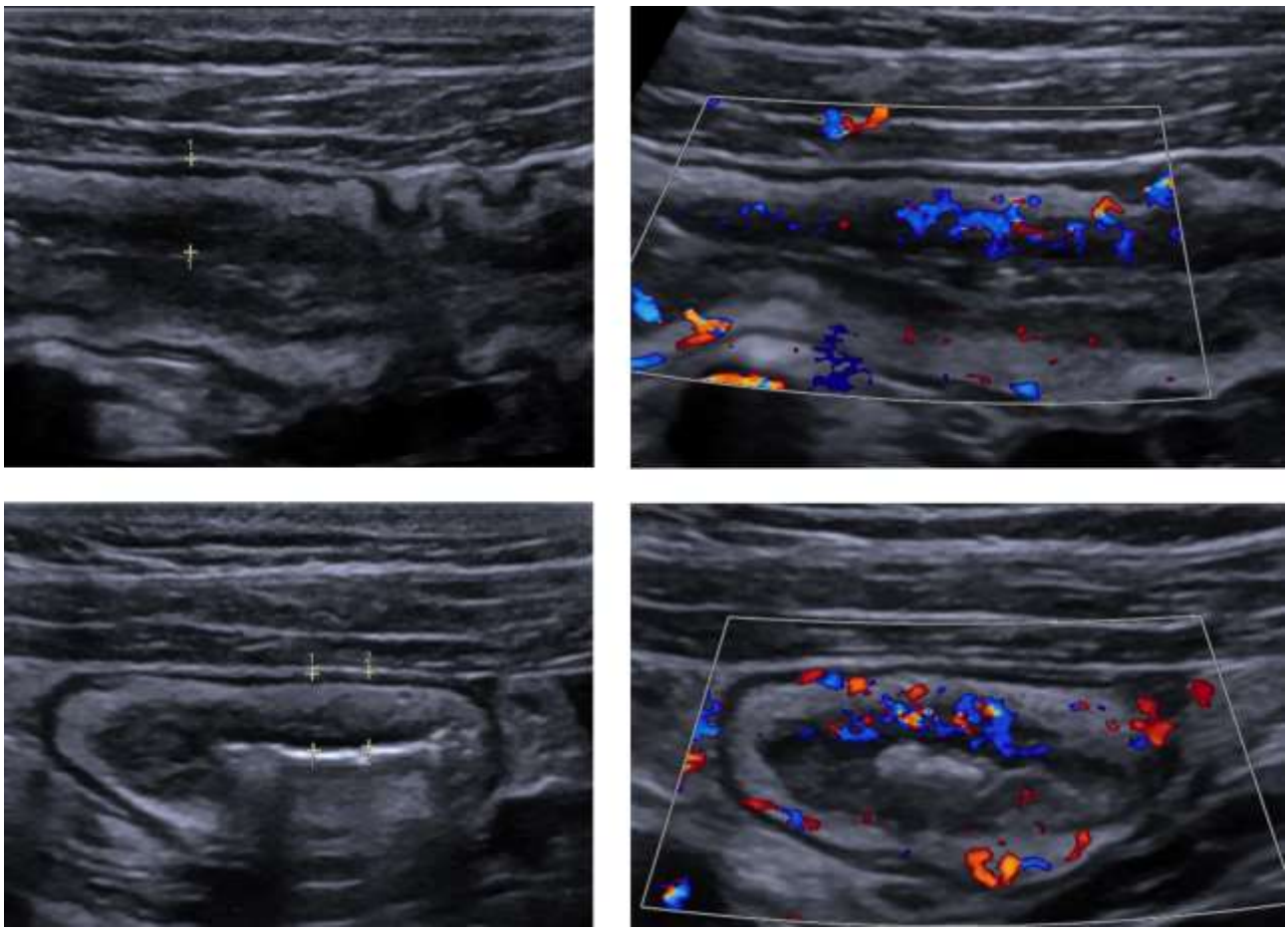

Figure 1. *Terminal ileum in a 26 years female with suspected CD. IUS with longitudinal and cross-sectional images of the terminal ileum, showing intestinal wall thickening (5mm) with preserved wall layers – color Doppler on the right.*

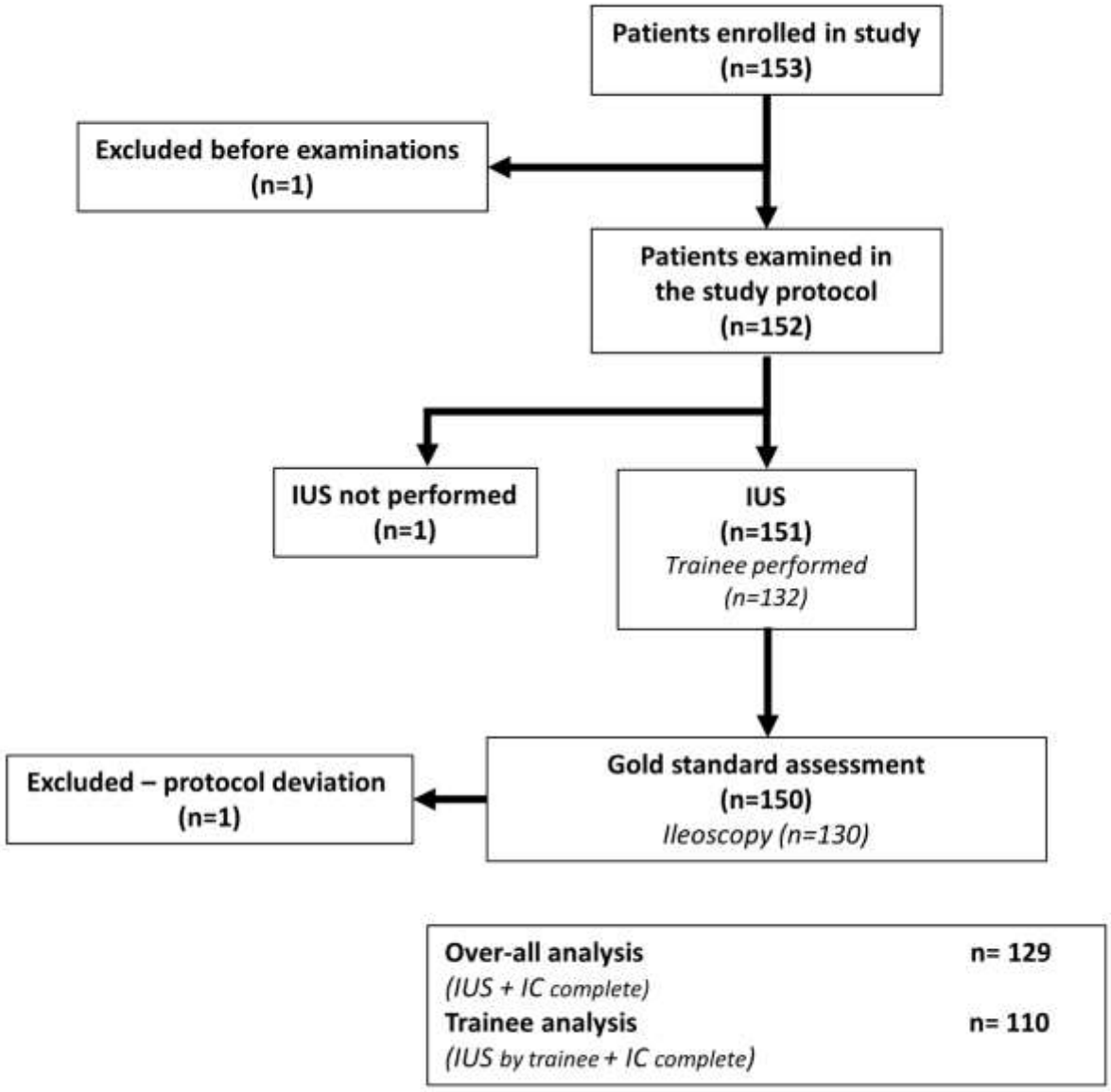

Figure 2. *Flow chart showing the number of patients entering the study and completing examinations in accordance with the study protocol.*

Table 1 Characteristics of 129 patients with suspected Crohn's disease included in the study.

Age (years)	
Mean	30.1
Range	16-68
Gender	
Male	35 (27%)
Female	94 (73%)
Abdominal pain (n)	128 (98%)
No. of bowel movements	
Mean	4.1
Range	every 3rd day-17
CDAI *(responders n=84)*	
Mean	172
Range	20-379
Family history of IBD (n)	39 (30%)
Smokers (n)	37 (29%)
Height (cm)	
Mean	172
Range	152-203
Weight (kg)	
Mean	77.0
Range	49-150
BMI	
Mean	26.1
Range	17.1-57.2
C-reactive protein (mg/L)	
Mean	16.0
Range	0.5-122
Fecal calprotectin (mg/kg)	
Mean	967
Median	443
Range	51-6000
Bowel resection prior to inclusion in the study (n)	0

Table 2. Diagnostic performance of IUS for diagnosing CD with IC as the reference standard. Results are subdivided into trainees only (all, first and the second half of the study) and all operators. Sensitivities and specificities are stated in percentages, with the corresponding 95% CI intervals in parentheses. The positive predictive value (PPV), negative predictive value (NPV), the area under the receiver operator curve (ROC), and prevalence of CD are displayed. The difference in ROC between the first and second half of the IUS performed by trainees was tested for statistical significance, and p-values are reported.

	Trainees				***All observers***
	All exams (n=110)	*First half* (n=55)	*Second half* (n=55)	*p-value*	*All exams* (n=129)
Terminal ileum + colon					
Prevalence	43%	38%	47%		40%
Sensitivity	66.0 (50.7 – 79.1)	57.1 (34.0– 78.2)	73.1 (52.2 – 88.4)		65.4 (50.9 - 78.0)
Specificity	82.5 (70.9 – 90.9)	76.5 (58.8 – 89.3)	89.7 (72.6 – 97.8)		80.5 (69.9 - 88.7)
PPV	73.8 (58.0 – 86.1)	60.0 (36.1 – 80.9)	86.4 (65.1 – 97.1)		69.4 (55.4 - 82.1)
NPV	76.5 (64.6 – 85.9)	74.3 (56.7 – 87.5)	78.8 (61.1 – 91.0)		77.5 (66.8 - 86.1)
ROC	0.74 (0.66 – 0.83)	0.67 (0.54 – 0.80)	0.81 (0.71 -0.92)	0.09	0.73 (0.65 - 0.81)
Terminal ileum					
Prevalence	31%	35%	27%		30%
Sensitivity	61.8 (43.6 – 94.5)	57.9 (33.5 – 79.7)	66.7 (38.4 – 88.2)		61.5 (44.6 - 76.6)
Specificity	89.5 (80.3 – 95.3)	86.1 (70.5 – 95.3)	92.5 (79.6 – 98.4)		88.9 (80.5 - 94.5)
PPV	72.4 (52.8 – 87.3)	68.8 (41.3 – 89.0)	76.9 (46.2 –95.0)		70.6 (52.5 - 84.9)
NPV	84.0 (74.1 – 91.2)	79.5 (63.5 – 90.7)	88.1 (74.4 – 96.0)		84.2 (75.3 - 90.9)
ROC	0.76 (0.67 – 0.85)	0.72 (0.59 – 0.85)	0.77 (0.64 – 0.91)	0.41	0.75 (0.67 - 0.84)
Colon					
Prevalence	25%	18%	33%		23%
Sensitivity	39.3 (21.5 – 59.4)	20.0 (2.5 – 55.6)	50.0 (26.0 – 74.0)		36.7 (19.9 - 56.1)
Specificity	93.9 (86.3 – 98.0)	93.3 (81.7 - 98.6)	94.6 (81.8 – 99.3)		92.9 (86.0 - 97.1)
PPV	68.8 (41.3 – 89.0)	40.0 (5.3 – 85.3)	81.8 (48.2 – 97.7)		61.1 (35.7 - 82.7)
NPV	81.9 (72.6 – 89.1)	84.0 (70.9 – 92.8)	79.5 (64.7 – 90.2)		82.9 (74.6 - 89.4)
ROC	0.67 (0.57 – 0.76)	0.57 (0.43 – 0.70)	0.72 (0.60 – 0.85)	0.10	0.65 (0.56 - 0.74)

Table 3. Patient experienced discomfort with IUS, MREC, and IC. Patients marked visual analog scales for physical and psychological discomfort after each examination. All scales were 10 cm long; 0 cm equaled no discomfort, and 10 cm the worst imaginable discomfort. IC is divided into 2 subgroups depending on the type of sedation used. The difference between IUS and MREC / IC was tested for statistical significance, and p-values are reported.

		VAS		***p-value***
		Median	Range	**IUS**
Physical discomfort	**IUS**	0	0-9	N/A
	MREC	2.5	0-10	<0.001
	IC	5	0-10	<0.001
	Midazolam, fentanyl	5	0-10	<0.001
	Propofol	2	0-10	<0.001
Psychological discomfort	**IUS**	0	0-4.5	N/A
	MREC	1	0-10	<0.001
	IC	2	0-10	<0.001
	Midazolam, fentanyl	2	0-10	<0.001
	Propofol	2	0-10	<0.001