



# Contrast-enhanced ultrasonography: Usefulness in the assessment of postoperative recurrence of Crohn's disease

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## KEYWORDS

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## Abstract

**Aim:** The aim of this study was to assess whether the contrast-enhanced ultrasonography (CEUS) can increase the value of the ultrasonography in the study of postoperative recurrence of Crohn's disease (CD).

**Materials and methods:** 60 patients with CD who had previously undergone ileocolic resection underwent prospectively both CEUS and colonoscopy within a 3-day period. The sonographic examination included evaluation of bowel wall thickness, transmural complications, colour Doppler grade and contrast-enhanced US. In addition a sonographic score was established. The capacity of CEUS to diagnose endoscopic recurrence, as well as its severity, was assessed by calculating the sensitivity, specificity and positive and negative predictive values, accuracy and odds ratio, with their respective 95% confidence intervals. The areas under the receiver operating characteristic (ROC) curves were also calculated.

**Results:** 49 out of 60 patients showed endoscopic postoperative recurrence. Severe endoscopic recurrence was present in 34 patients (57%). Classic ultrasound parameters (wall thickness >3 mm and colour Doppler flow) revealed an accuracy of 88.3% for the diagnosis of recurrence. Sonographic score 2, including thickness >5 mm or contrast enhancement >46%, improved the results with a sensitivity, specificity and accuracy of 98%, 100% and 98.3%, respectively, in the diagnosis of endoscopic recurrence. The area under the ROC curve was 0.99, in remarkable agreement with endoscopy ( $k$ : 0.946). Sonographic score 3, including thickness >5 mm, contrast enhancement >70% or fistula identified 32 out of 34 (94.1%) severe endoscopic recurrences. The area under the ROC curve was 0.836, in good agreement with endoscopy ( $k$ : 0.688).

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*Conclusion:* CEUS shows excellent sensitivity and specificity for the diagnosis of postoperative recurrence in CD and can also detect severe recurrences.

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## 1. Introduction

Ileocolonoscopy remains the gold standard for the assessment of presence and severity of postoperative recurrence of Crohn's disease (CD). However, endoscopy is an invasive technique and requires a bothering preparation that makes repeated use difficult. Therefore, alternative non-invasive techniques are emerging for assessing postoperative recurrence in CD.<sup>1</sup> Among these noninvasive techniques, ultrasound (US) has shown promising results in the study of postoperative recurrence of CD. Both B-mode US<sup>2–6</sup> and oral contrast US<sup>7–9</sup> allow for precise detection of the presence of endoscopic recurrence and determination of its severity.

The clinical usefulness of US has been shown to have increased with the recent introduction of contrast-enhanced ultrasound (CEUS); this technique, which is based on the application of second-generation intravenous contrast media, allows for evaluation of the microvasculature due to its increased sensitivity in detecting the nonlinear signals produced by the insonation of microbubbles. This has led to a significant advance in the characterisation of focal lesions in solid organs such as the liver or kidneys.<sup>10</sup> CEUS also allows for the precise evaluation of intestinal wall vasculature and has been shown to be a sensitive tool for estimating inflammatory activity in CD as the reflex of parietal hypervascularisation that takes place during exacerbations of the disease.<sup>11</sup> In addition, CEUS has demonstrated its usefulness in CD for characterisation of small inflammatory intestinal masses, making differentiation between phlegmon and abscesses possible.<sup>12</sup>

Initial studies on CEUS have demonstrated good correlation between contrast uptake in the intestinal wall and disease activity as estimated by the Crohn's Disease Activity Index (CDAI) or the plasma C-reactive protein level.<sup>13–15</sup> On the other hand, other studies have evaluated the utility of the technique in establishing the nature (fibrotic or inflammatory) of intestinal stenosis in CD with positive results<sup>16</sup> and, in more recent studies, contrast uptake in the intestinal wall has shown good correlation with the severity of endoscopic lesions caused by the disease.<sup>17,18</sup> Nevertheless, the role of this new ultrasound technique still has not been evaluated specifically in the postoperative recurrence of CD.

The aim of this study was to assess whether CEUS can increase the value of B-mode US in the study of postoperative recurrence of CD.

## 2. Materials and methods

### 2.1. Patients

This prospective study included patients diagnosed with CD who attended our Gastroenterology outpatient department. Patients were included consecutively if they met the following criteria: age over 17 years, having undergone

ileocaecal or ileocolonic resection with ileocolonic anastomosis as a result of their disease and with a clinical indication for an ileocolonoscopy study for any reason (monitoring for endoscopic recurrence in the anastomosis, screening for colon cancer or changes in their clinical condition). Patients were included regardless of whether or not they had symptoms of clinical recurrence. Patients who did not agree to participate in the study and pregnant women were excluded.

At the time of the study, demographic and clinical data (extent and behaviour of the disease and CDAI) were collected, serum C-reactive protein (CRP) levels were determined by immunonephelometry (Dade Behring, Marburg, Germany; normal value  $\leq 10$  mg/L). Current drug treatments and characteristics of the surgery (indication and type of surgery, number of surgeries and time from surgery until the study) were recorded for all patients.

Approval of the ethics committee of our institution was obtained. Prior to inclusion in the study, all patients were informed of the nature of the study and gave informed written consent.

### 2.2. Endoscopic protocol

All the examinations were carried out under sedation and analgesia monitored by an anaesthetist after the use of a polyethylene glycol electrolyte solution and a low-residue diet before the examination. All the examinations were performed by an endoscopy specialist who was unaware of the results of the other examinations.

The severity of the lesions in the neoterminal ileum was assessed according to the Rutgeerts scale,<sup>19</sup> which establishes four grades of lesion: Grade 0=no lesions; Grade 1=less than 5 aphthous lesions with normal mucosa between lesions; Grade 2=more than 5 aphthous lesions with normal mucosa between lesions or lesions confined to the ileocolonic anastomosis; Grade 3=diffuse aphthous ileitis and Grade 4=diffuse ileitis with large ulcers, nodules and/or stenosis. The patients were considered to have endoscopic recurrence when lesions were detected in the ileum proximal to the anastomosis, regardless of their severity. The recurrence was classified as mild (grade 1 and 2), or moderate–severe (grade 3 and grade 4).

## 3. Ultrasonographic protocol

### 3.1. Ultrasonographic examination

Two radiologists (M.J.M., T.R., with at least 15 years of experience in US of intestinal bowel diseases and 5 years of experience in contrast-enhanced US) performed the examinations. US examinations were performed within three days of the ileocolonoscopy, using a Toshiba Aplio 80 (Toshiba, Tokyo, Japan) initially employing a 3–6 MHz convex-

array transducer and then for a detailed examination a 6–10 MHz convex-array probe. Each patient underwent abdominal US specifically for the intestine, beginning with an initial grey-scale. Bowel wall vascularity by colour Doppler US with a special preset optimised for slow flow detection was then evaluated.

For the CEUS study, patients were examined with a 3–4 MHz convex probe in wideband contrast harmonic mode (pulse inversion-Toshiba Applio) at low MI ( $MI < 0.10$ ). The second-generation echo-signal enhancer SonoVue® (Bracco, Milan, Italy) was injected as a bolus in units of 1.2 ml through a three-way 20 gauge catheter into an antecubital vein, immediately followed by injection of 10 ml of normal saline solution (0.9% NaCl).

### 3.2. Image analysis

The ultrasound examination included evaluation of bowel wall thickness, vascularity pattern on colour Doppler and intestinal complications. Bowel wall thickness  $> 3$  mm was considered abnormal<sup>20</sup> and  $> 5$  mm as indicative of moderate–severe recurrence.<sup>4,6</sup> Colour Doppler flow was considered present when colour pixels persisted throughout the observation period and was always confirmed by obtaining an arterial or venous signal at the location of the colour pixel. The intensity of the colour Doppler flow was subjectively graded as absent (grade 0), barely visible vascularity (grade 1), moderate vascularity (grade 2) and marked vascularity (grade 3).<sup>21</sup> Intestinal complications (stricture, fistula and abscesses) were defined in accordance with previous literature.<sup>7,22</sup>

To assess the vascularisation of the involved bowel loop, the contrast uptake was measured over a period of 40 seconds by quantitative analysis of the brightness in regions of interest (ROI) located in the intestinal wall using the software installed in the Aplio 80 system. ROI was always localised in the brighter zone of the intestinal wall. Manually defined area of the ROI was variable in each patient depending on the thickness of the wall and the pattern of enhancement, but had to be at least 2 cm.<sup>2</sup> We did not annotate the range of size of ROI for each CEUS examination. The software automatically obtained a brightness-time curve. Quantitative measurement of contrast enhancement was assessed as the difference between the baseline brightness before contrast injection and the maximum enhancement value. We also calculated the percentage of increase in wall brightness by using the following formula:  $[(\text{brightness postcontrast} - \text{brightness precontrast}) \times 100] / \text{brightness precontrast}$ , and used this for data analysis. We perform two or three measures per injection. We always choose the maximum increase value that theoretically represents the highest degree of involvement.

### 3.3. Statistical analysis

Basic descriptive statistics included median and range for continuous variables, absolute frequency and percentage for discrete variables. The Mann–Whitney *U* test was employed for comparison of the quantitative variables. The capacity of CEUS to diagnose endoscopic recurrence, as well as its severity, was assessed by calculating the sensitivity (Se),

specificity (Sp) and positive (PPV) and negative (NPV) predictive values, likelihood ratios (LR), accuracy, and odds ratio (OR), with their respective 95% confidence intervals (95% CI). A receiver operating characteristic (ROC) curve was constructed to determine the best cut-off value for sonographic variables and their combinations in order to differentiate recurrence from no recurrence and mild from severe endoscopic recurrence. The areas under the ROC curves were also calculated, together with their respective 95% CI. Finally, Cohen's Kappa (*K*) measure was used to test the correlation between endoscopy and ultrasound variables.

The Statistical Package for the Social Sciences (SPSS) version 15.0.1 was used to describe and analyse the data, considering values of  $p < 0.05$  as significant.

## 4. Results

Between January 2007 and December 2010, 60 patients who met the study conditions were seen. Their main demographic and clinical characteristics are shown in Table 1.

**Table 1** Main demographic and clinical characteristics of the 60 patients who had surgery for Crohn's disease included in the recurrence study.

Variables	Absolute frequency (%)
Males	32 (53.3)
Age [median (standard deviation)]	39.0 (11.3)
Smokers	28 (46.7)
Months from surgery until the study [median (standard deviation)]	60.0 (71.0)
Illness behaviour before surgery	
Non-stricturing/non-penetrating	8 (13.3)
Stricturing	24 (40.0)
Penetrating	28 (46.7)
Illness location before surgery	
Ileal	34 (56.6)
Ileocolonic	26 (43.3)
Type of surgery	
Ileocaecal resection	44 (73.3)
Ileocolonic resection	16 (26.7)
Indication for the surgery	
Treatment failure	8 (13.3)
Perforation/abscess	28 (46.7)
Stenosis	24 (40.0)
Pathological findings at resection margins	
Affected	3 (5.0)
Not affected	57 (95.0)
Treatment during the study	
Aminosalicylates	30 (50.0)
Immunosuppressants	25 (41.7)
Anti-TNF	5 (8.3)
Two or more operations	8 (13.3)
Serum CRP $> 10$ mg/l	14 (23.3)
CDAI $> 150$ points	15 (25.0)

Anti-TNF: antibody to tumour necrosis factor alpha; CRP: C-reactive protein. CDAI: Crohn's disease activity index.

Endoscopic recurrence was detected in 49 patients (81.7%). Rutgeerts score was: grade 1 in 8 patients, grade 2 in 7 patients, grade 3 in 8 patients and grade 4 in 26 patients (stenosis were present in ten of these patients). Endoscopic recurrence was classified as mild in 15 patients and moderate–severe in 34/49 (69.3%).

At the time of the study, 15 patients (25%) had a CDAI greater than 150 points, all but one of whom (93.3%) had endoscopic signs of recurrence (mild: 2 [13.3%] patients; moderate–severe: 12 [80%] patients). Among the 45 remaining patients with inactive disease (CDAI < 150 points), endoscopic recurrence was shown in 35/45 patients (77.7%); this was moderate–severe in 22 (48.8%) of them. In 14 (23.3%) patients, serum CRP levels were increased (> 10 mg/L); endoscopic recurrence was shown in 13 (92.8%) of them (mild: 3 [23%] patients; moderate–severe: 10 [77%] patients).

#### 4.1. Ultrasonographic findings

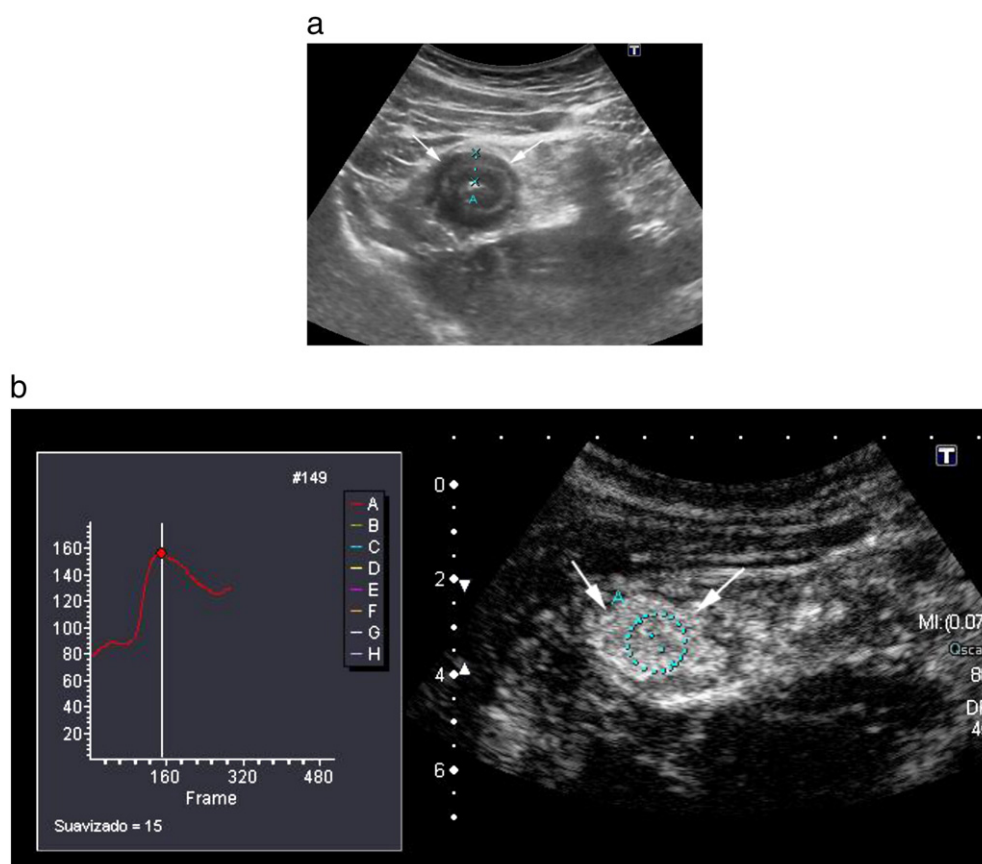
Ultrasonography, including CEUS, was technically possible in all 60 patients. All the studies were successfully performed without complications.

The median of neoterminal ileum thickness was 6.00 mm (range 2–14 mm); 2.50 mm (range 2–5 mm) in patients without

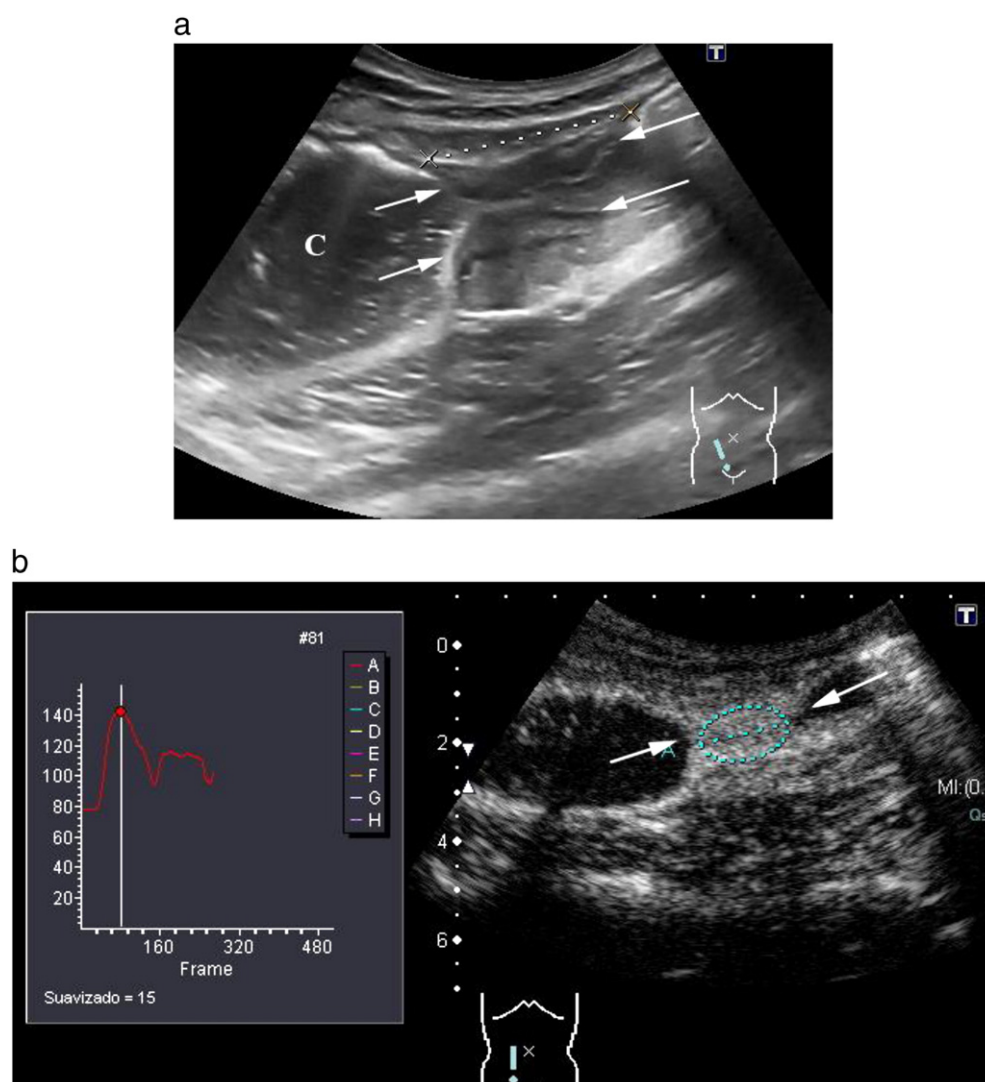
endoscopic recurrence and 6.00 mm (range 2–14 mm) in patients with endoscopic recurrence ( $p < 0.0001$ ). Parietal thickness was greater than 3 mm in 46 patients (76.7%), 44 of them with recurrence; all patients with a parietal thickness > 3 mm had a positive colour Doppler signal (grade 1: 18 [39.1%] patients; grade 2: 18 [39.1%] patients; grade 3: 10 [21.8%] patients). Wall thickness was greater than 5 mm in 34 patients (56.7%), 28 of them with moderate or severe recurrence. Mural enhancement of the neoterminal ileum after contrast agent injection was 52% (range 5–87%) (Figs. 1 and 2); enhancement was 20% (range 10–38%) in patients without recurrence and 55% (range 5–87%) in patients with endoscopic recurrence ( $p < 0.001$ ). Intestinal complications were present in 8 patients: seven patients had fistula and ultrasonographic findings of stenosis and one patient only had fistula. No patients had abscess.

#### 4.2. CEUS for assessment of endoscopic recurrence

Classic ultrasound parameters (wall thickness > 3 mm and the presence of colour Doppler flow) revealed an accuracy of 88.3% for the diagnosis of recurrence and a good correlation with endoscopic signs of recurrence ( $K = 0.64$ ;  $p = 0.0001$ ).



**Figure 1** 25-year-old man with previous ileocolonic resection for Crohn's disease with recurrence at the neoterminal ileum. a) Transverse ultrasound image shows circumferential thickening of the neoterminal ileum (arrows). b) Contrast-enhanced ultrasound after specific contrast agent injection shows marked enhancement of the neoterminal ileum. A=region of interest placed in bowel wall. Brightness–time curve shows a percentage of increase of enhancement of 100%.



**Figure 2** 38-year-old woman with previous ileocolonic resection for Crohn's disease with recurrence at the anastomotic site. a) Longitudinal ultrasoundscan of the right lower quadrant shows thickening of a short segment of the neoterminal ileum (arrows). C=Normal post-anastomotic colon.b) Contrast-enhanced ultrasound after specific contrast agent injection depicts intense enhancement of the neoterminal ileum allowing for the diagnosis of recurrent disease. Graph shows measurement of bowel wall vascularity in manually defined region of interest (ROI) obtaining a brightness-time curve over 40 seconds. Percent increase of enhancement was 87%. A=ROI in bowel wall.

The cutoff point for enhancement in CEUS that best discriminated for the presence of endoscopic recurrence was 34.5%, which was present in 50 (83.3%) of patients. This value increased diagnostic accuracy and improved correlation with endoscopy, achieving values of 94.4% and  $K=0.82$  ( $p<0.001$ ), respectively. The cutoff point of 46% of enhancement achieved 90% of accuracy in the diagnosis of endoscopic recurrence ( $K=0.724$ ,  $p<0.001$ ).

Table 2 shows the usefulness of the different ultrasound variables analysed for the diagnosis of recurrence.

#### 4.3. CEUS for assessment of moderate–severe endoscopic recurrence

Individually, the different variables using B-mode ultrasound revealed similar results in determining the severity

of the recurrence. The accuracy and correlation with endoscopy of wall-thickness  $>5$  mm and grade 2–3 colour Doppler in the detection of moderate–severe recurrence were, respectively, 80% and  $K=0.59$  ( $p: 0.0001$ ) for the first variable and 76.7% and  $K=0.53$  ( $p: 0.0001$ ) for the second.

Parietal enhancement  $>46\%$  after administration of contrast agent was the best CEUS cutoff point to differentiate moderate–severe recurrence from mild recurrence (accuracy: 81.6%;  $K=0.51$ ,  $p: 0.0001$ ). Parietal enhancement of 70% was the next value that best differentiated moderate–severe recurrence from mild recurrence (accuracy 70% ;  $K=0.41$ ,  $p: 0.001$ ).

Table 3 shows the usefulness of the different ultrasound variables analysed for the diagnosis of moderate–severe recurrence.

**Table 2** Value of the abdominal sonography for the diagnosis of endoscopic recurrence in patients with Crohn's disease undergone surgery.

	Parietal thickness of the neoterminal ileum > 3 mm and/or Doppler positive	Contrast-enhanced of the neoterminal ileum > 34.5%
Positive true	44	48
False positive	2	2
Negative true	9	9
False negative	5	1
Sensitivity (95% CI)	89.8% (78.2–95.6)	98.0% (89.3–99.6)
Specificity (95% CI)	81.8% (52.3–94.9)	81.8% (52.3–94.5)
PPV (95% CI)	95.7% (85.5–98.8)	96.0% (86.5–98.9)
NPV (95% CI)	64.3% (38.8–83.7)	90.0% (59.6–98.2)
Odds ratio (95% CI)	39.6 (6.6–237.1)	216 (17.6–2641.6)
PLR (95% CI)	5.4 (1.5–418.8)	5.3 (1.5–18.8)
NLR (95% CI)	0.02 (0.0–0.2)	0.03 (0–0.2)

95% CI=95% confidence interval; PPV=positive predictive value; NPV=negative predictive value; PLR=positive likelihood ratio; NLR=negative likelihood ratio.

## 5. Proposal for score to assess the endoscopic recurrence

With the values of different ultrasound variables that had the best results in ROC curves to assess the endoscopic recurrence and its severity, we constructed a semiquantitative score: (0) normal bowel wall thickness <3 mm and enhancement <34.5; (1) bowel wall thickening between 3 and 5 mm with enhancement <46%; (2) thickening >5 mm or contrast enhancement >46%; (3) bowel wall thickening >5 mm, or enhancement >70%, or presence of fistula.

The highest performance in detection of endoscopic recurrence was obtained with the following combination (Score 2): Wall thickness >5 mm or contrast enhancement

>46% (accuracy: 98.3%;  $K=0.95$ ,  $p=0.0001$ ). Moderate–severe recurrence was detected with greater precision by the following combination of variables (Score 3): Parietal thickness >5 mm or contrast enhancement >70% or fistula (accuracy: 85%,  $K=0.69$ ,  $p=0.0001$ ).

Table 4 shows the usefulness of the ultrasonographic scores for the diagnosis of endoscopic recurrence and for detection of moderate–severe endoscopic recurrence.

## 5.1. Global analysis of the ability of CEUS for evaluation of endoscopic recurrence

Fig. 3 shows the ROC curves of the ultrasound variables for the detection of endoscopic recurrence or the diagnosis of moderate–severe endoscopic recurrence. The best figures were obtained by the combination of the following ultrasound variables: sonographic score 2 for the diagnosis of endoscopic recurrence and sonographic score 3 for the diagnosis of moderate–severe endoscopic recurrence (Table 5).

## 6. Discussion

Ileocolonoscopy after ileocolonic resection in patients with CD aims to detect early anastomotic recurrence in order to adjust medical treatment in more severe cases and prevent further clinical recurrence. Accordingly, it is recommended that a colonoscopy be performed at 12 months after surgery to detect early signs of moderate–severe endoscopic recurrence and in some cases to repeat it annually.<sup>23</sup> Nevertheless, the drawbacks of the technique (invasiveness, need for preparation with laxatives and sedative analgesia, and greater difficulty in performing the study in patients who have undergone surgery)<sup>24</sup> make impossible the realisation of colonoscopy frequently in a patient. This has led to interest in studying the role of non-invasive techniques to evaluate postoperative recurrence of CD.<sup>1</sup> Among these types of noninvasive studies, ultrasound<sup>2–9</sup> and computed tomography<sup>25</sup> (CT) or magnetic resonance<sup>26,27</sup> (MRI) have been the most widely used radiologic techniques for this purpose. US has several advantages over the other imaging modalities: it is

**Table 3** Value of the abdominal sonography for the diagnosis of moderate–severe endoscopic recurrence in patients with Crohn's disease undergone surgery.

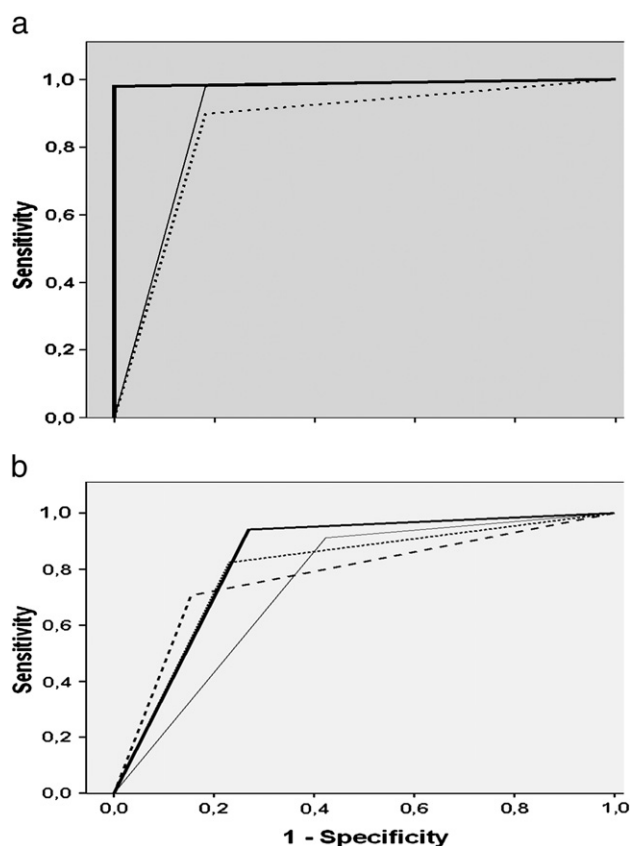
	Parietal thickness of the neoterminal ileum > 5 mm	Colour Doppler flow of the neoterminal ileum grades 2 or 3	Contrast-enhanced of the neoterminal ileum > 46%
Positive true	28	24	31
False positive	6	4	11
Negative true	20	22	15
False negative	6	10	3
Sensitivity (95% CI)	82.4% (66.5–91.7)	70.6% (53.8–83.2)	91.2% (77.0–97.0)
Specificity (95% CI)	76.9% (57.9–89.0)	84.6% (66.5–93.9)	57.7% (38.9–74.5)
PPV (95% CI)	82.4% (66.5–91.7)	85.7% (68.5–94.3)	73.8% (58.9–84.7)
NPV (95% CI)	76.9% (57.9–89.0)	68.8% (51.4–82.0)	83.3% (60.8–94.2)
Odds Ratio (95% CI)	15.5 (4.3–55.3)	13.2 (3.6–48.2)	14.1 (3.4–58.1)
PLR (95% CI)	3.5 (1.7–7.2)	4.5 (1.8–11.6)	2.1 (1.4–3.4)
NLR (95% CI)	0.2 (0.1–0.5)	0.3 (0.2–0.6)	0.1 (0.05–0.4)

95% CI=95% confidence interval; PPV=positive predictive value; NPV=negative predictive value; PLR=positive likelihood ratio; NLR=negative likelihood ratio.

**Table 4** Value of the sonographic scores for the assessment of endoscopic recurrence in patients with Crohn's disease undergone surgery.

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Odds ratio (95% CI)	PLR (95% CI)	NLR (95% CI)
<i>Diagnosis of endoscopic recurrence</i>							
Parietal thickness of the neoterminal ileum > 5 mm or contrast-enhanced > 46%	98 (89.3–99.6)	100 (74.1–100)	100 (92.6–100)	91.7 (64.6–98.5)	1056 (33.2–33513.6)	22.5 (1.5–339)	0.02 (0.0–0.2)
<i>Diagnosis of moderate–severe endoscopic recurrence</i>							
Parietal thickness of the neoterminal ileum > 5 mm or contrast-enhanced > 70% or fistula	94.1 (80.9–98.4)	73.1 (53.9–86.3)	82.1 (67.3–91.0)	90.5 (71.1–97.3)	43.4 (8.1–230.9)	3.5 (1.8–6.6)	0.08 (0.02–0.31)

95% CI = 95% confidence interval; PPV = positive predictive value; NPV = negative predictive value; PLR = positive likelihood ratio; NLR = negative likelihood ratio.



**Figure 3** ROC curve showing the diagnostic accuracy for the ultrasound variables. **a)** Ultrasound variables for diagnosis of endoscopic recurrence: parietal thickness of the neoterminal ileum > 3 mm (---); contrast enhancement > 34.5% (—); and parietal thickness of the neoterminal ileum > 5 mm or contrast enhancement > 46% (····). **b)** Ultrasound variables for diagnosis of moderate–severe endoscopic recurrence: parietal thickness of the neoterminal ileum > 5 mm (····); Doppler grade 2–3 of the neoterminal ileum (---); contrast enhancement > 46% (—); parietal thickness of the neoterminal ileum > 5 mm or contrast enhancement > 70% or fistula (—).

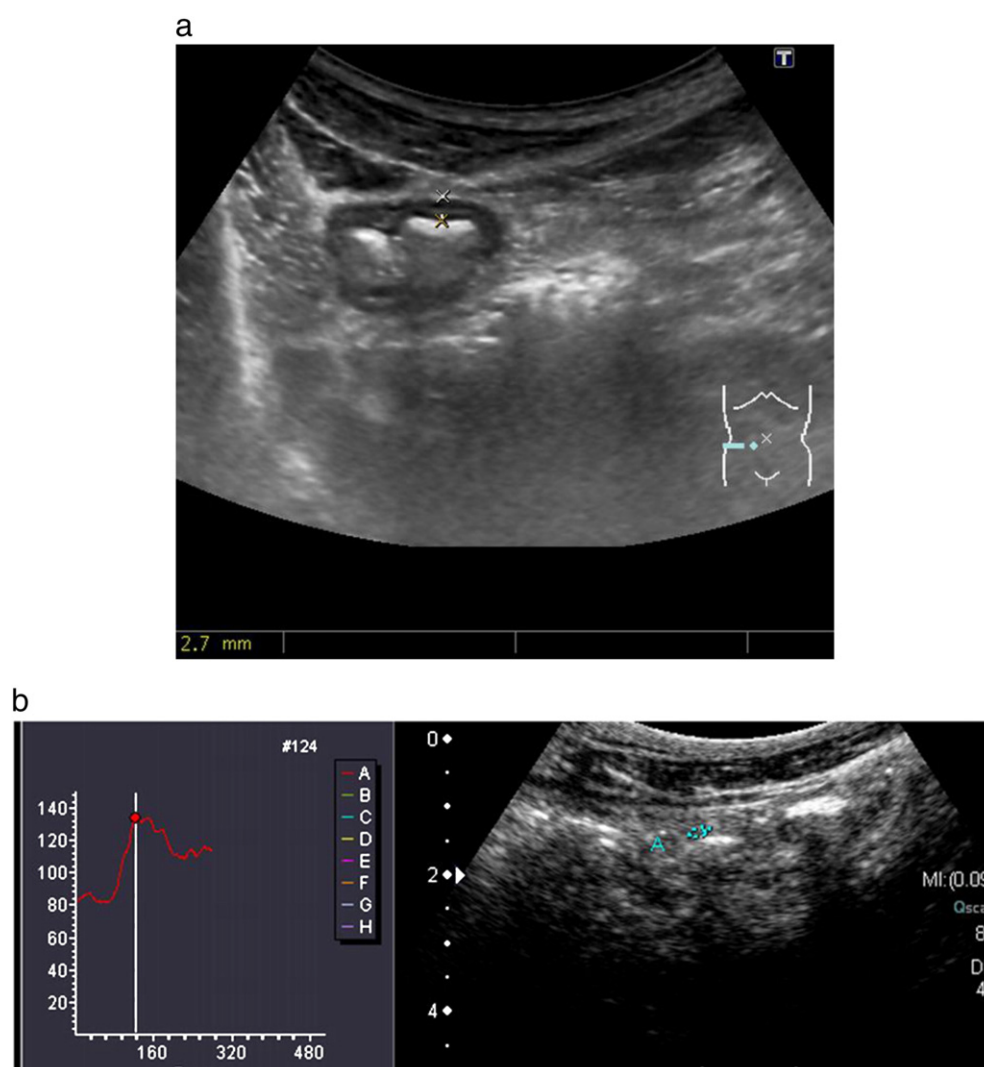
a non-invasive, non-ionising imaging modality, and it is well tolerated and accepted by patients, reasons that have led to its use in CD. B-mode ultrasound, with or without oral contrast, has already shown good results for the assessment of the recurrence of CD.<sup>2–9</sup> The recent application of second-generation intravenous contrast (SonoVue®) and the development of software that calculates contrast uptake allows us to precisely evaluate the microvasculature in the intestinal wall.<sup>28</sup> As far as we know, no studies have been reported about the accuracy of CEUS in patients with CD after ileocolonic resection in correlation with endoscopic findings.

In our study, CEUS was performed on all patients without causing side effects. This demonstrates the innocuous nature of the technique despite the application of intravenous contrast. We evaluate CEUS uptake in both detection and evaluation of the severity of the endoscopic recurrence. The degree of the endoscopic recurrence was based on the work of Rutgeerts et al.<sup>19</sup> Patients with grades 3 and 4 recurrence had worse prognosis than patients with grade 0 or grade 1 recurrence; symptoms and complications were very rare in patients with less severe endoscopic recurrence. Rutgeerts et al. considered endoscopic grade 2 recurrence as an intermediate grade with variable outcomes. We have included grade 2 as non-severe recurrence like most of the authors.<sup>4–8</sup> In the first aspect, in our series, B-mode ultrasound revealed similar results to those described in the literature<sup>20</sup> in using intestinal wall thickness greater than 3 mm to detect CD. Nevertheless, the application of intravenous contrast medium allowed us to detect 4 additional patients (three patients had Rutgeerts grade 1 and one patient grade 2) who have a normal wall thickness (<3 mm) but who have an enhancement of the intestinal wall greater than 46% and clear endoscopic signs of recurrence (Fig. 4). In all of these cases, the time between surgery and endoscopy was 12 months. The administration of sonographic intravenous contrast agent does not significantly increase the accuracy of US in the diagnosis of recurrence, but on the basis of our results we suggest that CEUS allows for early detection of inflammatory activity in the intestinal wall after resection. This finding is probably related to the results obtained in pathology studies where the increase in microvasculature in the intestinal wall presents as one of the early signs of disease.<sup>29–32</sup> Moreover, the use of a sonographic score, by combining several ultrasound features, improved

**Table 5** Areas under the ROC curves for the sonographic variables for the detection of endoscopic recurrence and moderate–severe endoscopic recurrence in patients with Crohn's disease undergone surgery.

Variables	Area under the curve	95% CI	p
<i>Endoscopic recurrence</i>			
Parietal thickness of the neoterminal ileum > 3 mm	0.85	0.71–1.00	0.0001
Contrast enhancement of the neoterminal ileum > 34.5%	0.89	0.76–1.03	0.0001
Parietal thickness of the neoterminal ileum > 5 mm or contrast enhancement > 46%	0.99	0.96–1.01	0.0001
<i>Moderate–severe endoscopic recurrence</i>			
Parietal thickness of the neoterminal ileum > 5 mm	0.79	0.67–0.91	0.0001
Colour Doppler flow grades 2 or 3	0.77	0.65–0.89	0.0001
Contrast enhancement of the neoterminal ileum > 46%	0.74	0.61–0.87	0.001
Parietal thickness of the neoterminal ileum > 5 mm or contrast enhancement > 70% or fistula	0.836	0.72–0.95	0.0001

95% CI=95% confidence interval.

**Figure 4** Transversal US scan of the abdomen in 41-year old men with previous ileocolonic resection and moderate endoscopic grade in neoterminal ileum. a) Short-axis sonographic view of the ileocolonic anastomosis shows a normal wall thickness (2.7 mm) of the neoterminal ileum. b) Post-contrast image shows homogeneous enhancement—68% of increase—of the neoterminal ileum wall. Quantitative measurement of contrast enhancement with CEUS is possible and reliable even with a normal bowel wall.

our results. Thus, in our series the best parameter for the diagnosis of postsurgical endoscopic recurrence was sonographic score 2, which includes a parietal thickness greater than 5 mm or a contrast enhancement >46%; this sonographic score showed a sensitivity, specificity and accuracy of 97.9%, 91.7% and 96.7%, respectively.

These figures are similar to those obtained with other cross-sectional images, such as CT or MRI.<sup>25,26</sup> Nevertheless, these techniques have some disadvantages in the evaluation of postoperative recurrence of CD. One important limitation of CT is the radiation dose to the patient which limits its repeated use. Alternatively, MRI does not irradiate but requires a detailed technique, oral contrast and an enema to obtain high quality images. Moreover, surgical clips can impair the image in at least 7–10% of cases.<sup>26,27</sup>

Regarding evaluation of the severity of endoscopic recurrence, the three sonographic variables evaluated in the wall of the neoterminal ileum (wall thickness >5 mm, colour Doppler grade 2 or 3, and enhancement greater than 46%) showed similar accuracy and correlation values without differences between the areas under the ROC curve. With the use of a sonographic score including parietal thickness >5 mm or contrast enhancement >70% or fistula, we detected almost all cases of severe endoscopic recurrence with a sensitivity of 94%.

In this aspect, contrast uptake showed similar sensitivity values to those described in other works where contrast uptake by CEUS was compared with endoscopic activity.<sup>17,18</sup> Our specificity was similar to that which was found by our group in a cohort of different patients, made up primarily of patients who had not undergone surgery,<sup>18</sup> but it was lower than the specificity obtained in the study of Migaleddu et al.<sup>17</sup> (93.7%) with a single false-positive result. This difference can be explained by several factors. In the Migaleddu et al. study,<sup>17</sup> only 5/47 patients had undergone bowel resections. We evaluated contrast uptake quantitatively using a software that is specific for this purpose, with an uptake level established in 46% after calculating the ROC curve. However, Migaleddu et al.<sup>17</sup> evaluated qualitatively the contrast uptake in the intestinal wall. Finally, this author included not only endoscopic data as a standard but also histological data. Other techniques, such as CT<sup>33</sup> and MRI<sup>34</sup> have also shown good correlations similar to those obtained in our study between intestinal wall thickness and contrast uptake in the intestinal wall when evaluating endoscopic activity in patients with CD.

In our series, there was only a low percentage (13%) of patients who suffered transmural complications, such as fistulae. Seven patients with a complication detected on ultrasound had severe endoscopic recurrence and one had moderate recurrence. Therefore, the detection of a transmural complication indicates that it is a severe recurrence, regardless of the thickness or enhancement of the wall. This finding is keeping with the study of Minordi et al.,<sup>25</sup> where 86% of the patients with fistulae had an endoscopic score of 3 or 4.

As with other sectorial imaging techniques,<sup>26</sup> we developed a semiquantitative score that allowed improving the usefulness of CEUS in the evaluation of endoscopic recurrence. This score should be validated in further studies. Our study had several limitations. First limitation of the study has been the use of a non-longitudinal cross-section design as has been used by other authors in the study of recurrence.<sup>9,35</sup>

A longitudinal study, with endoscopic and ultrasound follow-up, would allow us to evaluate if patients with greater contrast uptake in the neoterminal ileum at 12 months after surgery, or even beforehand, will have a more severe endoscopic recurrence or an earlier recurrence. Second, the relatively high prevalence of disease recurrence (in 49–82% of 60 patients), might have influenced our results for the diagnosis of recurrence. Another limitation was that we did not evaluate interobserver variability in regard to the selection of the most enhancing zone of the intestinal wall where the ROI was placed to measure the increase of enhancement in the maximum thickened intestinal segment. The selection of the ROI to measure the contrast enhancement depended on the radiologist, potentially introducing interobserver variability.

Finally, we performed all the examinations with the same machine. Quantitative measurements of enhancement may not be interchangeable between different commercial US equipments. Comparative studies obtained with different software packages should be performed.

In conclusion, the use of intravenous contrast improves the results of conventional ultrasonography for the study of recurrence. CEUS affords an early detection of endoscopic recurrence after intestinal resection and in combination with B-mode features (mural thickness and presence of transmural complications) allows better assessment of its severity in patients with CD.

## Conflicts of interest

None.

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