CONVENTIONAL AND NEW ULTRASOUND TECHNIQUES IN INFLAMMATORY BOWEL DISEASE - UPDATE 2014-

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Transabdominal ultrasound (TUS) has widely been accepted as a clinically important first line tool in assessing patients with Crohn’s disease. The value of the method is irrespective of disease activity. TUS is useful in detecting Crohn’s disease (initial diagnosis) by evaluating bowel wall thickness and surrounding structures including periintestinal inflammatory reaction, extent and localization of involved bowel segments and detection of extraluminal complications such as fistula, abscesses, carcinoma and ileus. TUS also helps to guide therapeutic decisions and to monitor the disease course in individual patients. In this review the updated literature will be analysed.

ТРАДИЦИОННЫЕ И НОВЫЕ МЕТОДЫ УЛЬТРАЗВУКОВОГО ИССЛЕДОВАНИЯ В ДИАГНОСТИКЕ ВОСПАЛИТЕЛЬНЫХ ЗАБОЛЕВАНИЙ КИШЕЧНИКА

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У пациентов с болезнью Крона трансабдоминальное ультразвуковое исследование (УЗИ) органов брюшной полости широко используется в клинической практике в качестве метода диагностики первой линии. УЗИ органов брюшной полости незаменимо при первичной диагностике болезни Крона (первоначальный диагноз), однако данное исследование обосновано при любой стадии заболевания. Так, может быть произведена оценка толщины кишечной стенки и анализ состояния окружающих структур (включая перифокальное воспаление), диагностированы степень и локализация пораженных сегментов кишечника, а также осложнения (такие как свищ, абсцессы, опухоли и кишечная непроходимость). У пациентов данной группы УЗИ также помогает координировать тактику лечения и контролировать течение заболевания. В этом обзоре проведен анализ современной литературы по теме.

[Ключевые слова: ультразвуковое исследование - рекомендации - осложнения - кишечник – диагностика]

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INTRODUCTION

Apart from the assessment of solid abdominal organs, transabdominal ultrasound has been established for the evaluation of the gastrointestinal tract (GIT). Improvements of technology and increasing experience with sonographic findings in inflammatory bowel disease (IBD) have strengthened the role of ultrasound as a clinically important, non-invasive and widely available imaging modality [(1-6)]. In addition, Color Doppler Imaging (CDI), Tissue Harmonic Imaging (THI), contrast-enhanced ultrasound (CEUS) [(7-9)] and elastography [(10;11)] are additional useful tools.

A general advantage of high resolution ultrasound compared with endoscopy and other imaging modalities (e.g., computed tomography [CT] and magnetic resonance imaging [MRI]) is that it permits high resolution evaluation of the mural and transmural aspects of the inflammatory pathology [(12)]. This can provide an important contribution for diagnosis and monitoring disease activity which is especially true using CDI and CEUS [(13-28)]. Compared with other recently developed imaging technologies such as computed tomography and magnetic resonance imaging, its major advantage is the absence of radiation exposure and low costs [(29-31)]. On the other hand, important limitations are that the alimentary tract cannot be visualized over its entire length, many of the findings are nonspecific and obtaining and interpreting the images is operator dependent [(32)]. The presented paper is an updated review of the literature 2014 [(33;34)].

Ultrasound examination technique

Ultrasound of the alimentary tract requires high frequency (5 to 17 MHz), high resolution multifrequent linear or convex array transducers and clinical experience. Reliable diagnoses under emergency conditions, such as ileus (obstruction, incarcerated hernia or intussuseption), appendicitis or diverticulitis can be performed at any time [(35)].

The ileocecal region and the sigmoid colon can be identified by ultrasound imaging in most patients [(12;36-38)]. Landmarks in the ileocecal region are the right iliac artery and vein while landmarks in the sigmoid region are the left iliac artery and vein. The remaining colonic segments also can be evaluated adequately by continuous scanning in many patients. Only the rectum and distal parts of the colon cannot always be displayed by the transabdominal route. Perineal ultrasound has been useful in the evaluation of the perianal region and the distal rectum [(39)]. The technique has been summarized recently and indications and limitations have been pointed out [(33;34)]. EFSUMB offers examination technique videos which are free to download [(38;40)].

Intestinal wall thickness and sonomorphology

The bowel wall thickness has been measured under varying conditions reporting a wide range of normal values from 1 up to 5 mm [(37;41;42)]. Table 1 summarizes the results from published studies [(33)]. In contrast, measurements from our ultrasound unit differ from several studies as we have found lower diameters of all segments [Table 2] which has been confirmed in the literature [(42)]. Major reasons for this discrepancy may be different examination techniques, equipment and frequencies used, particularly the presence or absence of externally exerted compression during the examination by the operator [(43)]. In our experience the normal intestinal tract thickness in the terminal ileum, cecum and right and left colon is generally below 2 mm when examined with mild dose compression. It is important to mention that a contracted intestinal segment can be misinterpreted as a thickened wall and that on the other hand, an inflammed ileal/cecal wall structure may appear normal. In addition to wall thickness, its overall echotexture and appearance within surrounding structures should always be carefully considered when interpreting data, as determination of wall thickness alone may be clinically of very limited value [(43-46)]. High resolution transducers usually permit visualization of five (up to nine) layers within the colonic and stomach wall, visualization being grossly enhanced in the presence of intraluminal fluid. Although the sonographic appearance cannot be completely assessed in terms of the exact anatomic wall structures, it can reasonably be assumed that these echolayers approximately reflect the structures as described in Table 3 [(12;20;43;44;47-49)]. In addition, the small and large bowel usually can be distinguished by scanning the haustra of the colon and/or the circular folds of Kerckring in the small intestine [(33;43;50)].

Table 1. *Bowel wall thickness at different intestinal sites in healthy controls [mm] [(33)]*

Jejunum	Ileum	Colon	Frequency [MHz]	Author year [reference]
2.0	2.0	2.0-3.0	3.5; 5.0	Worlicek 1986 [(161)]
<2.0	<2.0	2.0-5.0	5.0	Abu-Yousef 987 [(162)]
<3.0	<3.0	<5.0	3.5; 5.0	Kedar 1994 [(163)]
<4.0	<4.0	<4.0	5.0	Bozkurt 1994 [(73)]
<4.0	<4.0	<4.0	3.5; 7.5	Maconi 1996 [(13)]
<5.0	<5.0	5.0	2.4-5.0	DiCandio 1986 [(70)]
<5.0	<5.0	<5.0	Na	Dubbins 1984 [(164)]
<5.0	<5.0	<5.0	3.5; 5.0	Sheridan 1993 [(72)]
<3.0	<3.0	2.0-3.5	Na	Odegaard 2012 [(42)]
0.9	1.1-1.2	1.0-1.2	8.0; 12.0	Nylund 2012 [(41)]
Na	1.1-1.3	1.1-1.3	7.0	Dialer 2003 [(165)]

Studies using methods other than transabdominal ultrasound are not included in this table. Those comprised trials using endoscopic ultrasound [(75;145;166-168)], hydrocolon ultrasound [(169)], in vitro measurements [(170)] or postmortem examination [(171)]; <: indicates values below this level are considered normal; na: not available

Table 2. *Determination of wall diameter at the ileum, ascending colon, hepatic flexure and sigmoid in healthy volunteers (N=31) [(33)]*

Localization	Wall Thickness [mm]
terminal ileum	1.1+/-0.1[a] [1.0-1.2][b]

ascending colon	1.1+/-0.1 [0.9-1.3]
right flexure	1.1+/-0.1 [0.9-1.3]
sigmoid	1.4+/-0.1 [1.2-1.8]

Meaurements were performed after having identified corresponding landmarks for each bowel segment (see text) using a high resolution transducer (5.0 MHz) in the RES mode.[a] mean +/- SE, [b] range; Data compiled from [(43)].

Table 3. *Sonomorphology and intestinal wall structures from the lumen to serosa [(33)]*

Layer echogenicity	Anatomic structure
Lumen echopoor (fluid), echorich	(air)
echo-rich entrance echo	inner (luminal) layer transition lumen/mucosa
echopoor mucosa	inner layer
echorich submucosa	layer
echopoor muscularis propria	outer layer
echorich exit echos	outer layer serosa/surropunding structures

Summary of guidelines

Recommendations for ultrasound of the gastrointestinal tract in IBD are based on national and international guidelines. The management of patients with IBD requires evaluation with objective tools, both at the time of diagnosis and throughout the course of the disease, to determine the location, extension, activity and severity of inflammatory lesions, as well as, the potential existence of complications. ECCO (European Crohn's and Colitis Organisation) and ESGAR (European Society of Gastrointestinal and Abdominal Radiology) jointly elaborated in 2013 a consensus to establish standards for imaging in IBD using radiologic procedures, including ultrasound for different clinical situations. They stated the need for studies in order to compare the diagnostic accuracy between different techniques, the value for therapeutic monitoring, and the prognostic implications of particular findings [(51)].

The European Crohn's and Colitis Organisation (ECCO) introduced the first guidelines on the diagnosis and management of ulcerative colitis in 2008 [(52)], and the second one was published in 2010 [(53)]. The new ECCO guidelines from 2012 stated that transabdominal ultrasound is helpful in monitoring disease activity and extent as well as treatment success (EL3, RGC)(ECCO statement 3L) [(54)]. They described abdominal ultrasound as a usefull tool for screening for small bowel or colonic inflammation, having a sensitivity of 80-90% and the advantages of low cost, accessibility, and non-invasivity, being easy to perform without prior preparation. Still, the limitations are the dependence of accuracy on the skill of the operator and the low specificity for differentiating UC from other causes of colonic inflammation [(55-59)]. There is initial data that ultrasound might help to predict the course of the disease [(60)].

In 2007, and updated in 2008, Nuernberg and coworkers have published an overview on the current status of ultrasound in gastroenterology, regarding bowel and upper gastrointestinal tract examination. They focussed on the current role of ultrasound in the detection and assessment of chronic inflammatory bowel diseases and concluded that ultrasound can give important additional information regarding the extent and activity of disease, complications (fistula, abscess, stenosis) and differential diagnosis. It also plays an important role in follow-up and is useful as a method to guide interventional therapies for abscesses [(45;46)].

Updated German S3-guidelines on the diagnosis and treatment of Crohn's disease have been published in 2010, and brought some changes regarding the radiologic approach. Comparison was made to the European and German guidelines in the context of recently published radiological literature [(61)].

Other German guidelines are Clinical Practice Guideline on Diagnosis and Treatment of Crohn's Disease Results of a German Evidence-based Consensus Conference, 2008 [(1)] and Updated German Guideline on Diagnosis and Treatment of Ulcerative Colitis, 2011 [(62)].

The first guidelines on the use of CEUS were introduced by The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) in 2004 and mainly focussed on liver applications [(63)]. The update published in 2008 described applications on other organs as well [(64;65)]. The new EFSUMB guidelines and recommendations from 2011 [(9)] include among others a thematic section on the gastrointestinal tract. The role of CEUS in the diagnosis of IBD has been described in detail, including considerations on the disease activity, distinguishing between fibrous and inflammatory strictures, abscesses, and fistula. Limitations as well as recommended uses and indications have also been stated. "Comments and Illustrations of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) Non-Liver Guidelines 2011" which focus more on established applications are published in the same supplement to Ultraschall in der Medizin (European Journal of Ultrasound) [(66)].

Crohn's Disease

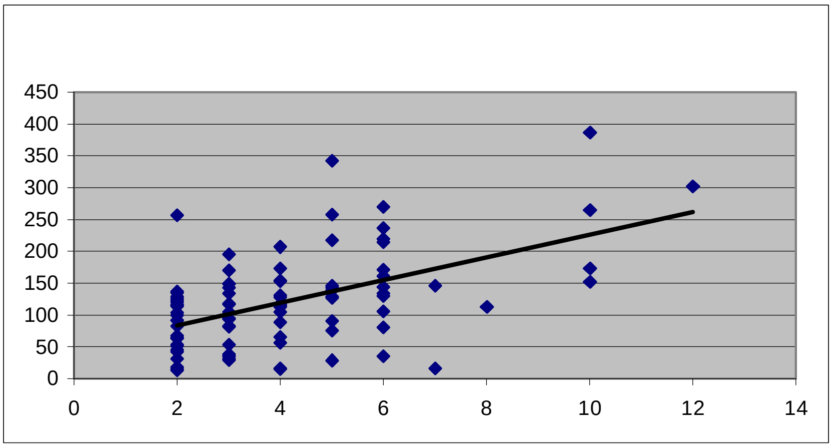
Transabdominal ultrasound is clinically useful in detecting Crohn's disease (initial diagosis) by evaluating bowel wall thickness and surrounding structures including periintestinal inflammatory reaction, extent and localization of involved bowel segments and detection of extraluminal complications such as fistula, abscesses, carcinoma and ileus [(33)]. In addition, several extraintestinal manifestation,s particularly mesenteric and perihepatic lymph node involvement as seen in primary sclerosing cholangitis, also can reliably be diagnosed [(67;68)].

Initial diagnosis by ultrasound

Sensitivity and specificity in detecting IBD were reported generally in the range from 70.0 to 94 percent and 67 to 97 percent, respectively [(69-76)]. When referring to Crohn's disease alone similar data were found as demonstrated by a series of additional studies comparing transabdominal ultrasound with other methods such as endoscopy and/or radiology [(58;77-87)]. In these trials the sensitivity ranged generally from 73.0 to 96.0 percent and the specificity from 90 to100 percent, respectively. The sensitivity, specificity, positive and negative predictive value in the detection of Crohn's disease have been summarized and the data are updated on a regular base [(88)]. It should be emphasized, however, that different values may be due to different reference methods (gold standard). Although positive and negative predictive values would be clinically more relevant as they take prevalence and incidence of disease into account [(89)], only a minority of studies have reported such values in the range from 79 to 100 percent and 57 to 95 percent, respectively [(33)].

Assessment of bowel wall thickness and disease activity

Assessment of bowel wall thickness and structures has been considered a particularly important issue. Attempts have been made to correlate wall thickness with disease activity, particularly measured by the Crohn's disease activity index (CDAI)[(20;37;43;48;71;90-92)]. Although an association of wall thickness and disease activity generally is assumed, detailed data including correlation coefficients (e.g. Spearman rank coefficient)(Rs) with corresponding significance levels have only rarely been reported. In a large series of patients (n=255) we have found that wall thickness is significantly higher compared to normal (4.9+/-2.7 mm versus <2.0 mm) and greater in active (CDAI >150) than in inactive disease (CDAI <150): 5.8+/-2.9 mm versus 4.3+/-2.2 (p<0.0001)) [(37)]. In addition, in a second trial including 100 consecutive patients we have found a weak, but significant correlation of wall thickness with the CDAI (R_s:0.44, p<0.00001) [Figure 1] [(33)].



CDAI

Figure 1. *Spearman Rank-Correlation of bowel wall thickness and CDAI in 92 patients with M. Crohn (R = 0.45; p < 0.00001) [(33)]*

Bowel wall thickness [mm]

In view of the conflicting results concerning a relationship between altered wall morphology such as a blurred aspect and/or transmural inflammatory reaction with disease activity [(20;43-45;47;48;71;90)] we have determined those characteristics and observed that a blurred wall layer morphology was significantly more frequent in active than in inactive disease (62.0 % versus 5.0 %, p<0.05) and that conversely, accentuated wall layers were more frequent in inactive than active disease [Table 4]. In contrast, transmural inflammatory reaction (definition see above) was present only in 8 percent of the patients. The differences between active and inactive disease was not significant [(33)]. However, this finding has to be further investigated with a greater number of patients in this category.

Table 4. *Sonomorphologic criteria and clinical actvity in patients with Crohn's Disease (n=100) [(33)]*

Criteria	Total (N)	CDAI<150	CDAI>150	Significance[a]
Wall Thickness				
Normal	33/100 (33 %)	26/71(37 %)	1/21 (5 %)[b]	P<0.05
pathologic (>2mm)	67/100 (67 %)	45/71 (63 %)	20/21 (95 %)	P<0.05
Mean	5.0+/-2.0 (3-12)[c]	4.0+/-1.0 (3-8)	6.0+/-3.0 (3-12)	P<0.05
Wall Layer				
Accentuated	49/100	41/71 (58 %)	7/21 (33 %)	P<0.05
Blurred	18/100	4/71 (5 %)	1§/21 (62 %)	P< 0.05
Transmural inflammation	8/100 (8 %)	4/8 (50 %)	3/8 (38 %)	P=0.1

[a] *comparison between CDAI >150 versus CDAI <150;*

[b] *the sum of the number of patients with CDAI <150 and CDAI <150 does not yield N=100 as eight patients with ileostoma were excluded from calculations, because the CDAI was not applicable*
[c] *mean +/- SD, range in brackets.*

Assessment of bowel wall involvement (length and extent) and disease activity
The evaluation of the length and extent of the involved bowel segments with possible relation to clinical disease activity may be an additional diagnostic goal of imaging methods. As Crohn's disease often comprises more than one bowel segment it may be important to estimate the overall length of the involved segments and to examine as many areas as possible. As this question has not been sufficiently addressed so far, we prospectively investigated 100 patients, of whom sixty-seven had a bowel wall thickness >2.0 mm at initial presentation. Thirty-nine showed uni-segmental and twenty-eight multi-segmental involvement. The majority of patients with unisegmental involvement (74.0 %) had quiescent disease (CDAI<150) and a mean length of involved bowel segments of 16.0+/-8.0 cm, the differences between patients with active and inactive disease, however, were not significant (p=0.8). In patients with multiple segment disease exact determination of the total length of involved segments was not possible, but sonographic and clinical features including disease activity were not different from those with unisegmental involvement [(33)].

Detection of complication
Besides morphologic evaluation of mural, transmural and adjacent structures ultrasound is able to detect complications such as fistulas (and the early stage of fistula, transmural inflammation), abscesses, carcinoma and ileus/subileus with a high sensitivity and specificity. Estimates of the sensitivity and specificity for detecting fistulas have ranged between 50 to 89 and 90 to 95 percent, respectively [(92)]. Estimates of the sensitivity and specificity for detecting abscesses have been reported in a higher range i.e. between 71 and 100 for the sensitivity and between 77 to 94 percent for the specificity [(82;93-96)]. Contrast enhanced ultrasound has been proven to be helpful in the delineation of abscess [(9;34;66;97-99)]. The risk of colorectal cancer in CD has been evaluated and summarized [(100)].

Ultrasound as screening procedure
A prospective study suggested that routine ultrasound in patients with Crohn's disease can reveal unexpected pathologic findings that have therapeutic implications [(37)]. The study included 255 patients with Crohn's disease who underwent regular ultrasound, irrespective of symptoms and disease activity. Patients with abnormal findings underwent further evaluation with additional radiologic and/or endoscopic imaging and treatment as needed. Of 17 patients with inactive disease, ultrasound revealed four with an interenteric fistula, seven with a mesenteric or perirectal fistula and six with transmural mesenteric inflammation without a fistula. Ultrasound of the remaining abdominal organs revealed pathologic findings with further diagnostic implications in 25 of 255 (10 percent) patients and with therapeutic implications in 4 percent [(37)]. In other series with 100 consecutive patients, we found 13 fistulas, seven of which were not previously known, a percentage very close to our previous findings [(37)]. The majority of the fistulas were again entero-enteric, one patient had an entero-vesical and another an entero-cutaneous fistula [Table 5]. In a third trial comprising 46 consecutive patients, nineteen cases with communicating fistulas were detected by ultrasound, 13 of which were entero-enteric with nine patients having a CDAI >150 (median 222), thus further supporting the view that fistula formation reflects a more active disease. Six of these had to be treated surgically, in seven immunosuppressive therapy was started. In this context the question arose whether the presence of a fistula per se is associated with greater bowel wall thickness and/or otherwise altered morphology. In this same series we found that the mean bowel wall thickness in patients with fistula formation was significantly greater than in those with no fistulas: 8.0+/-3.0 mm versus 4.3+/-1.2 mm (p<00002). Eight of 10 (80.0 %) patients with fistula showed a blurred wall structure compared to only nine of 54 without fistulas (17 %, p<0.0002). Signs of transmural inflammatory reaction were present in all patients with fistula formation. The median wall thickness in these patients was almost twofold higher than in those lacking these features (7.0+/-2.0 versus 4.0+/-1.0 mm, $p<3x10^{-8}$). In 42 percent mesenteric lymph nodes could be detected, however, no significant correlation to disease activity and/or sonographic/laboratory findings was found [(33)].

Table 5. *Sonographic detection of fistulas in patients with Crohn's Disease, data compiled from [(37)]*

Criteria	Total (N)	CDAI<150	CDAI>150	Significance[a]
Fistula	13/100 (13 %)	3/17 (4 %)	8/21 (38 %)[b]	P<0.05
Previuosly known	3/10 (30 %)	1/71 (1 %)	2/21 (5 %)	
Newly detected	7/10 (70 %)	5/71 (7 %)	2/21 (10 %)	
Entero-enteric	10/13 (77 %)	3/71 (4 %)	7/21 (33 %)	
Entro-vesical	1/13	0/71 (0 %)	0/21 (0 %)	

[a] *comparison between CDAI >150 versus CDAI <150*
[b] *the sum of the patients with CDAI <150 and CDAI <150 does not yield N=100, as eight patients with ileostoma were excluded from calculation, because the CDAI is not applicable.*

In the following figures symmetric bowel wall thickening [Figure 2], transmural inflammatory reaction [Figure 3] and fistula formation are shown.

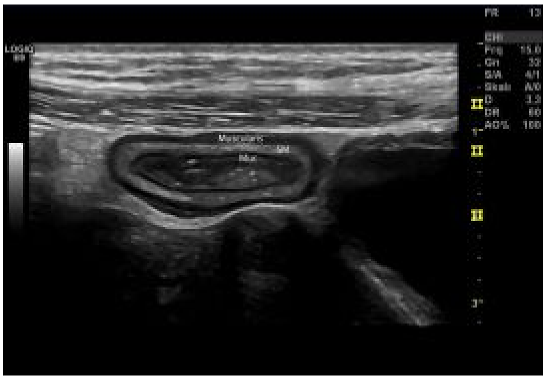


Figure 2. *Symmetric bowel wall thickening. Muc: Mucosa. SM: Submucosal layer. Muscularis: Muscle proper layer. The lumen is indicated as well*

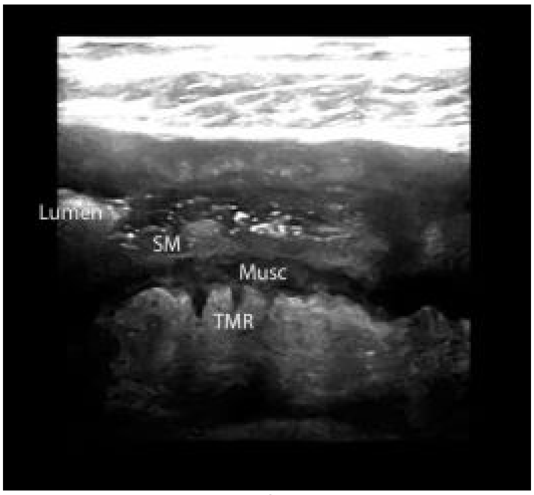


Figure 3. *Transmural inflammatory reaction (TMR). SM: Submucosal layer. Musc: Muscle proper layer. The lumen is indicated as well*

Figure 4. *Transmural inflammatory reaction (TMR) and fistula formation. The lumen is indicated as well*

Extraluminal findings

Transabdominal ultrasonographic examination of extraluminal phenomena such as free fluid collection and/or mesenteric lymph nodes also may reflect disease activity, but clinical data corroborating such a view are scanty. In the recent trial comprising 100 patients as mentioned above we have found free abdominal fluid in 13 percent of the patients, there was, however, no significant correlation with disease activity and/or laboratory parameters (p=0.236). Although lymph node enlargement is a common sonographic finding in Crohn’s disease [(37;67;68;101;102)], it appears that ultrasonographic assessment of lymph nodes with regard to clinical parameters particularly disease activity is only of limited value and the clinical implications remain to be further clarified. Very early manifestation of Crohn’s disease in children might be mesenterial lymphadenopathy with or without bowel wall thickening [(33)]. Other acute and chronic intestinal diaseses have to be excluded by appropriate stool and serological test.

In summary, transabdominal ultrasound presently is accepted as a clinically important first line tool in assessing patients with Crohn's disease. Irrespective of the clinical symptoms , transabdominal ultrasound can assess disease activity, extent and complications. It helps to guide therapeutic decisions [(33;37;67)].

Color Doppler imaging

Intestinal wall vascularity

As in a variety of inflammatory intestinal disease states, particularly in Crohn's disease, the vascularization is altered. This was conceived already more than a decade ago and exploited by qualitative assessment of perfusion and other flow parameters using special ultrasound techniques [(14-17;19;21;22;25;27;91;103-110)]. Although a number of authors have described the utility of colour Doppler imaging in gastrointestinal disorders such as Crohn's disease [(14;17;19;21;25;103;104)], celiac disease [(105)] and mesenteric artery stenosis [(106)], its exact role in diagnosis and/or monitoring disease activity remains to be further established. In a trial with twenty-two patients with confirmed Crohn's disease a high concordance between a power Doppler ultrasound score (measuring vascularization) and the degree of local inflammation assessed with an endoscopic severity score could be demonstrated with values from 0.83 to 0.98 [(22)]. A pilot study prospectively involving twenty patients could demonstrate a highly significant correlation between the mean blood vessel density assessed by power Doppler sonography and the semi-quantitative score tested by Limberg showing its potential applicability in routine clinical practice [(33;111)].

Intestinal wall vascularity combined with mesenteric inflow parameters

A newer promising approach is combining mesenteric inflow by Duplex scanning such as systolic and diastolic peak velocities and resistance index with end-organ vascularity by color Doppler imaging [(16;22;27)]. Recent advances including harmonic imaging, power Doppler and contrast enhanced ultrasound have been added to further improve sensitivity/accuracy with regard to different disease aspects and potential therapeutic decisions, but their definitive clinical role still has to be more precisely defined [(15;45;91;107-110;112;113)].

Mesenterial inflow and prognosis

Investigations by Ludwig et al. indicate that the pulsatility index measured postprandially as well as in the fasting state allows calculating the probality of a relapse in patients with active Crohn's disease. Positive and negative predictive values range between 0.77 and 0.89 [(25;114;115)]. Fifty-two patients were prospectively followed for one year. The major finding was that a decreased pulsatility index of the superior mesenteric artery was significantly associated with remission in Crohn's disease, but not in ulcerative colitis [(114)]. This has led the authors to the conclusion that repeated Doppler ultrasound measurements may predict response to immunosuppressive therapy. In view of other studies with discrepant findings [(116)], further research and experience in larger patient populations clearly is needed [(33)].

Contrast Enhanced Ultrasound (CEUS)

Newer techniques such as Power Doppler and the administration of echoenhancing agents (Levovist^{R} or SonoVue^{R}) have further improved sensitivity and accuracy [(15;91;108-110)]. Although 2D and Doppler techniques have been grossly improved over the last decade, the performance of these techniques still can be limited by a variety of factors such as tissue motion artifacts (peristalsis) and/or transmural vessel perfusion below the detection threshold [(110)]. To circumvent such limitations contrast harmonic imaging at a low mechanical index has been proposed [(18;23;117-123)], but its use in IBD presently is not yet widespread and confined to few specialized centers. Its introduction into clinical routine is depending on further developments and experience. Studies comparing new with more conventional approaches will help to clarify these issues. In a small pilot study including fifteen patients with ileal Crohn's disease contrast-enhanced power Doppler and conventional power Doppler were compared with regard to clinical disease activity and laboratory tests. Results were promising when bowel wall perfusion was evaluated at the site of maximum bowel wall thickness. As the major result contrast-enhanced ultrasound (CEUS) was found to be superior compared to conventional techniques with respect to those parameters [(117-120)]. In an other study one hundred four consecutive patients with Crohn's disease were prospectively examined using CEUS with respect to the disease activity index [(122)]. It was found that the pattern of contrast enhancement and the ratio of enhanced to entire wall thickness had a positive predictive value of 63.0 % and 58.6 %, respectively, in distinguishing active from inactive disease [(122)]. It was, therefore, proposed, that CEUS may be particularly able to more precisely characterize bowel wall thickness by differentiating fibrosis from edema and may, thus, grade inflammation by assessing presence and distribution of vascularity within the intestinal layers particularly the submucosa and/or the entire bowel wall including the supplying vessels [Figure 5] [(112)].

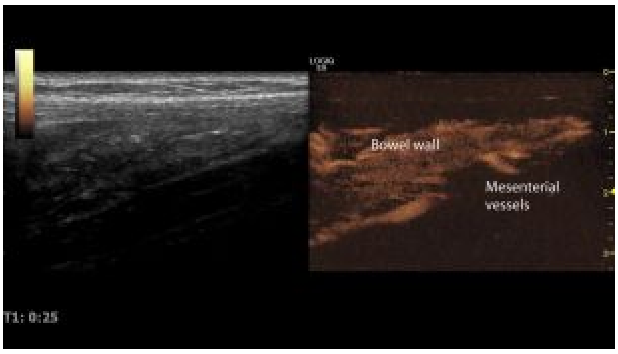


Figure 5. *Contrast enhanced ultrasound of the ileocecal region. The bowel wall and supplying mesenterial vessels are indicated [xx]*

Peri-intestinal inflammation also can be characterized in more detail [(112)], a view, however, which has to be confirmed in the up-coming future. Some authors postulate that CEUS can also provide prognostic data concerning relapse and/or response to therapy.
In a preliminary trial with twenty patients CEUS was suggested to be useful in the follow-up of infliximab treatment [(119)]. In addition, surgical issues recently have been focused using this technique particularly in helping the decision of conservative versus surgical treatment [(123;124)]. Although results are promising, much more work is needed before CEUS can be considered a clinically useful tool in such decisions [(122;125)].
Differential diagnosis of inflammatory and fibrotic bowel wall changes
In patients with Crohn's disease, the analysis of vascularity may facilitate the differentiation between inflammatory or cicatricial-fibroid stenosis but results are controversial discussed [(110;111)]. It has to be taken into account that cicatricial-fibroid stenoses are mostly in segments with wall thickening < 20 - 30 mm whereas inflammatory segments are > 30 mm which is more important for differential diagnosis of inflammatory and fibrotic bowel wall changes. Recently 200 consecutive patients with Crohns disease have been examined displaying hypervascularity in 180 patients with adequate visualization of the bowel wall [Siemens Elegra advanced, 7 MHz] [(112)]. In 15 patients hypervascularity could not be displayed due to reduced sensitivity in patients with a body mass index > 30 (n = 14), depth penetration > 40 mm (n = 14) and therefore, inadequate visualisation and insensitivity of the methods. In three patients the thickened bowel wall segment was <20 mm and hypovascularity was observed indicating cicatricial-fibroid stenosis. In the remaining two patients hypovascularity was found. It was concluded that patients with Crohns disease and thickened bowel wall with a segmental length of more than 30 mm hypervascularity can virtually always be displayed. Lack of hypervascularity might be due to insensitivity of the equipment, inadequate chosen Doppler parameters, and depth penetration > 40 mm with loss of sensitivity. In certain cases contrast enhanced sonography with a 2 – 5 MHz transducers can be helpful because there is less depth dependency as in Doppler techniques. Analysis of time intensity curves using contrast enhanced techniques might be more promising than colour Doppler imaging alone [(33;112)].
Elastography
Elastography has been described recently in patients with IBD [(126-128)] but studies so far lacking.
Strain imaging techniques (“elastography”) are new tissue-characterising sonographic techniques, which allow noninvasive imaging of the mechanical characteristics of tissues. Elastography, generally speaking, is therefore the study of tissue stiffness and orients the diagnosis towards different pathological entities, based on the elastographic values. Inflammation and neoplastic infiltration lead to changes in normal tissue structure causing hardening of the tissue and alteration of its elasticity [(129)].
Since very early on, when the first animal test results have been published [(130)], areas of applications of elastography in medical diagnostics and treatment monitoring are steadily expanding. Published data in recent years indicate that shear elasticity modulus of tissues is one of their most wide ranging physical parameter, being also highly sensitive to tissue structural changes accompanying physiological and pathological processes. Most of the new applications are still in the early stages of research, but a few are becoming common applications in clinical practice [(131)].
Therefore, in 2011 the European Federation for Ultrasound in Medicine and Biology (EFSUMB) developed a set of recommendations for the use of elastography, given the growing general interest, number of available techniques and level of scientific evidence in this field. First EFSUMB Guidelines and Recommendations on the Clinical Use of Ultrasound Elastography have been published in 2013, including clinical applications on the gastrointestinal tract, also regarding the wall pathology as well as the motility. Practical points, limitations and recommended uses and settings have been stated [(10;11)]. The stiffness of the gastrointestinal wall and of separate wall layers can be evaluated by compressing the tissue with the transducer. This is indicated for characterising bowel wall lesions and possibly discerning the active phase of inflammation from fibrotic stenosis using strain elastography. For gastrointestinal purposes, the intraluminal pressure may be used as the excitation force [(132)]. A special method, Strain Rate Imaging (SRI), which shows the sign of the strain, is used to assess contractility of the gastrointestinal walls thus being usefull for evaluation of gastric contractility and gastrointestinal wall strain [(11;133)]. A major

challenge when diagnosing lesions in the gastrointestinal wall, as in many other organs, is to distinguish between malignancy and benign conditions, such as adenomas, myomas, ulcers or inflammatory changes [(42)].
In Crohn's disease the main issue is to evaluate whether a stenosis is caused by inflammation or fibrosis, since the latter requires surgical intervention while an inflammatory stricture requires medical treatment. Strain elastography has been tested in this setting and helps the distinction between these two conditions, since fibrotic stenoses appear stiff and inflammatory stenoses soft [(134)]. Furthermore, patients with active Crohn's disease have a higher strain ratio between the inflamed and normal regions than patients in remission [(135)] and than patients with active ulcerative colitis. In general, acute inflammatory lesions are softer and chronic lesions harder [(136)].
Most studies of the gastrointestinal tract have used the endoscopic approach, as the percutaneous access can be limited. Gilja et al. focuses on possible indications for elastography in evaluating intestinal diseases. Acute and chronic inflammation, which is of importance when it comes to a therapeutic strategy, might be differentiated by analyzing the stiffness of the bowel wall. [(137)]. In a study on inflammatory bowel disease, the findings on elastography were significantly correlated with the endoscopic findings [(138)].
In a study conducted by Havre and published online in 2012, sonoelastography with strain ratio measurements and visual evaluation of strain differences could not differentiate stenotic Crohn's lesions (fibrosis in chronic inflammation) from adenocarcinomas in resected bowel specimens. Still increased tissue hardness was vizualised in both Crohn's lesions and adenocarcinomas, without significant differences in strain assessment on the basis of inflammation grade in Crohn's lesions and by tumor stage or grade in adenocarcinomas [(139)]. Studies in vivo are needed in order to assess the utility of the method.
Assessment of the relative strain of the muscle layers of the gastric wall has been proved to be feasible and allows detailed mapping of strain distribution [(133;140)]. Given these results, further studies on other locations of the gastrointestinal tract are expected.
Endoscopic ultrasound (EUS) elastography has also been suggested as a method for the in vivo characterisation of gastrointestinal wall layers (especially in the anorectum) [(128)].
So far, elastography has not been evaluated in respect of fistula and abscess diagnosis. Any available descriptions are related to the acuity and chronicity of these changes, for example in chronic inflammatory bowel disease or spontaneous fistula [(136)].
The combination of elastography with other techniques such as contrast-enhanced ultrasound, fusion imaging or 3D elastography examinations might also be feasible [(137)] and give additional value.
Ultrasound elastography is a promising clinical method, but increased strain may be observed in malignant and benign lesions and further studies on strain data of different lesions, as well as regarding the role of strain imaging in the evaluation of gastrointestinal tract motility in vivo are required.

Endorectal ultrasound (ERUS), perianal ultrasound

Perianal (transcutaneous) ultrasound [(39;99;141;142)], endorectal ultrasound and other techniques are of utmost importance but not part of the review.

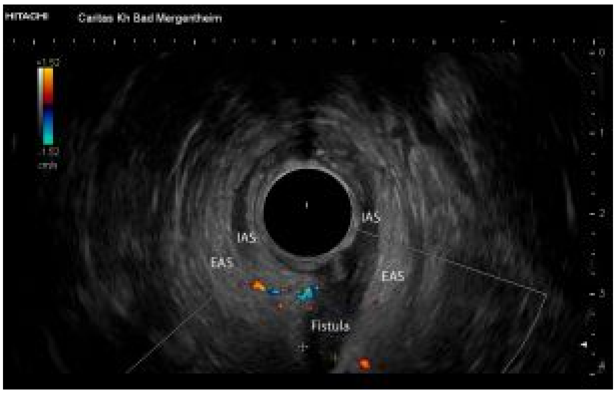


Figure 6. *Endorectal ultrasound [(143-145)]. Transsphincteric fistula with a larger proportion of the intersphincteric course of the fistula. EAS: external anal sphincter. IAS: internal anal sphincter*

Ulcerative colitis (UC)

The diagnosis of ulcerative colitis is usually based on the patient's history, the typical endoscopic appearance of the mucosa and histology after exclusion of infectious agents by microscopic examination and stool cultures [(5;62)]. As the decision for treatment options is partly based on the extent of the disease, it is useful to document the extent of inflammation at the initial presentation, This can be accomplished by combining flexible sigmoidoscopy and ultrasound, when complete colonoscopy is not possible and/or contraindicated. Early sonographic signs of active ulcerative colitis may include a thickened hypoechoic layer, reflecting endoscopic findings of congestion of the swollen mucosa with petechiae, exudates and friability. More severe cases may be associated with transmural bowel wall thickening and patients with fulminant disease may reveal also transmural inflammation similar to Crohn's disease [(58;71;81)]. However it should be mentioned that all these sonographic findings are not specific and may be seen also in a number of other colonic disorders due to infectious agents and/or drugs [(43;146;147)]. As a

consequence the value of transabdominal ultrasound in ulcerative colitis is less well established than in Crohn's disease but recommended as well [(33)]. The authors have contributed to the German guidelines [(62)].
In order to address the role of ultrasound in ulcerative colitis in more detail we evaluated in a series of thirty-six consecutive patients sonomorphologic characteristics including wall thickness, symmetry of thickness, thickened mucosa/submucosa, transmural reaction and extraluminal signs (>2 lymph nodes) in a similar fashion as in Crohn's disease [(37)]. Disease activity was assessed by the Ulcerative Colitis Index (CAI), a numerical index indicating active disease when >4 points and inactive disease <4 points. Taken together there were no significant correlations/associations between any of these sonographic features and the clinical disease activity and/or laboratory parameters [Table 6]. Based on the data from the literature [(58;71;81)] and these findings we consider the role of transabdominal ultrasound in ulcerative colitis less important than in Crohn's disease, but helpful in evaluating the extent of the disease for treatment decisions.

Table 6. *Sonomorphologic criteria and clinical activity in patients with ulcerative colitis (n=36) [(33)]*

	Total	CAI>4	CAI>4	Significance
Number	36	11	22	
Wall Thickening	27/36 (75.0 %)	11/11 (100.0 %)	16/22 (73.0 %)	n.s.
Wall Thickness [mm])	4.5+/-1.3 (3.0-8.0)	4.6+/-1.2 (3.0-7-0)	4.4+/-1.3 (3.0-8.0)	n.s.
Symmetric thickening	27/33 (82.0 %)	11/12 (92.0 %)	16/22 (73.0 %)	n.s.
Accentuated mucosa	3/33 (9.0 %)	1/11 (9.0 %)	2/22 (9.0 %)	n.s
Thickened mucosa/submucosa	21/33 (64.0 %)	9/11 (82.0 %)	12/22 (55.0 %)	n.s.
Transmural reaction	3/33 (9.0 %)	1/11 (9.0 %)	2/22 (9.0 %)	n.s.
Pancolitis	17/33 (52.0 %)	9/11 (82.0 %)	8/22 (36.0 %)	n.s.
Left-sided colitis	16/33 (48.0 %)	2/11 (18.0 %)	14/22 (64.0 %)	n.s.
>2 mesenteric lymph nodes	4/36 (11.0 %)	2/11 (18.0 %)	2/22 (9.0 %)	n.s.

n.s. not significant. CAI: Ulcerative Colitis Actvity Index, for details see text. Wall thickness, symmetric thickening, accentuated mucosa, thickened mucosa/submucosa, transmural reaction and lymph nodes were assessed in the same manner as in Crohn's disease.

Ultrasound versus other techniques in IBD

Despite the impact of transabdominal ultrasound in helping managing patients with IBD, particularly Crohn's disease, sonography has to compete with other modalities, primarily magnetic resonance imaging [(32)]. A series of studies has compared MRI and computed tomography (CT) with sonography or other modalities in patients with Crohn's disease with particular emphasis on luminal and extraluminal complications such as fistulas and abscesses [(24;26;69;148-157)]. As CT is associated with considerable radiation exposure, particularly when repeated examinations are necessary, this technique is less desirable especially in young individuals. A recent metaanalysis comparing ultrasound, MRI, CT, scintigraphy and positron emission tomography (PET) with respect to sensitivity and specificity found no significant differences in diagnostic accuracy among these techniques, but stated that non-ionizing modalities are preferable [(157)]. Attempts to quantify gut wall inflammation have been made using administration of paramagnetic contrast media with a high sensitivity and specificity with regard to the involved segments [(24)], direct comparison with contrast-enhanced ultrasound techniques, however, have not yet been undertaken [(9)]. As a result the present state of the knowledge in comparing ultrasound with MRI suggests that each method has its advantages and disadvantages and that a major factor also may be the corresponding local expertise with one technique or the other. Whereas in evaluating intestinal pathologies ultrasound seems to be preferable, particularly under the aspect of low costs and repeatability, MRI may be preferred in cases with extraintestinal involvement particularly those not directly accessible to transabdominal ultrasound such as the lower pelvic regions [(151)] and/or bone involvement [(152)]. Disadvantages of MRI are its susceptibility to air and motion artefacts, extended examination time and high costs. The major drawback of ultrasound is its high operator dependence [(33)].
Interventional ultrasound techniques have been recently summarized [(158-160)].

Conclusion

Transabdominal ultrasonography is useful for the detection of inflammatory bowel disease (initial diagnosis) by evaluating bowel wall thickness and surrounding structures including periintestinal inflammatory reaction, extent and localization of involved bowel segments. The detection of extraluminal complications such as fistula, abscesses, carcinoma and ileus is also possible. TUS helps to guide therapeutic decisions and to better characterize the disease course in individual patients which has been proven in the literature. In ulcerative colitis, the sonographically assessed extent of disease can also guide therapy decisions.

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