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REVIEW

SICUS and CEUS imaging in Crohn's disease: an update

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Abstract Endoscopy remains the main technique in the diagnosis and treatment of Crohn's disease (CD); nevertheless, the recent development of innovative and non-invasive imaging techniques has led to a new tool in the exploration of small bowel in CD patients. This paper reviews the available data on ultrasound imaging used for the evaluation of CD, highlighting the role of small intestine contrast-enhanced ultrasonography with the use of oral and intravenous contrast agents.

Keywords Crohn's disease · Contrast-enhanced ultrasound · Small intestine contrast ultrasonography

Sommario Nell'iter diagnostico e terapeutico della malattia di Crohn l'endoscopia rappresenta la principale metodica strumentale. Tuttavia, la recente introduzione di tecniche di imaging innovative e non invasive ha implementato lo studio dell'intestino nelle malattie infiammatorie croniche intestinali. La seguente revisione raccoglie i dati disponibili in letteratura relativi all'utilizzo dell'ecografia con mezzo di contrasto, sia orale (SICUS) sia endovenoso (CEUS), nella valutazione dei pazienti affetti da malattia di Crohn.

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Introduction

Crohn's disease (CD) is a chronic transmural intestinal inflammatory disease characterized by episodes of inflammation alternating with periods of remission [1]. CD can be localized to any part of the gastrointestinal tract, although ileal and colonic involvement is most frequent. The diagnosis of CD is based on a combination of clinical symptoms, laboratory tests and imaging data, and a single gold standard is lacking [2]. Ileocolonoscopy is the first line of investigation in the diagnosis, management, and monitoring of CD [3]; however, endoscopy is not always complete, and there are several limitations related to the invasiveness, procedure-related discomfort, risk of bowel perforation and relatively poor patient acceptance. Ileocolonoscopy also does not evaluate the extent of ileal disease, transmural damage, and lesions in the perineal region, such as fistulas and abscesses. Thus, looking beyond the mucosa surface, over the past few years, non-invasive cross-sectional imaging techniques, including ultrasound (US), computed tomography (CT), positron emission tomography (PET) and magnetic resonance imaging (MRI), have been increasingly used for the evaluation of patients with CD [4]. The applications of these techniques in the field of CD are manifold. In cases of suspected CD, cross-sectional imaging allows the assessment of the site, and extent and complications of CD. In established CD, they are crucial tools for grading of disease activity, the differentiation between small bowel stricture due to inflammation or mural fibrosis, and the assessment of the response to specific therapy [2, 4, 5].

There are substantial data that all the cross-sectional imaging techniques, such as US, CT, MRI, or positron emission tomography (PET), perform equally well in CD [6, 7]. The European Crohn's and Colitis Organisation

(ECCO) and American College of Gastroenterology guidelines considered CT or MRI as radiological imaging techniques with the highest diagnostic accuracy for the detection of intestinal involvement of CD, including extramural complications [3, 8]. In a recent consensus conducted by the ECCO and European Society Gastrointestinal and Abdominal Radiology (ESGAR), no significant differences in diagnostic accuracy among the imaging techniques (US, CT, MRI) were observed [9]. However, CT and MRI also have disadvantages in the assessment of the disease. First, both scanning methods require the intake of a contrast agent or colonic luminal distension or bowel cleansing, which requires long preparation and discomfort. Second, with regard to CT, patients are exposed to a large dose of radiation, and it is a difficult issue because IBD patients often require frequent re-evaluations of the disease status [10, 11]. Finally, MRI, despite being radiation-free, remains time consuming, expensive, and is not widely available in all centers.

Transabdominal US is non-invasive, does not impart ionizing radiation, and is more comfortable for patients. Within the last two decades, among the cross-sectional imaging techniques, the US has had a growing role in the development and application of techniques for the diagnosis of gastrointestinal diseases, such as appendicitis, diverticulitis and inflammatory bowel diseases (IBD) [12]. Today, bowel US is currently accepted as a clinically important first-line imaging technique in both patients with suspected CD and in follow-up patients known to have CD [13–19]. Furthermore, the introduction of oral contrast has improved the image quality, overall sensitivity and diagnostic accuracy in the detection of small bowel lesions in CD patients [20], and thus contrast-enhanced ultrasound (CEUS) has become an important imaging modality in patients with CD for grading of disease activity, differentiation between small bowel stricture due to inflammation or mural fibrosis, and the assessment of the response to specific therapy [21, 22].

This article provides a general review of the current literature data regarding ultrasound imaging used for the evaluation of CD, highlighting the role of small intestine contrast-enhanced ultrasonography by use of oral (SICUS) or intravenous (CEUS) contrast agents.

Ultrasound findings in IBD

US for IBD requires high-frequency (5–17 MHz) linear assay probes to increase the spatial resolution of the intestinal wall and to assess the wall diameter and wall layer discrimination [14]. Conventional bowel US with a 3.5–5 MHz convex probe is recommended prior to high-frequency US of the GI tract to not overlook other potential extraintestinal causes of abdominal discomfort. However, convex transducers with lower frequencies may be useful for visualizing bowel loops located deep within the abdomen or pelvis and for examining obese patients.

The US criteria for CD lesions include [23–26]: increased wall thickness ($\geq$3 mm), reported as the average of at least 3 measurements; “stiff loop” with increased bowel wall thickness; loss of stratification of the bowel wall; small bowel dilation, which is defined as a lumen diameter greater than 2.5 cm; bowel stricture, which is defined as a lumen diameter less than 1 cm with or without prestenotic dilation; fistulae, which are defined as the hypoechoic tract with or without hyperechoic content; mesenteric enlargement, lymph nodes and abscess, which are defined as a round-like mass with a diameter >2 cm.

SICUS

SICUS is performed by an experienced intestine-dedicated operator using a convex transducer (frequency 3.5–5 MHz) and then a high-frequency linear-array transducer (5–12 MHz) [23, 27, 28]. A preliminary assessment of the small bowel is made. Patients are examined in the fasting state without any preparation, after ingestion of an oral macrogol contrast solution consisting of polyethylene glycol (PEG) at a dose ranging from 125 to 800 mL (usually 375 mL), dissolved in 250 mL of tap water. After the ingestion of the macrogol contrast oral solution, the contrast is observed to flow through the neo-terminal ileum into the colon. A retrograde follow-through assessment of the entire small bowel is then performed to visualize the contrast-filled ileal and jejunal loops in a caudo-cranial sequence. The median SICUS duration is 30–45 min.

Introduction of the oral contrast agent has overcome the inherent limitation of conventional ultrasound, as it distends the intestinal lumen, allowing a more accurate characterization of the bowel wall. SICUS has emerged as a valuable, well-accepted and radiation-free technique in the detection of intestinal damage in CD [29], and no previous studies have reported significant side effects or major complaints during or immediately after PEG ingestion. Studies comparing conventional ultrasonography with the use of oral contrast agents have shown an overall superior sensitivity in the detection of small bowel CD lesions with SICUS (sensitivity ranged from 57 to 96% and 96 to 100% for conventional ultrasound and SICUS, respectively) [23, 25, 27, 28, 30], and reduced inter-observer and intra-observer variability [27]. SICUS also appears to demonstrate reasonable accuracy in detecting CD-related complications, including strictures, abscesses, and internal fistulae that occur in approximately 50–70% of affected patients during the course of their disease [31]. In

a recent study by Pallotta et al., SICUS identified at least one stricture or fistulae in 39/40 and 27/28 patients, respectively, and excluded them in 9/9 and 19/21 patients, respectively (97.5 and 96% sensitivity, 100 and 90.5% specificity, respectively) using surgery as the gold standard [24]. Furthermore, due to its radiation-free nature, SICUS is easily repeatable if the patient's condition changes and may be used to monitor progression over time [32].

Another group of studies examining SICUS have evaluated the diagnostic accuracy of this technique for the CD site, disease extent, complications, and its consistency with traditional gold standard techniques, such as small bowel follow-trough (SBFT), CT enteroclysis, MR enterography (MRE), capsule endoscopy (CE), histological findings, and surrogate markers of inflammation [30, 33–36]. In a retrospective study [33], SICUS was performed in a cohort of patients attending a UK regional hospital with the aim of evaluating this technique in clinical practice and assessing the level of consistency with SBFT, CT, histological findings and C-reactive protein (CRP). One hundred and forty-three patients underwent SICUS; of these patients, 68 (60%) patients had a known diagnosis of CD, and 57 (40%) patients were undiagnosed cases with signs and symptoms suggestive of intestinal disease. SICUS was performed by a single operator with little experience of this technique prior to the inception of the study. SICUS identified active small bowel CD in known CD and undiagnosed cases with a sensitivity, specificity, positive predictive value (PPV) and negative predictive value of 93, 99, 98, and 95%, respectively. The level of agreement between SICUS and SBFT or CT was good in the detection of the features of small bowel CD (κ coefficient 0.88 and 0.91, respectively), and a good level of agreement was observed between SICUS and histological data, which was demonstrated upon colonoscopy or surgical resection. Furthermore, similarly to other literature data [37], there was a poor level of agreement between CRP and disease activity with SICUS.

In another study [34], Calabrese et al. performed a retrospective analysis of data obtained from 59 patients with established CD who underwent SICUS and CT enteroclysis 3 months apart. Unlike the study of Chatu et al. [33], SICUS was performed by one independent experienced gastroenterologist. In the small bowel, the sensitivity, specificity and diagnostic accuracy of SICUS in identifying the site of CD was 98, 67, and 95%, respectively, whereas in the colon, it was 83, 97.5, and 93%, respectively. A significant correlation was observed between the SICUS findings and CT enteroclysis, in terms of both maximum bowel wall thickness and disease extent. SICUS also appears to have good sensitivity, specificity, PPV, NPV and diagnostic accuracy in detecting ileal stenosis and prestenotic dilation, as well as fistulas and abscesses, and showed a lower accuracy in detecting stenosis of the colon [34].

These studies have some important limitations. First, both are retrospective studies and there is a time lag between SICUS and other techniques. This delay could allow for spontaneous recovery, disease progression, or response to treatment. Above all, SICUS was performed by a single operator, and thus inter-observer variability was not assessed. Operator dependence is the most important limit reported for SICUS, as for all ultrasonographic procedures. However, in the UK study, although the operator was only an experienced sonographer without subspecialist interest in SICUS, the results were similar to those produced by the experienced operator [23, 25, 38].

SICUS was also proposed as a safe, accurate alternative for the assessment of small bowel disease in paediatric CD patients. An Italian group reported a higher sensitivity and specificity of SICUS in their cohort than seen in adults (96 and 100%, respectively) compared with ileocolonoscopy [30]. More recently, in a tertiary referral paediatric IBD centre, the same group performed a prospective comparative study between MRE, SICUS and CE. The researchers assessed the specificity, sensitivity, and accuracy of each technique in detecting active lesions in the three small bowel segments (jejunum, proximal and mid-ileum, and terminal ileum) in a cohort of children with suspected or known CD [35]. Ileocolonoscopy was used as the criterion standard for detecting terminal ileum involvement, as well as a consensus reference standard was used to determine active CD in the upper small bowel. Thirty-four consecutive patients were enrolled, 82% of patients with established CD and 18% of patients with suspected CD. Overall, the authors concluded that there was no statistically significant difference among the three tools for their performance in detecting active small bowel lesions. Moreover, considering singularly the three components of small bowel, SICUS demonstrated the best performance with a high NPV in the proximal and mid-ileum MRE, and CE have demonstrated more sensibility and NPV compared to SICUS. However, in the terminal ileum, SICUS and MRE showed higher sensitivity and accuracy than CE, even if their specificity was lower compared with previously published data [30].

Interestingly, the authors also evaluated the correlation between imaging results and biomarkers of inflammation, such as CRP, and found that the combination of SICUS with CRP significantly increased its specificity in detecting CD active lesions in the entire small bowel.

SICUS has also been proposed in the preoperative assessment of CD [36, 39]. Using surgical pathology as a gold standard, a prospective longitudinal study aimed to compare the sensitivity, specificity and accuracy of SICUS, and computed tomography enteroclysis (CTE) was

performed ≤3 months before surgery to assess the presence of small bowel lesions in 15 CD patients undergoing elective ileo-colonic resection [39]. There was no significant difference between the two techniques for detecting the presence of small bowel fistulae and abscesses, whereas SICUS showed a slightly higher accuracy for detecting the presence of dilation above the strictures.

More recently, a study comparing retrospectively SICUS and MRE with surgical findings in sixty-seven CD patients undergoing elective bowel surgery within 6 months was published [36]. Of these 67 patients, twenty-five performed both SICUS and MRE before surgery, whereas 25 and 17 underwent only SICUS or MRE, respectively. The results indicated high sensitivity of SICUS in detecting small bowel complications and a good correlation between SICUS and MRE in identifying stricturing disease, fistulae and mucosal thickening.

The use of SICUS has also been evaluated in the follow-up of CD patients after ileo-colonic resection [19, 40]. The recurrence of CD after a ileo-colonic resection is one of the most important issues in the management of IBD and frequently results in repeated surgical procedures. Endoscopy has proven to be the most sensitive method to detect post-surgical endoscopic recurrence. Rutgeerts et al. demonstrated in a prospective cohort study that the post-operative clinical course of CD is predicted by the severity of endoscopic lesions during the first year after resection [41]. Several authors had stressed the value of transabdominal ultrasonography, which demonstrated 77–81, 86–94, 83, 93–96, and 57–90% of sensitivity, specificity, accuracy, positive predictive and negative predictive values in diagnosing post-operative recurrence (POR), respectively [18, 42]. Power Doppler looks to be another useful prediction tool for CD patient with post-surgical recurrence [43]. Amongst the 40 CD patients, oral contrast-enhanced sonography diagnosed severe POR with high sensitivity (86%) and specificity (96%), considering a cutoff for bowel wall thickness (BWT) of 5 mm [42].

SICUS was as accurate as ileocolonoscopy for diagnosing POR, with a small trend towards false positives [44]. Although the sonographic criteria of POR, such as BWT, bowel dilatation and stricture, had a different definition in available trials, SICUS appeared to be accurate for detecting early POR lesions [40], differentiating mild from severe POR using BWT [45] and for assessing the length of diseased bowel. Furthermore, Calabrese et al. showed that BWT detected by SICUS was correlated with the Rutgeerts' score [19].

Mucosal healing is likely to become an important therapeutic target in CD, being associated with sustained clinical remission, and reduced rates of hospitalization and surgery [46–49]. Anti-tumour necrosis factor (TNF) α agents are effective in the treatment of Crohn's disease CD because they can induce clinical remission and mucosal healing in most patients. Nevertheless, CD is a transmural process and data on transmural healing induced by these molecules are still lacking [50–53]. A recent study has evaluated transmural healing, which is defined as normalization of bowel wall thickening, using bowel sonography in patients with CD treated with biologics and immunosuppressors and its correlation with clinical remission and mucosal healing [52]. The authors showed that transmural healing could be achieved in approximately 25% of CD patients treated with anti-TNFα and significantly correlated with mucosal healing.

More recently, an Italian group proposed a SICUS quantitative sonographic lesion index (SLIC) [32, 54] proved to be a useful tool in assessing and monitoring transmural bowel damage in CD patients treated with biologics. The SLIC index takes into account both the extent and severity of the small bowel damage, including stricturing and penetrating lesions as assessed by SICUS. Its features were expressed in terms of wall thickness, lesion length, lumen narrowing, dilation, and identified five classes of severity from the lower (class A) to the higher score (class E), with a score ranging from 0 to 200 [32]. In a small prospective study, these authors enrolled 29 ileal or ileocolonic CD patients treated with anti-TNF agents (10 infliximab, 35%; 19 adalimumab, 65%) [54]. At baseline, patients underwent ileocolonoscopy, SICUS, clinical and biochemical evaluations, assessed with CD activity index (CDAI) and CRP level, respectively. The assessment was repeated at the end of induction, except for endoscopy, and after 1 year of maintenance therapy. The study showed that there was a significant improvement of SLIC and SLIC subscores after induction with biologics. An improvement of the wall thickness score after 12 months of therapy with anti-TNFs was observed. Interestingly, differentiating between responders and non-responders, it was observed that the SLIC and SLIC subscores decreased only in the group of responders.

Moreover, similarly to previously recently published data [51], the authors did not observe a complete healing of the lesions and most of the patients had persistent signs of inflammation and lesions at SICUS, which had improved but were not resolved after biological therapy.

Even though all SICUS studies reported and demonstrated a higher diagnostic accuracy in the detection of CD lesions compared to conventional US, SICUS remains a technique with a low diffusion in the last years and a prerogative of very few centers. The long duration of exam and the inter-observer variability represent SICUS main limits.

CEUS

The use of high-frequency probes with a low-mechanical index and the introduction of second-generation US contrast agents have improved the US exam because it provides more information about perfusion of the bowel wall. The contrast agent is administered intravenously and excreted through the lungs without risk of nephrotoxicity or ionizing radiation as in the case of computed tomography contrast agent; it does not remain in the body longer than 15 min. It consists of microscopic bubbles of gas (size 3–5 lm), which are encapsulated in a shell of flexible and stiff phospholipids: they enhance the backscatter signal from blood cells, oscillating when exposed to a low-intensity US field and disrupting when exposed to a higher intensity, thereby demonstrating tissue perfusion in real-time "blood-pool" imaging. The "mechanical index" represents the force with which the US waves compress the microbubbles: a low-mechanical index reduces their destruction, enabling the evaluation in real time over several minutes. Advanced scanning programs are installed in US devices to increase the difference between the signal emitting from the microbubbles and the signal emitting from the tissues [55, 56]. SonoVue (SV, Bracco, Italy) is actually the second-generation US contrast agent used for CEUS, consisting of phospholipid-stabilized microbubbles filled with sulphur hexafluoride. The recommended dose of SonoVue is 2.4 mL. Every injection should be followed by a flush with 5 mL of 9 mg/mL (0.9%) sodium chloride solution. Approximately, 10–15 s after intravenous injection, the SonoVue arrives to the intestinal wall, thereby achieving the maximum concentration (peak intensity) after approximately 30 s. This stage is followed by a venous phase, and it is finally excreted by the lungs. No adverse event was reported with SonoVue use: the only contraindication is severe cardiomyopathy [57, 58].

Recently, a meta-analysis, published in March 2015, which included a total of 8 articles and 428 CD patients, analysed CEUS performance and accuracy in the detection of active CD, using endoscopic and clinical indices as the reference standard: the CEUS sensitivity and specificity for active CD were 93 and 87%, respectively, the diagnostic odds ratio was 80 and the area under the curve was 0.96 [59].

Several previous studies have shown that the CEUS qualitative evaluation is correlated with CD clinical activity. Robotti et al. examined a series of 52 CD patients with colour power Doppler, B-mode US and CEUS using intravenous injection of SonoVue, to evaluate intestinal wall vascularization as an index of disease activity. Next, they compared US findings with clinical and laboratory tests and follow-up, and found a significant correlation among the groups [60]. Similarly, using SonoVue at low-mechanical index, US assessment of vascularization in 48 patients affected by ileal CD was performed by Serra et al., demonstrating that the presence of ''abundant'' (as opposed to ''poor''—both subjectively defined) enhancement in the thickened terminal ileum identified active disease (CDAI > 150) with 81% sensitivity and 63% specificity ($p < 0.001$). The disease activity was significantly and inversely related to the pattern of enhancement (''abundant pattern 1 and 2'': 62.5 and 63.2%, respectively; ''poor pattern 3 and 4'': 23.5 and 0%, respectively; $p = 0.004$) [61]. In the same study, a quantitative method was introduced to assess vascularization of the bowel wall as a reflection of disease activity in ileal CD. The *E*/*W* ratio (which is the ratio between the major thickness of the enhanced layer, *E*, and the thickness of the entire wall section, *W*) showed a significant correlation with CDAI values ($p = 0.007$) and was significantly higher in active (CDAI > 150) compared to inactive CD patients (CDAI < 150) ($p = 0.024$) [61]. In Migaleddu's work, 47 CD patients with a CDAI > 150 or <150 were recruited. CEUS revealed 3 bowel wall perfusion patterns after SonoVue injection: submucosal enhancement and inward and outward transparietal enhancement. CEUS showed the highest performance, with 93.5% sensitivity, 93.7% specificity, and 93.6% overall accuracy. The linear correlation coefficient for CEUS versus CDAI was 0.74 ($p < 0.0001$) [21]. Moreover, CEUS could be useful to differentiate between fibrotic or inflamed stenosis in CD patients, although this question is controversial: according to some authors, increased echogenicity of the submucosal layer of the bowel wall results in inflammation [21], while others report a clear visibility of all intestinal layers, suggesting fibrosis [62].

The introduction of modern specific software integrated into US devices has improved the CEUS properties via a quantitative and semi-quantitative analysis of contrast enhancement, reducing the subjective evaluation. The softwares most commonly used are Qontrast (Bracco, Milan, Italy) and QLAB (Philips, Koninklijke, Belgium). Quantitative data of the contrast enhancement of the inflamed area are derived from a selected "region of interest", in which the intensity values of the pixels and the mean and median values of the image intensity are calculated, to enable the generation of a time-intensity curve. The following parameters were derived from the perfusion analysis: max intensity peak, time to peak velocity, wash out time, and intensity.

Qontrast software was created to design chromatic maps of the region of interest and to quantify the contrast enhancement with time-intensity curves and the above-mentioned parametric values. Girlich performed

several studies using Qontrast in search of a good correlation between CD inflammatory activity and quantitative assessment of bowel wall vascularization by CEUS [63, 64]. Their recent study revealed that a peak [%] ≥25 showed a close association of clinical activity Harvey–Bradshaw Index (HBI) and C-reactive protein. Moreover, they found a strong negative correlation between HBI and time to peak (s) ($r = -0.645$, $p < 0.01$) and, thus, the higher the clinical activity, the shorter the time-to-peak [65]. The same study found a strong correlation between the time to peak and single parameters of the histopathology scoring system [64]. A comparison using surgical histopathology analysis was performed by Ripolles and reported that transmural complications, colour Doppler grade and percentage of increase in contrast-enhanced were significantly associated with the pathology inflammatory scores ($p = 0.018$, $p = 0.036$, $p = 0.005$, respectively), as well as inflammation and fibrostenosis [66]. The difference between inflammatory and fibrotic lesions in CD patients is crucial for surgical or clinical treatment of the disease: in this regard, some studies have determined the feasibility of CEUS to obtain an absolute perfusion measurement in the gastrointestinal wall. In patients with fibrotic disease, blood volume and blood flow appear to be reduced [67]. Quaia et al. demonstrated that inflammatory versus fibrotic ileal strictures differed in the percentage of maximal enhancement (45 vs. 37%; $p < 0.05$) and area under the enhancement curve (1168 vs. 570; $p < 0.05$), whereas the difference in time to peak enhancement was not significant ($p > 0.05$) [68]. In addition, quantitative CEUS measurements of bowel enhancement correlated with the severity grade determined at endoscopy: mural contrast enhancement was markedly increased compared with enhancement in patients with inactive disease ($p < 0.001$); a threshold brightness value of a percentage of increase of 46% had a sensitivity and specificity of 96 and 73%, respectively, in the prediction of moderate or severe grade for endoscopic inflammation [69].

Indeed, immunomodulators and biological agents allow the achievement of therapeutic goals in CD patients. To evaluate the usefulness of CEUS in the assessment of mucosal healing in CD patients receiving immunosuppressants or biological drugs, Moreno et al. reported a good correlation between endoscopic remission and sonographic normalization in terms of bowel wall thickness, colour Doppler grade and percentage of increase of parietal enhancement after SonoVue injection ($p < 0.001$) [70]. Quaia et al. used Qontrast software to assess the value of small bowel wall vascularization after SonoVue injection to evaluate the efficacy of anti-inflammatory therapy in patients with ileal CD. The slope of the first ascending tract of the curve and the area under the enhancement curve were significantly lower after 6 months of treatment ($p < 0.05$) and correlated significantly with CDAI score ($p < 0.05$) [71]. Another study also showed that the area under the time-intensity curve obtained after microbubbles injection was the only parameter to discriminate between responders and non-responders among CD patients during pharmacological treatment ($p < 0.05$) [72]. Recently, it was demonstrated that CEUS showed high sensitivity, specificity and accuracy (97, 91, 96%, respectively) for the early detection of endoscopic recurrence after intestinal resection in CD patients, with the simple combination of parietal thickness >5 mm and contrast enhancement >46% [73].

Significant results were obtained using QLab software. Kratzer analysed 21 CD patients with a bowel wall thickness of at least 5 mm, using CEUS with QLab software. Quantitative parameters after SonoVue injection revealed a positive correlation with powerDoppler assessment of vascularization and with the length of the thickened bowel segment. De Franco et al. reported a series of 54 patients with terminal ileal CD to CEUS. Their results demonstrated a strong correlation between quantitative CEUS parameters and ileal CD activity. The ‘‘maximum peak intensity, MPI’’ and “coefficient of the wash-in slope, *b*” were significantly higher in patients with active disease ($p < 0.0001$). Both parameters also displayed a significant positive correlation with the C-reactive protein level, CDAI, and endoscopic score. Moreover, ROC analysis revealed that they were highly sensitive and specific for discriminating between active and inactive disease [74]. QLab software was also used in another study to evaluate US changes of bowel wall enhancement in ileal CD during biological treatment with infliximab, an anti-TNF agent [75]: a positive correlation was found between SonoVue enhancement of the affected bowel loop with C-reactive protein, alpha1-glycoprotein and white blood cell number; after infliximab treatment in 6/8 cases, a definite improvement was detected. As reported in Quaia’s study, analysis of time-intensity curves obtained after microbubbles contrast injection after 6 weeks of biological treatment with infliximab or adalimumab could be used to differentiate responders from non-responders among patients with clinically active CD [76].

Recently, it was demonstrated that quantitative CEUS parameters integrated into inflammatory assessments by established grey-scale US with colour Doppler imaging reduce indeterminate results and improve CD activity level determinations [77].

The introduction of dedicated US software for elastographic assessments would greatly improve the diagnostic potential of CEUS for assessing bowel wall fibrosis grade in patients with CD [78–81].

Conclusion

As explained in this review, abdominal ultrasonography performed with oral or intravenous contrast (SICUS or CEUS) is a useful method in the assessment of CD activity, and is non-invasive, non-ionizing, easily repeatable, well tolerated by patients and has significant diagnostic accuracy. SICUS is a technique useful to evaluate the presence, extension, and possible extramural complications of CD, although it is burdened by low diffusion, long execution time, inter-observer variability and poor quantitative assessment. Instead, great advantages can be achieved using CEUS. The introduction of specific software has improved this technique. The possibility to monitor response to therapies, describing and quantifying contrast enhancement behaviour by quantitative parameters, represents an interesting aspect of its use. Efforts should be made to standardize the results and to obtain quantitative measurements to avoid subjective evaluations.

Compliance with ethical standards

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Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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