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Role of bowel ultrasound in the management of postoperative Crohn's disease

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Abstract

The use of biological and immunosuppressive therapy in Crohn's disease (CD) changed favorably the course of the disease and is currently suggested in the prevention of clinical recurrence. Symptomatic exacerbation is a feature of the natural course of the disease. Endoscopic recurrence may occur earlier than clinical manifestations and its rate is still high ever since the first year after surgery. The severity of mucosal lesions is highly predictive of a new flare of the disease so that the early detection of recurrence warrants strong therapeutic changes or a closer monitoring of the case. Endoscopy is at present the gold-standard technique for the diagnosis and grading of recurrence severity, but is poorly accepted by patients for its invasiveness. A simple and easy repeatable examination able to detect early signs of recurrence could be useful in the follow-up as an alternative or as a backing in the choice of the right timing for endoscopy in questionable cases. The use of bowel ultrasound (B-US) in the management of CD has grown in the past twenty years. Its accuracy in the real time detection of the disease and its complications, known since the 80's, together with the non-invasiveness, low cost and wide availability of the technique have influenced the extension of its clinical use in many referral centers in Europe. The latest generation of ultrasound scanners

allows a precise and reproducible morphological assessment of the intestinal tract and the surrounding tissues and enables a complete evaluation of the disease. This review analyzes the literature history about B-US in the diagnosis of postoperative recurrence of CD and outlines the clinical implications of its use. Published works confirm a very good accuracy of B-US in the diagnosis of CD recurrence compared to endoscopy, also in the early phase. B-US shows a good correlation with Rutgeert's score grading, but does not prove significant association with C-reactive protein or CD Activity Index values. A wider use of B-US in the daily practice could allow to set a prompt diagnosis and an earlier and targeted treatment, probably sparing more invasive tests.

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Key words: Ultrasound; Endoscopy; Postoperative; Crohn's disease; Recurrence

Core tip: In the recent years, after the introduction of new drugs, prevention of recurrence is one of the emerging issues in the management of Crohn's disease because a more aggressive and earlier therapy is supposed to change the clinical course of the disease. Endoscopy, that is presently the standard reference for the diagnosis, is not well tolerated by patients. To assess pre-clinical signs of recurrence a non-invasive alternative is needed. Magnetic resonance imaging shows accurate results but with high costs and low availability. Bowel ultrasound can detect early specific signs of recurrence. Advantages, limits and clinical implications of the technique are discussed below.

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INTRODUCTION

The therapeutic management of Crohn's disease (CD) patients is an open challenge. The correct use of steroids, antibiotics, immunomodulators and biological therapies requires an appropriate timing in the decision making process. From this point of view an early diagnosis of postoperative recurrence is extremely important in order to identify patients with a more aggressive course and to address the correct therapeutic choice. Recurrence is endoscopically present in around 70% of patients at 1 year after surgery. Early endoscopic signs of recurrence have been detected even three months after surgery and the severity of mucosal lesions is highly predictive of future clinical manifestations of the disease^[1,2].

Endoscopy is at present the gold-standard for the diagnosis of recurrence but less invasive, repeatable techniques would fit better to follow the evolution of chronic disease if they showed comparable results. The use of computed tomography (CT) should be limited because of its biological invasiveness while magnetic resonance (MR) can not be carried out routinely for its substantial costs and inadequate availability.

Starting from the first reports in the 80's on the possibility of detecting inflammatory bowel diseases using ultrasounds, the role of this technique in characterizing inflammatory bowel disease (IBD) in terms of extension, activity and complications compared to radiology or endoscopy has steadily increased^[3-8].

In the last decade the continuous improvement in ultrasound technology enabled a better definition of the bowel wall morphology. The addition of color-power doppler, oral or intravenous contrast to advanced ultrasound (US) technical equipment made it possible to distinguish fibrotic from inflammatory involvement of the intestinal tract, phlegmons from abscesses and to select a portion of patients at increased surgical risk or with optimal response to new pharmacological approaches^[9-13].

Advantages and limits of the technique and the technical aspects of potential impact on clinical practice are discussed below.

LITERATURE ANALYSIS

All the studies available in literature define post-surgical US recurrence as an increased bowel wall thickness at the anastomosis level and the majority of them correlates US findings with endoscopy. Major obstacles to a correct interpretation of the literature are due to a significant heterogeneity in the studies' design (different reference standards and variability in the timing of procedures), in technical aspects (different cut-offs for bowel wall thickness, BWT) and in the use of additional technical equipment (Power Doppler, Enteral or Intravenous Contrast Agents).

Since 1986 DiCandio *et al.*^[14] described the possibility of detecting post-surgical recurrence using transabdominal US compared to contrast radiography and endoscopy. His pioneering work on 32 patients showed a good

sensitivity (82%) and an excellent specificity (100%) of the technique with an overall accuracy of 93.7%. In this study the possibility to distinguish between inflammatory and neoplastic lesions is shown through a structural study of the bowel wall, paying particular attention to the integrity of its layers^[14].

In 1998 Andreoli studied the US detection rate of CD recurrence in 47 patients who underwent terminal ileum resection for CD using endoscopy at the anastomotic site as the gold standard. Bowel US sensitivity was 81%, specificity 86% and the overall accuracy 83%. The authors suggest to perform US in case of clinical suspected recurrence, reserving ileocolonoscopy to negative or uncertain cases^[15].

In 2001 and 2004 two studies have been published on the role of ultrasonography in the detection of recurrence after conservative surgery (strictureplastic and/or miniresections)^[16,17]. Thickness and echopattern (the sequence of layers that constitute the sonographic appearance of the intestinal wall) of the diseased wall were considered before and 6 mo after surgery in patients with ileal strictures in order to understand if these characteristics and their postoperative behavior have a prognostic value. Both thickness and echopattern, in different measure, are relevant in order to reliably predict recurrence (hazards ratio 8.8 and 4.1 respectively).

A possible role of US as a predictor of endoscopic recurrence has been evaluated by Orlando *et al.*^[18] in 2006. Looking for the best calprotectin cut-off to assess recurrence, 50 resected patients were studied with US and fecal calprotectin every three months after surgery. Endoscopy was performed at one year. US sensitivity with a 5 mm BWT cut-off was 26% and specificity 90%. The best calprotectin cut-off value to predict the highest number of endoscopic recurrences was > 200 mg/L (sensitivity 63% and specificity 75%). Considering such a high specificity of US, the authors suggest that a positive ultrasound 3 mo after surgery, may be an indication to colonoscopy. In case of US negative, faecal calprotectin with a cut-off value of 200 mg/L could be a useful tool in order to decide if performing colonoscopy in asymptomatic patients.

In the study of Biancone *et al.*^[19] Bowel US was performed with oral contrast (small intestine contrast ultrasound - SICUS). Twenty-two asymptomatic patients, prospectively followed after surgery, underwent clinical controls every 3 mo and SICUS, wireless capsule endoscopy (WCE) and colonoscopy 1 year after surgery. Seventeen patients underwent all the 3 procedures. SICUS showed 100% sensitivity, 0% specificity (16 TPs, 1 FP), whereas WCE 100% sensitivity, 100% specificity (16 TPs, 1 TN). The small serie was then split in smaller subgroups. Considering only neo-terminal ileum recurrence and excluding patients in which disease was limited to the anastomosis the sensibility was 86% and specificity 33 %. In a very small subgroup (10 patients) SICUS and WCE were performed at 3, 6 and 12 mo. SICUS identified four of the nine WCE positive at month 3. At month 6, eight of the nine WCE positive were detected by SICUS. No

significant correlation between BWT and Rutgeert's score was found.

A part of a long term prospective follow up study on severity of CD recurrence after ileal resection published in 2010 by Pallotta *et al*^[20] reports on 58 CD patients scheduled to SICUS and ileocolonoscopy at 6 mo regular intervals after surgery. Ileocolonoscopy was performed within 2 wk from SICUS. Bowel wall thickness at the anastomosis site was measured and it correlated with the anastomotic recurrence degree sec. Rutgeerts. SICUS could detect extension of intramural lesions even in patients with tight anastomotic stenosis.

In 2010, Onali *et al*^[21] performed a longitudinal prospective study in 25 patients 3 years after surgery using oral contrast US and obtaining a very good correlation between SICUS and endoscopy. The correspondence of SICUS detected lesions with Rutgeert's grade was moderate and the attempt of identifying a bowel wall thickness value predictive for clinical recurrence did not reach statistical significance^[21].

Between 2006 and 2010 other four prospective studies comparing US performance with endoscopy have been published^[22-25]. In these studies sensitivity varies from 79% to 92% and specificity from 20% to 95%. In two of them oral contrast was used^[23,24]. For all of them ileocolonoscopy was the reference standard and bowel wall thickness (> 3 mm) the only pathological feature considered. In one paper Doppler findings were considered, slightly strengthening the accuracy only in moderate-severe recurrence and with no impact on recurrence detection^[25]. Bowel wall thickness was compared with Rutgeerts' score obtaining a good correlation between ultrasonographic findings and endoscopic lesions. Using a cut-off of 5 mm for bowel wall thickness mild from severe disease can be distinguished. No significant correlations between CD activity index (CAI) and SICUS were found^[24], while SICUS showed a higher sensitivity and specificity in detecting recurrence compared to CRP and CAI values^[23].

The use of intravenous contrast enhancement ultrasonography (CEUS) to emphasize B-US findings was reported by Paredes *et al*^[26] in a study on postoperative recurrence of CD. The sample size of the study is consistent (60 patients) and the interval between ileocolonoscopy and CEUS was 3 d only. The study considered bowel wall thickness (cut-off 3-5 mm recurrence present, > 5 mm moderate-severe), color doppler vascularity (subjectively graded) and CEUS. The authors quantify ultrasonographic activity, with a software processing of the difference in brightness of contrast enhancement maximum uptake and the baseline and worked out a US activity score that correlates with Rutgeert's degree of severity. B-US sensitivity rises with CEUS from 89.8% to 98% while specificity keeps 81%.

In the same year Cammarota *et al*^[27] published the largest retrospective study on the subject and investigate in particular the possible predictive role of BWT on surgical recurrence. All the patients included (196) were fol-

lowed for 114 mo on average and the rate of surgical recurrence was 20.4%. Bowel US was performed 6-15 mo after surgery; bowel wall thickness > 3 mm was predictive of surgical recurrence. Moreover the authors describe an increased percentage of surgical recurrence in higher values of BWT at 1 year after surgery^[27].

CONCLUSION

Several studies have been performed on bowel ultrasound and post-surgical recurrence in CD. Although most of them have a small sample size and different study designs, a very good correspondence between US and ileocolonoscopy is reported even in the early stages after surgery^[18,24]. Bowel wall thickness is the main US parameter in the detection of recurrence. The majority of the studies compare ultrasonographic with endoscopic findings and BWT values > 3 mm shows, except in two cases^[18,19], high percentage of sensibility and specificity (until 100% both) in identifying recurrence^[14,15,20-26]. Some studies demonstrate also a correlation between BWT values (> 5 mm) and Rutgeert's score severe disease grade^[19-24].

Few studies consider the echopattern performance before and after surgery in addition to bowel wall thickness^[16,17]. Morphological alterations of the echopattern are a relevant parameter in the follow-up of CD, and a good correspondence of different echopatterns with histologic findings has been shown^[28]. Moreover the predictive value of different echopatterns on the relative risk of surgical treatment and the normalization of the echopattern after biologic therapy have been reported^[9,13].

Despite the positive data supporting its use, this technique is not widespread and its use is substantially limited to some European countries. The main criticism raised by some authors is the supposed low reproducibility of the method.

Ultrasonography is by definition a subjective technique and its employment in the study of ileum and colon may be particularly difficult considering the scarcity of repere points, the high anatomical variability especially in post-surgical patients and the presence of gas in the bowel which implies the use of graduated pressure to display the deepest loops. On this issue (the reproducibility of B-US in the evaluation of Crohn's disease) a multicenter study has been performed which brought together gastroenterologists sonographers and radiologists from six referral centers for inflammatory bowel diseases, including our group. We found in different clinical settings of CD a good k value concerning BWT ($K = 0.72-1$) and the presence of complications ($K = 0.81-1$)^[29].

The performance of the examination, blinded, sequentially conducted by different operators, was preceded by a long theoretical comparison that led to the choice of parameters to be measured and methods of detection.

The results of this experience, combined with the well known positive characteristics of ultrasound (optimal tolerance, low invasiveness, low costs, wide availability) and the comparable accuracy values of B-US, CT and

MRI in different controlled settings of CD attest B-US as an added value in the clinical management of IBD^[30-32].

In our opinion features needed for a correct use of B-US are an adequate learning curve, a good clinical knowledge in inflammatory bowel diseases and the basics of ultrasound technique. The use of B-US should be included in pathways of clinical management at different levels in the management of inflammatory bowel diseases (screening IBS-IBD, therapy monitoring, follow up of complications, emergency, young children) because it raises an efficient clinical work up and reduces the use of more expensive and invasive tests with similar results in terms of clinical impact^[31,32].

It is conceivable that new technologies can improve the correspondence between imaging and the bowel wall morphology in intestinal inflammation. A wider confrontation among experienced operators on this and other interesting US parameters in B-US would be desirable.

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