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Prognostic role of intestinal ultrasound in Crohn's disease

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Abstract

The majority of patients affected by Crohn's disease (CD) develop a chronic condition with persistent inflammation and relapses that may cause progressive and irreversible damage to the bowel, resulting in stricturing or penetrating complications in around 50% of patients during the natural history of the disease. Surgery is frequently needed to treat complicated disease when pharmacological therapy fails, with a high risk of repeated operations in time. Intestinal ultrasound (IUS), a non-invasive, cost-effective, radiation free and reproducible method for the diagnosis and follow-up of CD, in expert hands, allow a precise assessment of all the disease manifestations: Bowel characteristics, retrodilation, wrapping fat, fistulas and abscesses. Moreover, IUS is able to assess bowel wall thickness, bowel wall stratification (echo-pattern), vascularization and elasticity, as well as mesenteric hypertrophy, lymph-nodes and mesenteric blood flow. Its role in the disease evaluation and behaviour description is well assessed in literature, but less is known about the potential space of IUS as predictor of prognostic factors suggesting response to a medical treatment or postoperative recurrence. The availability of a low cost exam as IUS, able to recognize which patients are more likely to respond to a specific therapy and which patients are at high risk of surgery or complications, could be a very useful instrument in the hands of IBD physician. The aim of this review is to present current evidence about the prognostic role that IUS can show in predicting response to treatment, disease progression, risk of surgery and risk of post-surgical recurrence in CD.

Key Words: Intestinal ultrasound; Crohn's disease; Postoperative recurrence; Bowel wall thickness; Remission; Intestinal surgery

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Core Tip: Intestinal ultrasound (IUS) and magnetic resonance enterography are better tolerated and safer than endoscopy, with IUS more easily available and less expensive than magnetic resonance imaging. Moreover, IUS allows complete visualization of the small-bowel even in patients with stenoses and/or severe inflammation, and can assess for extraintestinal disease. In addition, IUS may predict outcomes better than endoscopic mucosal assessment, possibly identifying more relevant therapeutic targets. This review discusses the role of IUS in Crohn's disease not only as first line investigation but as an extremely useful instrument in predicting response to medical treatment, disease evolution and risk of recurrence before and after surgery.

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory condition that can affect the whole gastrointestinal tract, more frequently involving the ileum and colon, usually presenting in its active phases with abdominal pain, diarrhoea (bloody or non-bloody), urgency, fatigue and weight loss[1]. The majority of patients affected by CD show chronic relapsing disease with potential chronic continuous abdominal symptoms after diagnosis[2].

The available treatments often fail to achieve disease remission or lose their efficacy over time. Moreover, in CD, chronic inflammation and relapses may cause progressive and irreversible damage to the bowel[3], which results in stricturing or penetrating complications in approximately 50% of patients during the natural history of the disease, with a high risk of surgery or repeated surgery[4].

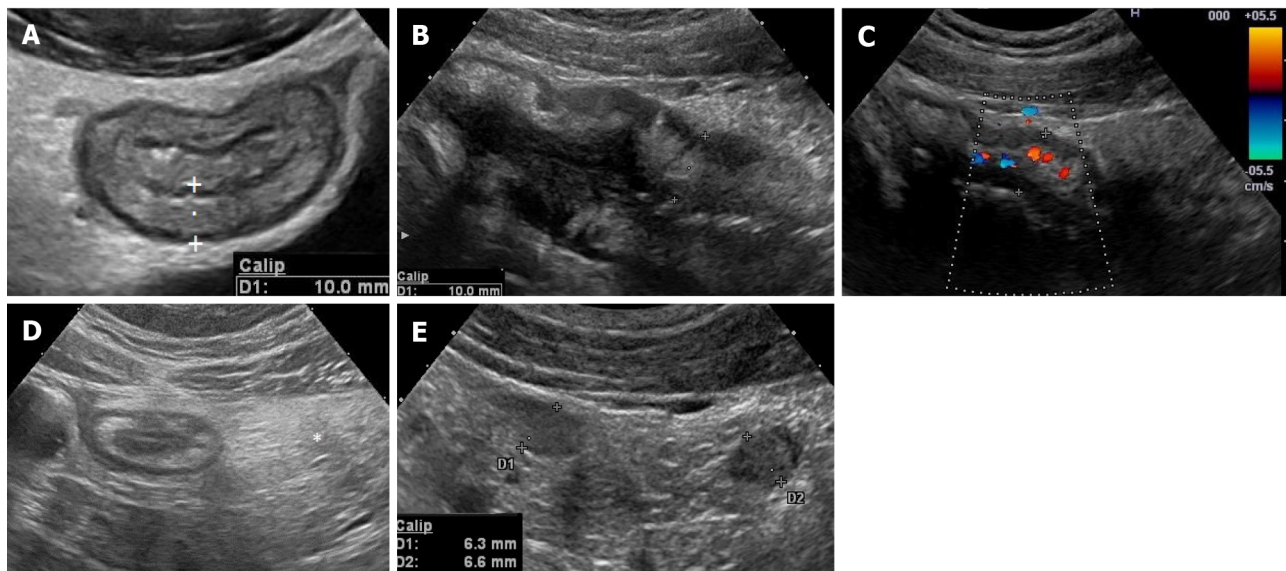
It has been realized that patients' symptoms in CD do not necessarily reflect the underlying inflammatory burden of the disease and that, independent of clinical symptoms, patients can have different rates of disease progression and outcomes[2]. Most CD patients at the time of diagnosis have a disease with inflammatory features, but in some patients, it can evolve to a stenosing or penetrating pattern during follow-up[5]. Therefore, the possibility of identifying which patients are nonresponsive to medical treatment and prone to develop stricturing and penetrating CD would be very important to properly address the treatment. Prognostic factors for favourable or unfavourable outcomes of CD have been extensively researched and assessed with both invasive and noninvasive methods.

Intestinal ultrasound (IUS) is a non-invasive, cost-effective, radiation free and reproducible method for the diagnosis and follow-up of CD, with an accuracy comparable to magnetic resonance imaging and computed tomography[6,7]. IUS can assess several features of the bowel wall and surrounding tissue: Bowel wall thickness (BWT) (Figure 1A), bowel wall stratification (echo-pattern) (Figure 1B), vascularization (Figure 1C) and elasticity, as well as mesenteric hypertrophy (Figure 1D), lymph-nodes (Figure 1E) and mesenteric blood flow. IUS is also able to assess complications such as stenosis, dilations, fistulas and abscesses[8]. During the follow-up of CD patients undergoing biological therapy, IUS features have been correlated with clinical activity, endoscopic activity, laboratory markers (faecal calprotectin and C-reactive protein) and drug serum levels[9-13]. However, IUS specific features have also been suggested as predictive factors for evaluating the response to medical treatment, the risk of clinical relapse or surgery, and the risk of postoperative recurrence[14-17]. We present the current evidence on the prognostic value of IUS and especially the IUS features of the bowel wall in predicting response to treatment and risk of relapse in CD.

LITERATURE REVIEW

Search strategy and selection criteria

Two authors (Manzotti C and Maconi G) searched the literature using the PubMed database from January 2000 to January 2022. The search used the following terms in different combinations: "intestinal ultrasound", "bowel ultrasound", "transabdominal ultrasound", "IUS", "bowel wall thickness", "Doppler", "CEUS", "transmural healing", "Crohn", "Crohn's disease", "IBD", "inflammatory bowel disease", "surgery", "clinical remission", "remission", "predictive value", "outcome", and "post-surgical recurrence". In particular, the following string was used: [(ultrasound OR sonography) AND (bowel OR intestinal) AND (Crohn's disease OR IBD) AND (remission OR response OR transmural OR outcome OR predictive)].



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Figure 1 Intestinal ultrasound assess several features of the bowel wall and surrounding tissue. A: Bowel wall thickness should be measured perpendicular to the anterior wall of the bowel (or where it is better visible) avoiding haustrations and mucosal folds. The cursor/calipers should be placed at the end of the interface echo between the serosa and the proper muscle to the start of the interface echo between the lumen and the mucosa; B: Bowel wall stratification. The wall layers in case of active disease may appear focally or extensively disrupted (disrupted or hypoechoic echo pattern); C: Bowel wall vascularity. Bowel wall vascularity can be determined both by colour Doppler or power Doppler signal at the level of the most thickened segments, using special presets optimized for slow flow detection; D: Mesenteric hypertrophy. Mesenteric hypertrophy also called fat wrapping or creeping fat appears on ultrasound (US) as hyperechoic tissue or “mass effect” encircling the diseased bowel; E: Lymphnodes. Enlarged inflammatory mesenteric lymph nodes related to Crohn’s disease are usually described at US as oval or elongated with lesser diameter > 5 mm and seem to be correlated with young age, early disease, or disease with shorter duration, and with the presence of fistulae and abscesses.

Additional potentially eligible articles were manually searched through the bibliography of relevant articles. Eligible articles were randomized controlled trials, prospective or retrospective cohort studies, reviews, and systematic reviews with a meta-analysis; duplications and studies in languages other than English were excluded. In each eligible paper, we searched for information on the predictive value of IUS for patients affected by active or quiescent CD in terms of response to treatment, disease course, transmural healing, risk of surgery, and risk of postsurgical recurrence. Two authors (Manzotti C and Maconi G) screened the title and abstract of potentially eligible papers, followed by a full-text analysis of relevant articles. Starting from a total of 1040 articles, 49 were considered suitable and were included in this review.

DISCUSSION

Active disease

Intestinal US, before and early after the start of biologic treatment, showed high accuracy in predicting long-term clinical and endoscopic remission and response[17,18]. Although few data have shown that pretreatment IUS features may predict the outcome and somewhat drive the choice of treatment, much more data have shown that sonographic improvement of BWT, echopattern and vascularization as early as weeks 2-4 of biologic treatment may predict a better long-term response compared to those of patients without an early treatment response[19]. Studies considering predictive value of IUS parameters for response to treatment and course of CD are shown in Table 1.

Intestinal US to predict response to treatment and disease course

Increased BWT and bowel wall vascularity assessed by colour Doppler or IV contrast-enhanced ultrasound (CEUS), variably powered in bowel US scores, was identified as an independent predictor of a negative disease course, namely, the need for steroids, change of therapy, treatment intensification, hospitalization, or need for surgery through 6-12 mo[20,14]. In addition, increased echopatterns coupled with disrupted echopatterns of the bowel wall or lack of bowel wall stratification were independent predictors for the need for subsequent therapeutic optimization[20].

Sonographic response and clinical response

It seems that sonographic response after 12 or 14 wk of therapy with anti-tumor necrosis factor (TNF)

Table 1 Predictive value of intestinal ultrasound parameters for response to treatment and course of Crohn's disease

Ref.	Treatment	Timing of IUS after start of treatment	IUS parameter	Predictive value for
Albshesh <i>et al</i> [18], 2020	Anti-TNF	> 14 wk	BWT > 4 mm BWT < 4 mm	Treatment failure Duration of failure-free response
Calabrese <i>et al</i> [52], 2022	Anti-TNF, vedolizumab, ustekinumab	Baseline	"Higher BWT" Colonic localization	Low risk of TR High risk of TR
Chen <i>et al</i> [19], 2022	Anti-TNF	Baseline-2 wk	Reduction in BWT, vascularization, SWE	Response to treatment
De Voogd <i>et al</i> [17], 2022	Anti-TNF	Baseline-4/8 wk	BWT reduction > 18%	Endoscopic response and remission at 12-34 wk
Helwig <i>et al</i> [32], 2022	All available biological therapies	Baseline-12 wk	BWT reduction > 25%	Clinical remission and no therapy change at 52 wk
Les <i>et al</i> [20], 2021	5-ASA, budesonide, AZA, anti TNF		Worsened BWT, echopattern, vascularization	Need for treatment escalation, negative disease course
Orlando <i>et al</i> [29], 2018	Anti-TNF	Baseline	SWE strain ratio > 2	Surgery
Paredes <i>et al</i> [53], 2019	Anti-TNF	12 wk	BWT ≤ 3 mm	"Good outcome" (no treatment intensification, no surgery) at 1 yr
Ripollés <i>et al</i> [21], 2016	Anti-TNF	Baseline-12 wk	Sonographic response (BWT decrease > 2 mm, diminution of one grade of ECD, decrease > 20% of mural enhancement, disappearance of transmural complications or stenosis)	1-yr sonographic response and further 1-yr clinical response and treatment efficacy
Smith <i>et al</i> [22], 2022	All available biological therapies and thiopurines	Baseline-14 wk	Sonographic response (BWT decreasing > 0.5 mm and vascularity improvement by ≥ one grade)	Treatment response at 46 wk
Zorzi <i>et al</i> [23], 2020	Anti-TNF, budesonide, thiopurines	Baseline-18 mo	Normalization of SICUS (BWT, disease extension, complications)	Long term lower cumulative probability of need for surgery, hospitalization, and need for steroids
Laterza <i>et al</i> [54], 2021	Anti-TNF	12 wk	CEUS increased PI and Pw	Clinical relapse within 6 mo
Ungar <i>et al</i> [55], 2020	Adalimumab	NA	Terminal ileum BWT < 4 mm	Therapy retention
Quaia <i>et al</i> [56], 2019	Anti-TNF	Baseline-6 wk	CEUS pretreatment values and % variations of peak enhancement, AUC, AUC during wash-in, AUC during wash-out	Long term response to therapy

IUS: Intestinal ultrasound; BWT: Bowel wall thickness; ECD: Eco-color-doppler; SWE: Shear wave elastography; UEI: Ultrasound elastography imaging; TR: Transmural remission; CEUS: Contrast enhanced ultrasound; AUC: Area under the curve; TNF: Tumor necrosis factor; NA: Not available; 5-ASA: 5-aminosalicylic acid; AZA: Azacitidine.

drugs predicts the 1-year sonographic response, which in turn correlates with the 1-year clinical response, predicts efficacy of further treatment and inversely correlated with the need for surgery. Strictureing behaviour, namely, the detection of strictures with prestenotic dilatation, seems to be the only sonographic feature associated with a long-term negative predictive value of clinical response[21, 22].

Similar results were demonstrated by using small intestinal contrast US (SICUS), which is used to monitor patients undergoing anti-TNF therapy. An improvement in BWT, a reduction of disease extension, or the absence of intestinal complications as detected by SICUS predicted a better response after 1 year of therapy, as well as a reduction in steroid therapy and hospital admissions[23].

Monitoring BWT with IUS also showed predictive value for patients starting therapy with ustekinumab. A decrease in BWT > 1 mm at week 8 after the start of therapy was a helpful parameter for selecting patients with an early response to ustekinumab and for providing assistance in terms of further treatment intervals[24]. The thickening of each single layer of the bowel wall and its clinical significance in CD have been poorly investigated thusfar. It seems that the thickening of the proper muscle layer in active CD patients is correlated with poor clinical and sonographic responses to vedolizumab treatment[25]. In this regard, smooth muscle hyperplasia has been underlined as a central

contributor to the stricturing phenotype, whereas fibrosis is less significant, and the 'inflammation-smooth muscle hyperplasia axis' seems to be the most important step in the pathogenesis of Crohn's strictures[26].

Additionally, the assessment of bowel wall vascularity by CEUS seems to provide relevant prognostic information regarding treatment efficacy in patients with CD. The improvement of several perfusion parameters, such as peak contrast enhancement, rate of wash-in and wash-out and the area under the time intensity curve of the intestinal wall 4-6 wk after starting anti-inflammatory treatment (anti-TNF- α), were correlated with a favourable response[25,27,28]. Finally, the evaluation of ultrasound elasticity of the bowel wall may have a predictive role as well, correlating with therapeutic outcomes for CD patients treated with anti-TNF[29].

With regard to extra bowel findings, especially mesenteric lymphadenopathy and mesenteric fat hypertrophy, their prognostic role in response to treatment remains controversial. Regional mesenteric lymphadenopathy detected by IUS is a common but nonspecific sonographic finding in early CD and could be linked to young age, early disease, and the presence of abscesses or fistulae[30]. However, its prognostic significance remains poorly investigated. Mesenteric fat hypertrophy is associated with clinical and biochemical disease activity, and it may disappear or improve in patients who have responded to medical treatment[31]. However, its prognostic value in predicting response to therapy and risk of relapse is debatable[16,31].

IUS to predict transmural remission

Transmural remission (TR) or transmural healing with different definitions in literature, is now considered as an objective and relevant target in CD. It may be assessed by IUS taking into account BWT normalization (≤ 3 mm) with or without normalization of Doppler vascular signs and peri-intestinal inflammatory signs[32]. It is correlated with improved clinical outcome, such as a reduced demand of medication escalation, corticosteroid use, hospitalization and CD-related surgery.

The rate of TR, with more or less extensive definitions, in patients undergoing biological therapy was obtained from 12% to 46.2% of patients after 12 wk to 2 years of therapy (see Table 2). TR was strictly correlated with time, being higher at later assessments compared with early assessments. Moreover, it is more prevalent in colic CD than in ileal CD and it is associated with lower BWT and lower shear wave elastography strain ratio at baseline (see Table 2). However, a few studies have evaluated baseline or early IUS factors predictive of TR. Further prospective trials are needed to reach more consistent evidence on IUS predictive value, to help in properly selecting the right treatment for the right CD patient and plain maintenance therapy.

IUS to predict the risk of surgery

The ileal localization and stricturing and perforating behaviour of CD are well-known risk factors for surgery both in children and in adults. Children with ileal CD requiring surgical resection may have more severe IUS manifestations (such as loss of mural stratification and severe fibrofatty proliferation) associated with both active inflammation and chronic fibrosis than those managed medically[33].

Even in adults, the routine use of IUS in CD patients may identify a subgroup at high risk of surgery, taking into account that nearly half of patients with CD may require surgery within 10 years of diagnosis[1]. Irrespective of the treatment performed, BWT > 7 mm at IUS, altered bowel wall echopattern, and the presence of complications such as fistulas or stenosis are risk factors for intestinal resection over a short period of time[34-36]. In particular, the presence of strictures, fistulae, and abscesses at baseline bowel US seems to predict the need for surgery through 12 mo[14].

The assessment of fibrosis by means of strain elastography may identify patients who are nonresponsive to anti-TNF and need surgery. Orlando *et al*[29] in a small series of patients, showed that the strain ratio of the thickened bowel wall may predict surgery much better than the degree of its thickening and vascularization and that a strain ratio ≥ 2 before starting anti-TNF was the cut-off value correlated with poor lack of improvement, surgery and worst outcome. Likewise, the lack of improvement or the increase in BWT after the start of treatment is correlated with a high risk of surgery[21,34]. It is debatable whether in selected populations at high risk of surgery, such as CD patients with well-known strictures and fistulas, the features of BWT may suggest the response to treatment and ultimately surgery. In the STRIDENT study, 77 CD patients with a *de novo* or postoperative anastomotic intestinal stricture with symptoms consistent with chronic or subacute intestinal obstruction were randomly assigned to receive adalimumab alone or combined with thiopurines. IUS at 12 mo showed improvement ($> 25\%$) in BWT in 45% of patients, with no significant difference between the two groups of patients and an overall low risk of surgery, but no predictors of improvement were given[10].

IUS to predict post-surgical recurrence

Several studies and systematic reviews have assessed the role of IUS in postoperative follow-up, showing that a BWT > 3 mm of the anastomosis or neoterminal ileum is an accurate indicator for recurrence[11]. In this regard, prospective studies have shown that the use of PEG solution (SICUS)[37] and colour Doppler or CEUS[38] can increase the sensitivity, albeit with a decrease in specificity in detecting postoperative recurrence at 1 year after surgery. Moreover, both IUS and SICUS, adopting

Table 2 Rate of transmural remission and intestinal ultrasound parameters predictive of transmural remission in Crohn's disease patients treated with biologics

Ref.	Patients, n	TR definition	Study drug	Treatment duration	Rate of TR	IUS parameters predictive of TR
Calabrese <i>et al</i> [52], 2022	188	Normalization of BWT, no ECD, no extra bowel signs of inflammation	Adalimumab, infliximab, vedolizumab, ustekinumab	52 wk	27.5% (26.8% adalimumab; 37% infliximab; 27.2% vedolizumab; 20% ustekinumab)	Colonic localization, lower BWT at baseline
Castiglione <i>et al</i> [57], 2013	66	NA	Anti-TNF	2 yr	25%	
	67		Thiopurines		4%	
Castiglione <i>et al</i> [58], 2017	40	BWT ≤ 3 mm	Anti-TNF	2 yr	25%	
Castiglione <i>et al</i> [59], 2019	218	BWT ≤ 3 mm	Anti-TNF	12 wk	31.2%	
Helwig <i>et al</i> [32], 2022	180	BWT ≤ 2 mm terminal ileum or ≤ 3 mm colon; BWT ≤ 2 mm terminal ileum or ≤ 3 mm colon + two factors among no ECD, no fibrofatty proliferation, normal stratification; normalization of all parameters	All available biologics	12 wk	33.3%; 38.5%; 24.4% (18.4% I; 29% C)	
	78			46 wk	46.2%; NA; NA	
Kucharzik <i>et al</i> [60], 2023	77	Normalization of all IUS parameters	Ustekinumab	48 wk	24.1% (13.2% I; 50.0% C)	
Miranda <i>et al</i> [61], 2021	35	BWT ≤ 3 mm	Ustekinumab	52 wk	31.4%	
Orlando <i>et al</i> [29], 2018	30	BWT ≤ 3 mm	Anti-TNF	14 wk	29%	UEI strain ratio
				52 wk	30%	
Paredes <i>et al</i> [53], 2019	36	BWT ≤ 3 mm	Anti-TNF	52 wk	39%	
Ripollés <i>et al</i> [21], 2016	51	BWT ≤ 3 mm, no ECD, absence of complications	Anti-TNF	12 wk	14%	
				52 wk	29.5%	
Civitelli <i>et al</i> [62], 2016	32	BWT < 3 mm, no ECD, normal stratification, absence of strictures and dilatation	Anti-TNF	9-12 mo	14%	
Paredes <i>et al</i> [63], 2010	24	BWT < 3 mm, no increased ECD	Anti-TNF	2 wk	20.8%	
Vaughan <i>et al</i> [64], 2022	79	BWT ≤ 3 mm, no increased ECD	Infliximab	12 wk	41%	
Han <i>et al</i> [65], 2022	92	BWT ≤ 3 mm, no increased ECD	Anti-TNF	14 wk	12%	
				52 wk (only 22 patients)	22.7%	
Dolinger <i>et al</i> [66], 2021	13	BWT ≤ 3 mm	Infliximab	14 wk	23%	
Zorzi <i>et al</i> [23], 2020	80	SICUS normal value for BWT, absence of any length of disease, and absence of perienteric inflammation, fistulas, phlegmon, or abscess)	Anti-TNF, budesonide, thiopurines	18 mo	41%	

TR: Transmural remission; BWT: Bowel wall thickness; ECD: Eco-color-doppler vascular signal; I: Ileal Crohn's disease; C: Colonic Crohn's disease; UEI: Ultrasound elastography imaging; SICUS: Small intestine contrast ultrasonography; IUS: Intestinal ultrasound; TNF: Tumor necrosis factor; NA: Not available.

different cut-off levels for bowel thickness (> 5 mm for conventional sonography and > 4 mm for SICUS), can suggest severe endoscopic postoperative recurrence and could accordingly replace endoscopy in postsurgical follow-up[37] (for detection of recurrence).

IUS is accurate not only in detecting postoperative clinical recurrence but also in predicting endoscopic and surgical recurrence. IUS assessment 3 mo after surgery showed high sensitivity in predicting postoperative recurrence at 12 mo, with lower sensitivity[38] but higher specificity than calprotectin[39]. A retrospective study showed that in postoperative CD patients, independent of the

time elapsed from earlier surgery, patients with BWT > 3 mm had a doubled risk of surgical recurrence compared with patients with BWT < 3 mm, and that the absolute incidence of new surgical interventions positively correlated with increased BWT[40]. In this respect, the prognostic value of increased BWT, as assessed by IUS several years after surgery, needs further confirmation, and in particular, the usefulness of therapy escalation for these patients remains unconfirmed[12].

Additionally, in CD patients treated with conservative surgery (*e.g.*, strictureplasty or minimal bowel resections), IUS is useful for monitoring the postoperative behaviour of BWT and can provide prognostic information: US detection of unchanged or worsened wall thickness 6 mo after surgery or the postoperative persistence of wall thickness > 6 mm is predictive of a high risk of recurrence[41].

In this subset of patients, the estimated 5-year survival probability of symptomatic CD recurrence was 90% and 33%, respectively, for unchanged/worsened BWT *vs* improved BWT at 12 mo after surgery. A BWT > 6.0 mm at 12 mo after surgery was directly associated with the risk of CD recurrence. Hence, systematic IUS follow-up of diseased bowel walls after conservative surgery seems to allow the early identification of patients at high risk of clinical/surgical recurrence[42].

Clinical remission

In CD patients, bowel wall changes such as increased BWT and vascularization may persist after therapy and despite clinical remission. The meaning and prognostic significance of these IUS findings have been widely investigated. In quiescent CD, increased vascularity, detected either by colour Doppler or CEUS, after treatment may suggest an increased risk of relapse[21,43,44].

Vascularization and BWT currently represent the main features of sonographic activity scores, and the investigation on prognostic significance of these scores in clinical studies is still ongoing. However, it is clear that normalization of the bowel wall (the so-called TR), namely, a BWT < 3 mm[45] or a more stringent definition such as the combination of BWT < 3 mm, normalization of vascularity and wall stratification, absence of mesenteric fat hypertrophy, node enlargement, or disease complications (*i.e.*, strictures, fistulas)[46,47], is associated with favourable prognostic long-term outcomes[40,43,46,48,49].

Indeed, it has been demonstrated that sonographic remission evaluated after one year of anti-TNF therapy is associated with a longer remission without the need for a therapy change and a reduced need for surgery[21]. In patients with CD in clinical remission, achieving TR is associated with reduced clinical complications, including medication escalation, corticosteroid use, hospitalization, and surgery. When examining clinical complications occurring more than 90 d following IUS, sonographic inflammation remains associated with an increased risk of clinical complications such as medication escalation, hospitalization, and surgery[46,50,51].

CONCLUSION

IUS is a useful imaging method to assess CD disease activity and can have a prognostic role in predicting response to treatment, disease progression, risk of surgery and risk of postsurgical recurrence. Response to treatment may be predicted by increased BWT and vascularization, reduced elasticity and absence of CD complications. Disease progression or risk of surgery may be predicted by increased BWT, loss of bowel stratification and the presence of CD complications. Postoperative clinical and surgical relapse may be predicted by increased BWT. As more biological therapies become available in the coming years, further prospective trials will be needed to reach definite evidence on IUS predictive value at baseline, to recognize which patients are more likely to respond to a specific therapy and which patients are at high risk of surgery or complications, needing early intensive treatment.

FOOTNOTES

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