

Introduction

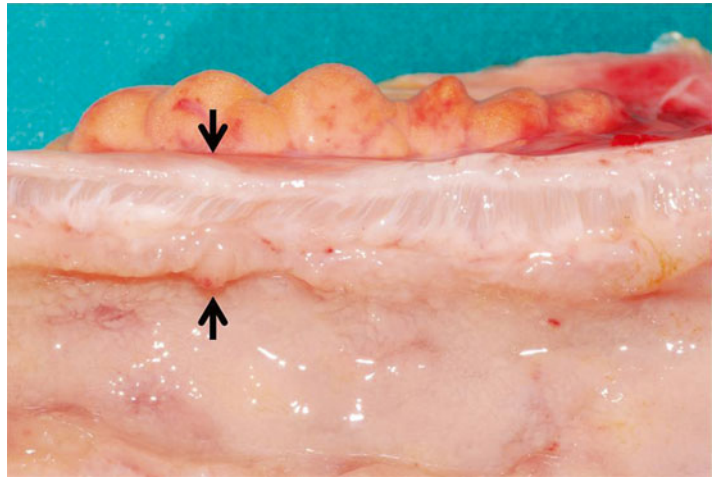
The inflammatory bowel diseases (IBD) include primarily Crohn's disease (CD) and ulcerative colitis (UC). In the diagnostic work-up of patients with IBD, the early and accurate assessment of site, extension, activity and severity of intestinal lesions as well as of possible complications—at the time of diagnosis and throughout the course of the disease—is mandatory in order to plan the appropriate treatment and for prognostic implications. The diagnosis of IBD relies on a combination of clinical symptoms and endoscopic, histological, radiological, and/or biochemical investigations [1]. UC involves the mucosa continuously from the rectum proximally, and colonoscopy with biopsy is the reference standard for assessment of disease extent, activity, and severity. Unlike UC, CD may affect any part of the gastrointestinal (GI) tract and causes, typically, transmural inflammation that in turn determines a profound alteration of the

multilayered structure of the intestinal wall due, to some extent, to an increased presence of collagen in the muscular layer (Fig. 2.1). Whereas in the suspicion of IBD, ileo-colonoscopy with biopsies from the terminal ileum and from each colonic segment, is a well-established and currently performed diagnostic step in the assessment of lower GI tract, the assessment of small bowel (SB) has been for many years a challenge for clinicians due to its anatomy, location and inaccessibility to routine endoscopy. Although in CD any part of the gastrointestinal tract may be affected, involvement of the ileum is the most prevalent and the disease is limited to the small bowel in about 40 % of the patients [2, 3]. Moreover patients with ileal disease are more likely to develop intestinal complications such as strictures and fistulas [4, 5]. Therefore, assessment of the small bowel is mandatory in the evaluation of patients with suspected CD in differentiating CD from other enteropathies as well as in the follow-up of patients with proven CD. Fluoroscopic barium studies—i.e., SB follow-through (SBFT) and SB enteroclysis (SBE)—have been for many years the cornerstone for the diagnosis of CD of the small bowel [6–8]. Recently evidence-based guidelines available through the American College of Radiology (ACR) recommend CTE as a first-line test for adult patients with suspected Crohn's disease and CTE is considered acceptable also in the pediatric population [9]. SBFT is usually considered suboptimal even if less expensive and more avail-

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Fig. 2.1 Surgical section of small bowel from a patient with Crohn's disease. The wall (arrows) is significantly thickened especially at the level of *muscularis propria*. By courtesy of Prof. Chiara Montesani and Anna Maria Pronio, University of Rome "Sapienza", Italy



able. However, due to the radiation exposure and the infrequency of small bowel pathology, radiology, either CTE or SBFT, is not recommended as a screening investigation without significant clinical suspicion of intestinal disease. Notably, radiology should be avoided in CD patients who require repetitive follow-up assessments in the setting of a chronic disease that often progresses with complications. As such, it has been shown that CD patients, including children, receive a mean of 8.1 mSv of diagnostic radiation *per* year of follow-up and in those with complications cumulative effective dose (CED) is even higher, reaching up to 75 mSv [10–13].

Therefore, recent interest has focused on implementing radiation-free, cross-sectional techniques, primarily ultrasound (US) and magnetic resonance (MRI). US and MRI, like CTE, and unlike traditional barium studies and endoscopy, assess the entire intestinal wall, can evaluate mucosal as well as transmural alterations, and allow a complete and accurate staging of the bowel, abdomen and perineum with the unique advantage to assess mural and extramural disease.

In this chapter we will target the applications and limitations of bowel US in IBD, focusing on the usefulness of bowel US in the early detection and follow-up of Crohn's disease, affecting mostly the small bowel. Endoscopy continues to be the reference standard to evaluate the upper and lower GI tract.

Bowel Ultrasound in Ulcerative Colitis and Crohn's Disease

Due to noninvasiveness, low cost, radiation-free and widespread availability, transabdominal ultrasound (TUS) is a very useful modality for IBD imaging [14–16], while disadvantages include operator dependency and difficulty to thoroughly visualize the entire GI tract, since the lumen is virtual and it may contain gas, a condition that hinders sonographic reflection [16, 17]. Over the past few years, technological development, including high frequency transducers (typically 7–12 MHz), harmonic imaging combined with the use of oral (small intestine contrast ultrasonography, SICUS) [18–20], and intravenous contrast agents (CE-US), have improved performance of ultrasound in the assessment of the gastrointestinal tract [21, 22].

The detection of bowel diseases relies on the assessment of intestinal wall and lumen, on the detection of enlarged mesenteric nodes, and/or of fluid in the peritoneal cavity.

At ultrasound the normal bowel wall is characterized by the presence of five concentric layers alternately hyperechoic and hypoechoic (Fig. 2.2). *Normal stratification* of the bowel wall is defined by the presence of the five layers, while *loss of stratification* is defined by the lack of one or more layers [16]. The normal bowel wall

Fig. 2.2 Small Intestinal Contrast Ultrasonography (SICUS) image of two adjacent jejunal loops after oral administration of the anechoic contrast solution. The five layers of the wall are recognizable (*white lines*) starting lumenally: (1) a thin echogenic layer, (2) hypoechoic layer, (3) hyperechoic layer, (4) hypoechoic layer, and (5) a hyperechoic layer

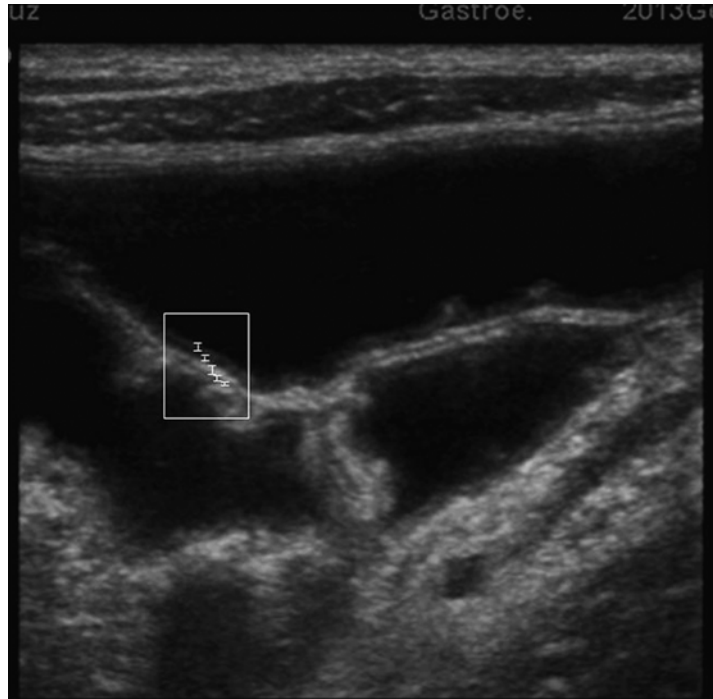
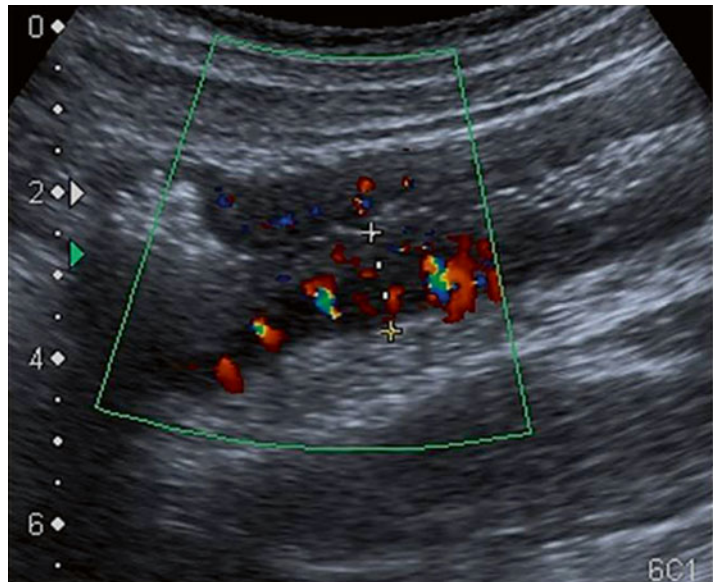


Fig. 2.3 Color Doppler examination of the descending colon in active CD. Mural thickening, loss of stratification of the bowel wall, and increased vascularity on color Doppler denoting inflammatory hyperemia. *By courtesy of Fortunata Civitelli, MD Department of Pediatrics, Pediatric Gastroenterology and Liver Unit, Sapienza University of Rome*



thickness has been reported to be $<3\text{--}4$ mm and $<1.5\text{--}3$ mm in the terminal ileum, and ≤ 5 mm and <2 mm in the colon, in adults and in children, respectively. The assessment of bowel vascularisation by color Doppler provides additional

information, particularly on disease activity (Fig. 2.3). The vascularity of bowel wall can be assessed according to the intensity of color signals or by the analysis of Doppler curves from vessels within the bowel wall [23].

Crohn's Disease

Bowel TUS has become the first-line imaging procedure in the diagnostic work-up of patients with suspected Crohn's disease [1, 24] and in the follow-up of patients with known CD. In CD the intestinal wall is often macroscopically greatly thickened (Fig. 2.1). In addition, the transmural inflammation progresses deeply into the serosa

and outside, potentially producing fissures and fistulae (Fig. 2.4), which may reach adjacent loops, organs, and skin or end blindly in the mesentery or resulting, at times, in intra-abdominal or retroperitoneal abscesses. The mesentery surrounding diseased loops is often thickened and fatty (Fig. 2.1 and Fig. 2.2) and may contain enlarged lymph nodes (Fig. 2.5). The diagnosis of CD with ultrasound relies on the assessment

Fig. 2.4 Surgical section of small bowel from a patient with Crohn's disease. The lumen is narrowed and the forceps show a fistula arising from the lumen through the thickened wall. *By courtesy of Prof. Chiara Montesani and Anna Maria Pronio, University of Rome "Sapienza", Italy*

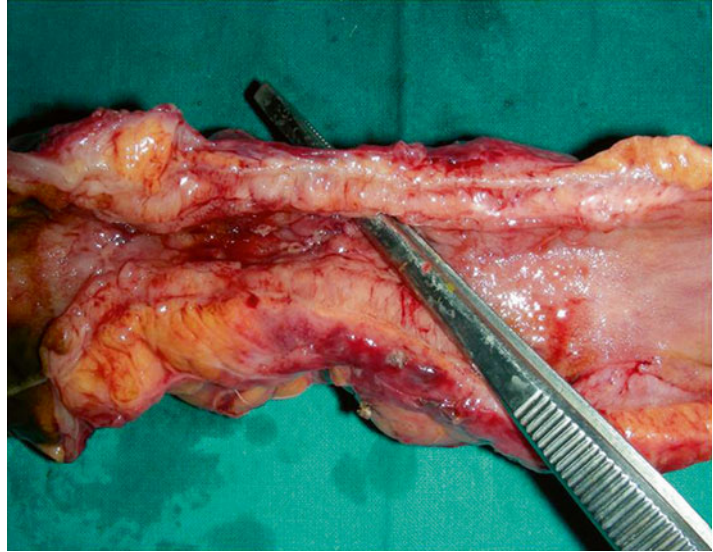
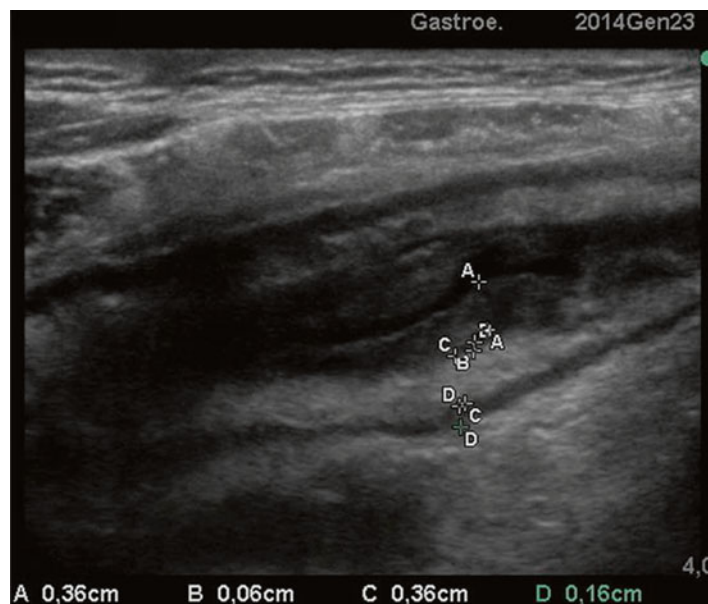


Fig. 2.5 SICUS. Thickened hyperechoic mesentery with enlarged mesenteric node (A). The intestinal lumen is distending by anechoic contrast



Fig. 2.6 CD of small bowel at SICUS: thickened small bowel wall characterized by a stratified echopattern with thickening of mucosa (A-A) and submucosa (C-C)

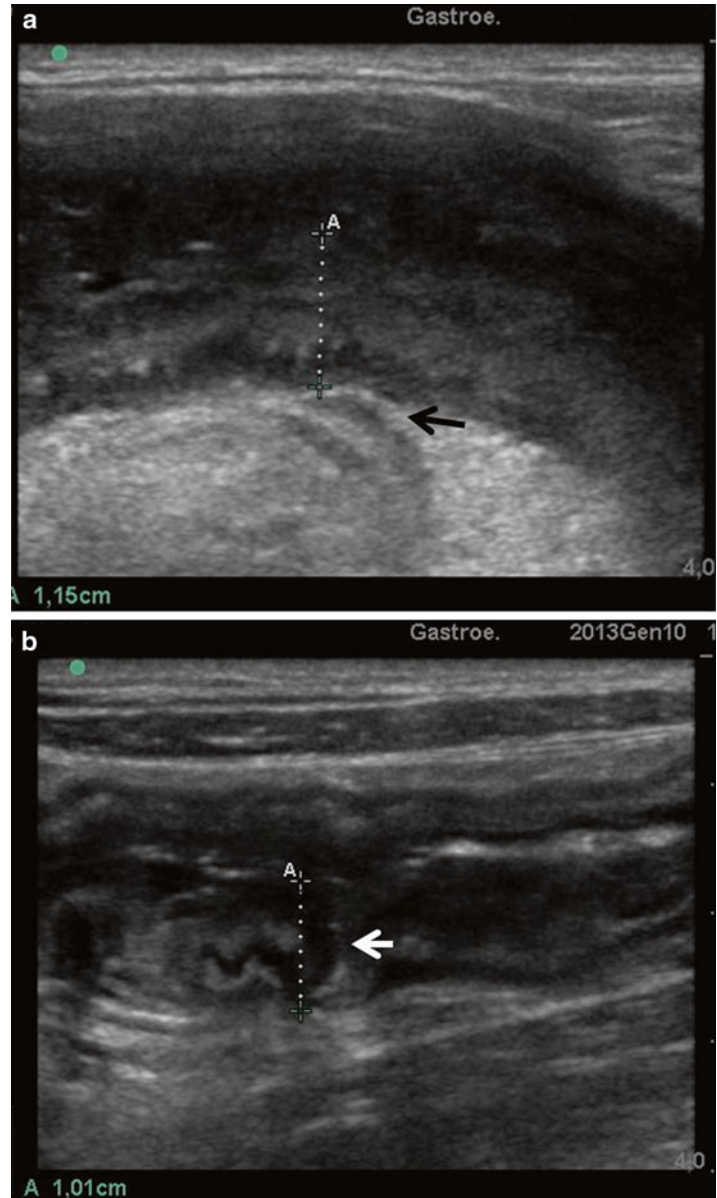


of those pathological features that may be essentially differentiated in *mural* and *extramural* features [16]. At ultrasound the *pathological mural alterations* appear as: (1) increased thickness of intestinal wall (Fig. 2.6), (2) variation of transmural echopattern (Fig. 2.7a), (3) interruption or loss of echo-stratification (Fig. 2.7b), (4) presence of variable enlargement of the different five layers, (5) increased Color-Doppler signal (Fig. 2.3), and (6) loss or reduction of peristalsis in the small bowel and of *haustra coli* in the colon. In *early CD* the wall stratification is usually preserved, the submucosa is thickened and appears as a hyperechoic band (Fig. 2.6), while in severe disease the stratification may disappear (Fig. 2.7a, b). In *longstanding disease* fibrosis results in thickened bowel wall, which is hypoechoic with loss of normal stratification; moreover fibrofatty proliferation of the mesentery tends to isolate pathologically stiff loops. At ultrasound the pathological *extra-mural changes* are assessed by the presence of: (1) fatty hypertrophy of the surrounding mesentery (Fig. 2.8), (2) enlarged lymph nodes (Fig. 2.5), (3) abscesses (Fig. 2.9), (4) fistulas (Fig. 2.10).

Bowel Ultrasound in the Early Assessment of Patients with the Suspicion of Crohn's Disease

Abnormal *bowel wall thickness* (BWT) is the most important TUS sign of CD and in unselected groups of patients, based on BWT values, sensitivities of 75–94 % with specificities of 67–100 % have been reported [15, 25, 26]. The wide variability of sensitivity and specificity values across studies reflects differences in the study design, size, and characteristics of the study samples and in the different reference standard value as threshold for a positive diagnosis. These methodological issues were evaluated in a meta-analysis [27] that, starting from 44 full-text studies, recognized only 7 prospective and appropriately designed studies (5 case control and 2 cohort studies). The results of this analysis showed that when more than 3 mm cut-off level was applied for abnormality in wall thickness, the sensitivity and specificity of TUS in the diagnosis of CD were 88 % and 93 %, while when a cut-off level of more than 4 mm was used, sensitivity was 75 % and specificity 97 %. The role of US to

Fig. 2.7 CD of small bowel at SICUS. **(a)** The wall is thickened with loss of multilayered stratification with a hypoechoic peri-intestinal lesion (arrow) arising from the thickened intestinal wall through a wrapping mesentery. **(b)** The wall is thickened (A) with loss of multilayered stratification with a hypoechoic lesion (arrow) penetrating the thickened intestinal wall



assess CD has been most extensively investigated for small bowel CD and the highest reported level of diagnostic sensitivity of TUS was achieved in investigations performed in populations mainly affected by known CD located in the terminal ileum [24]. This study, however, lacks a control group and was carried out by qualified investigators with specific expertise in tertiary referral centers. Several studies evaluated the accuracy of TUS in localizing Crohn's disease lesions and

most of them agreed in reporting the highest sensitivity (approximately 90 %) of TUS in detecting CD located in the terminal ileum and the lowest accuracy for those located in the upper small bowel and in the rectum [17, 28]. Few studies have evaluated the diagnostic accuracy of TUS as a screening technique for yet undiagnosed small bowel pathology [17], and most report unsatisfactory sensitivity (74–85 %). The main limit of bowel TUS is its inability to visualize the

Fig. 2.8 SICUS appearance of mesenteric fat hypertrophy (*arrow-head*), and of entero-mesenteric fistula (*arrows*)

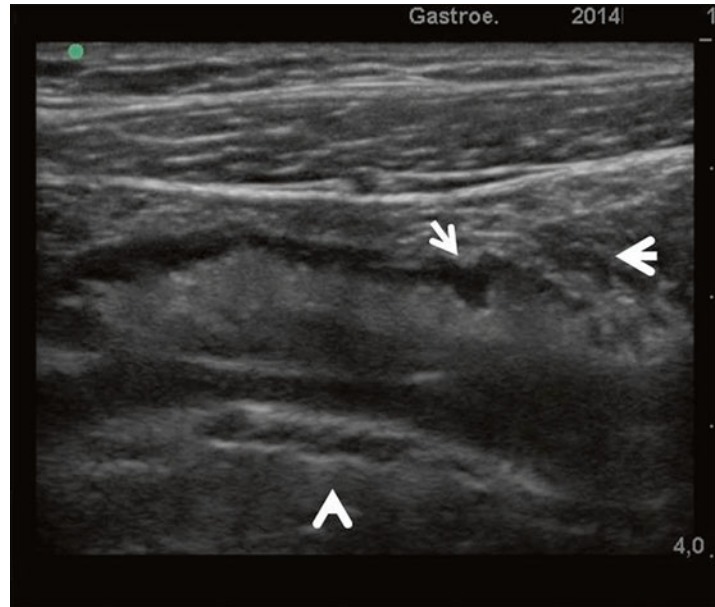
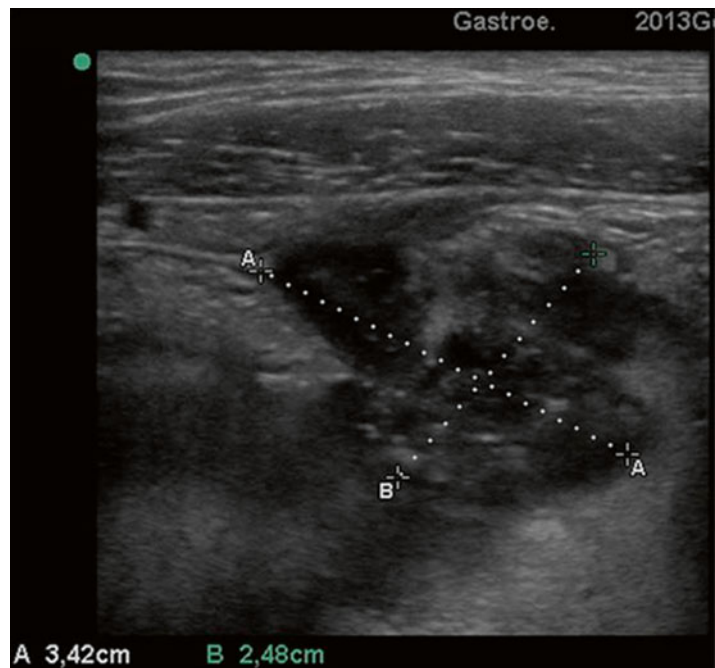


Fig. 2.9 Transverse US section (3.5 MHz probe) at level of the lower abdominal right quadrant. A round-shaped hypoechoic image of 3.4 cm (see calipers) is shown



entire gut that has a virtual lumen and may contain gas making the intestinal wall barely visible. However, the difficulty in visualizing bowel wall is overcome by distending the intestinal lumen with anechoic fluid. After the ingestion of small amounts (250–375 mL) of polyethylene glycol

3,350–4,000 (macrogol) solution [17, 18], the entire small bowel from the duodenal-jejunal angle to ileocecal valve can be visualized with the Small Intestine Contrast US (SICUS). SICUS undertaken in healthy controls in vivo and independent of the volume of oral contrast used,

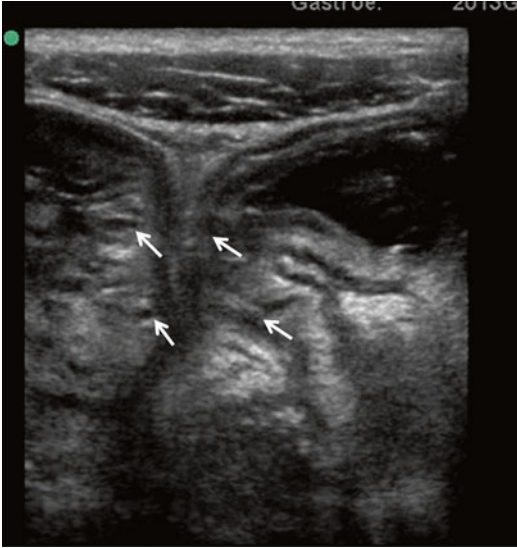


Fig. 2.10 Entero-enteric fistula appearance at SICUS as hypoechoic ducts between the intestinal loops (arrows). Note the anechoic contrast distending the lumen and the mesenteric fat hypertrophy

Table 2.1 SICUS: Normal values of wall thickness and lumen diameter of small bowel in healthy controls assessed in two consecutive evaluations

Location	Wall thickness (mm)		Lumen diameter (mm)	
	1st	2nd	1st	2nd
Jejunum	1.7±0.4 1–2	1.2±0.4 1–2	18.4±2.3 15–21	16.8±2.2 15–21
Ileum	1.9±0.3 1.3–2	1.2±0.4 1–2	18.4±1.8 16–20	17.8±2.8 13.7–20
Terminal ileum	1.9±0.3 1.3–2	1.7±0.6 1–2.3	17.2±2.2 14–20	15.7±2.8 11.3–19

Table 2.2 Sensitivity and specificity of TUS and SICUS in detecting small bowel lesions in undiagnosed patients

	Patients	TUS		SICUS	
	n (%)	TP	FN	TP	FN
IBS	36 (39.6)	–	0	–	0
Crohn's disease	16 (17.6)	11	5	16	0
Ulcerative colitis	7 (7.7)	–	0	–	0
Malignant tumors	6 (6.6)	3	3	6	0
Celiac disease	5 (5.5)	2	3	4	1
Undefined colitis	4 (4 %)	–	0	–	0
Polyps	4 (4 %)	0	4	3	1
Others	13 (14.3 %)	4	0	4	0
Total	91 (100 %)	20	15	33	2

TP true positive, FN false negative, IBS Irritable Bowel Syndrome

Table 2.3 Sensitivity and specificity of TUS and SICUS in detecting small bowel lesions in patients with known CD

Lesion	Patients	TUS		SICUS	
	n (%)	TP	FN	TP	FN
Terminal ileum	18 (32.7)	14	4	17	1
Ileum-jejunum	23 (41.8)	20	3	23	0
Ileo-colonic	14 (25.5)	14	0	14	0
Total	55 (100)	48	7	54	1

TP true positive, FN false negative

Table 2.4 Agreement between TUS and SICUS and surgery and SBFT in the detection of the small bowel CD lesion site

	Patients	TUS	SICUS
	N	k	k
Surgery			
Proximal lesions (≥1)	8	0.54	0.93
Distal lesions (≥1)	39	0.68	0.93
SBFT			
Proximal lesions (≥1)	12	0.31	0.83
Distal lesions (≥1)	45	0.61	0.93

allowed objective normative values of wall thickness (≤ 3 mm) and lumen diameter (≤ 25 mm) to be defined (Table 2.1, Video 2.1) [19]. These normative values provide useful measurements to discriminate normal from abnormal findings. Based on these normal cut-off values, it has been shown that SICUS is comparable to radiology and superior to standard TUS in detecting intestinal lesions both in patients with undiagnosed small bowel diseases and in those with known CD (Tables 2.2 and 2.3) [17, 20]. Sensitivity of TUS and SICUS were 57 % and 100 % and 87.3 % and 98 %, in the undiagnosed and in known CD patients, respectively. In addition, it has been shown that SICUS is more accurate than TUS in detecting both proximal and distal small bowel CD lesions compared to radiology [17] and surgery [29] (Table 2.4, Video 2.2). These results have subsequently been confirmed by other authors in several studies [30–32].

Notably SICUS enables initial assessment of wall alteration limited to the mucosa and sub-mucosa in CD (Fig. 2.11). The latter is associated with slight thickening of the intestinal wall, which may be missed in absence of the lumen distension by oral contrast (Video 2.3).

Fig. 2.11 SICUS: the thickness of intestinal wall appears slightly increased with a multilayered structure and mucosa enlargement (A-A)

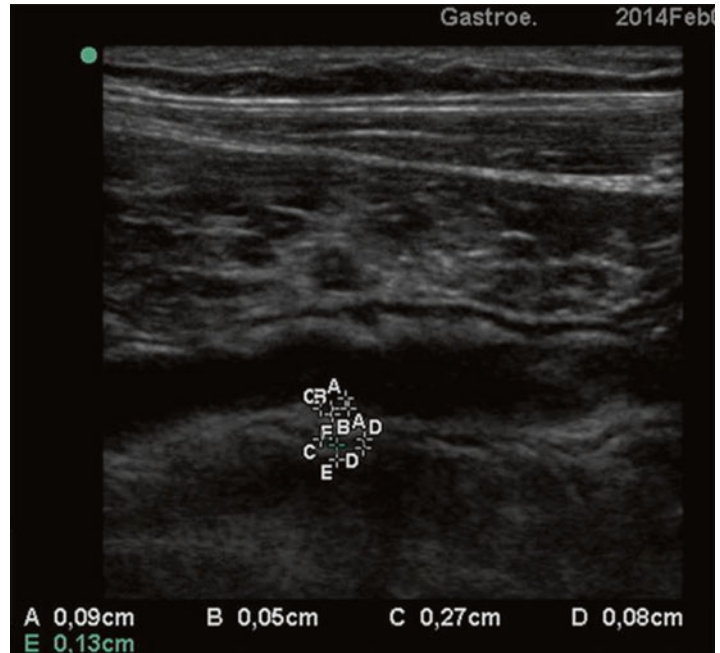
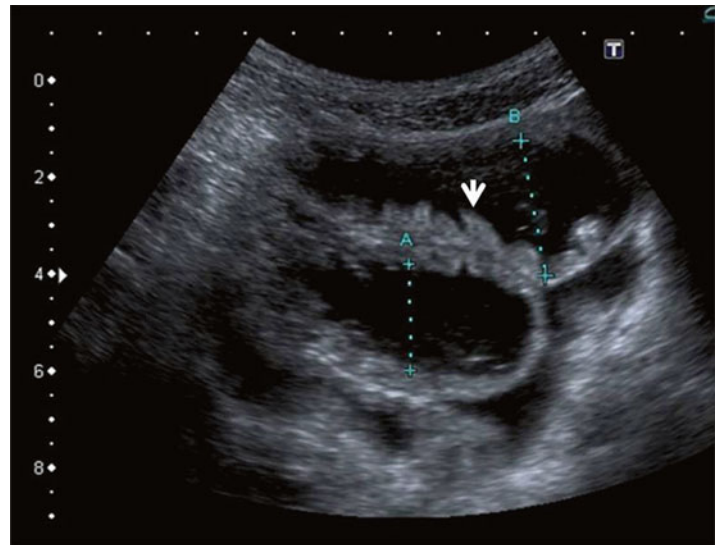


Fig. 2.12 SICUS: The longitudinal scan demonstrates anechoic contrast filled lumen; intestinal folds are seen as tiny intraluminal echogenic indentations of the intestinal wall (arrow)



Furthermore, SICUS allows identification and assessment of the characteristic distribution of intestinal folds (Fig. 2.12) and recognition of endoluminal structures such as polyps from the intestinal wall (Fig. 2.13, Video 2.4).

It has been recently shown that SICUS is a safe, accurate, radiation-free alternative for the assessment of small bowel disease also in pediatric

patient population [28]. The reported ability of SICUS to accurately identify the presence of small bowel disease compared to small bowel follow-through (SBFT) and ileocolonoscopy in a pediatric cohort of patients is even higher than in adults with a sensitivity and specificity of 96 % and 100 %, respectively (Table 2.5). In addition, as in adults, this study confirmed that SICUS is as

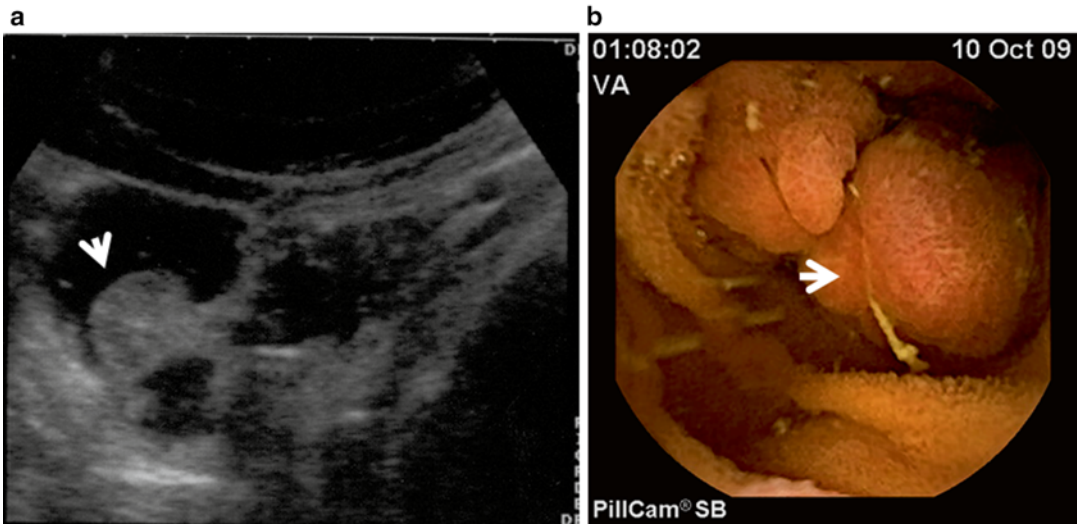


Fig. 2.13 Polyp of the small bowel. *Panel A:* SICUS: a fixed round echogenic structure (arrow) is visible within the contrast-filled ileal lumen. *Panel B:* Wireless capsule endoscopy: a corresponding endoscopic image. *By Courtesy of Erminia Romeo, MD and Luigi Dall'Oglio, MD Ospedale Pediatrico Bambino Gesù Rome, Italy*

Table 2.5 Sensitivity, specificity, PPV, NPV and statistical agreement of SICUS and TUS with SBFT in detecting presence and site of small bowel CD lesions in pediatric patients

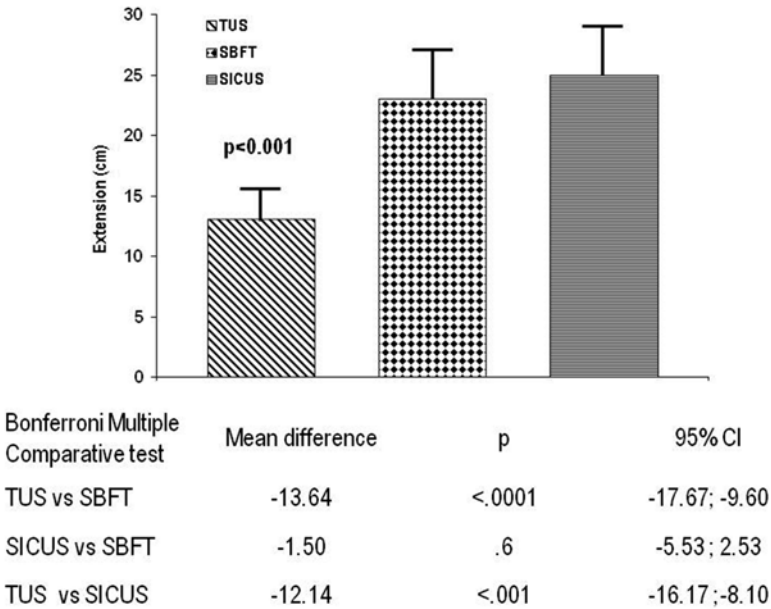
Modality	Site	SE % (95 % CI)	SP % (95 % CI)	PPV % (95 % CI)	NPV % (95 % CI)	k	p
TUS	Proximal	50 (23–76)	100 (87–100)	100 (60–100)	79 (62–91)	0.40	ns
	Distal	83 (64–94)	100 (68–100)	100 (83–100)	69 (45–91)	0.68	0.05
SICUS	Proximal	93 (66–100)	100 (87–100)	100 (75–100)	96 (81–100)	0.93	<0.05
	Distal	97 (81–100)	100 (68–100)	100 (85–100)	92 (60–100)	0.94	<0.001

Proximal SB: jejunum and proximal ileum; distal SB: distal and terminal ileum; *SE* sensitivity; *SP* specificity, *NPV* negative predictive value, *PPV* positive predictive value, *k* kappa-statistics

accurate as SBFT in detecting both proximal and distal small bowel lesions, whereas agreement with SBFT was markedly lower for TUS without oral contrast, mainly for the proximal sites lesions (Table 2.5). Although feasibility and reliability of this technique in pediatric clinical practice ought to be confirmed in further studies, the diagnostic accuracy of SICUS, with a considerable negative predictive value and such high level of agreement with radiology, suggests that a normal SICUS at the initial diagnostic workup in a child with suspected CD could avoid radiation exposure and invasive and/or more expensive investigations.

It should be pointed out that compared to standard TUS, SICUS is a time-consuming technique, the duration of the examination being on average 45 min. Although SICUS may appear to be a more expensive technique than traditional TUS, the lack of radiation actually makes it a cost-effective alternative to the less available and more expensive MRI. When considering colonic CD, US is more accurate in the assessment of intestinal wall pathology located in the sigmoid/descending colon, followed by the cecum/ascending, and transverse colon, while accuracy for rectal disease is poor [33]. A systematic review of

Fig. 2.14 One-way ANOVA with Bonferroni post-test for comparative evaluation of the extent of small bowel lesions at transabdominal ultrasonography (TUS), SICUS, and small bowel follow-through (SBFT)



6 studies investigating US for assessment of ileocolonic CD found sensitivities ranging from 63 to 100 % and specificities from 77 to 100 % [27]. The accuracy of standard ultrasound compared to endoscopy in the assessment of presence and severity of CD located in the colon improves markedly with hydrocolonic sonography [34], but these findings have not been reproduced.

The effectiveness of intravenous contrast agents in the detection of Crohn’s disease remains, despite some positive findings, largely uninvestigated [21].

Assessment of Extension of Lesions of Crohn’s Disease

To date few studies have assessed the accuracy of ultrasound to assess extension of CD intestinal involvement and reports have been equivocal regarding the correlation of TUS with radiology and intraoperative findings [33, 35–37]. Two studies [33, 35] performed in the same group of patients reported a significant correlation ($r=0.51$) between TUS and small bowel enema in the assessment of CD lesion extension. However, this finding was not confirmed by a study that, while not contradicting such correla-

tion, showed that when an appropriate test of comparative analysis is employed, (i.e., ANOVA), the accuracy of TUS in the assessment of extension of small bowel lesions is lower than that observed at SICUS and confirmed by SBFT or surgery [17, 29].

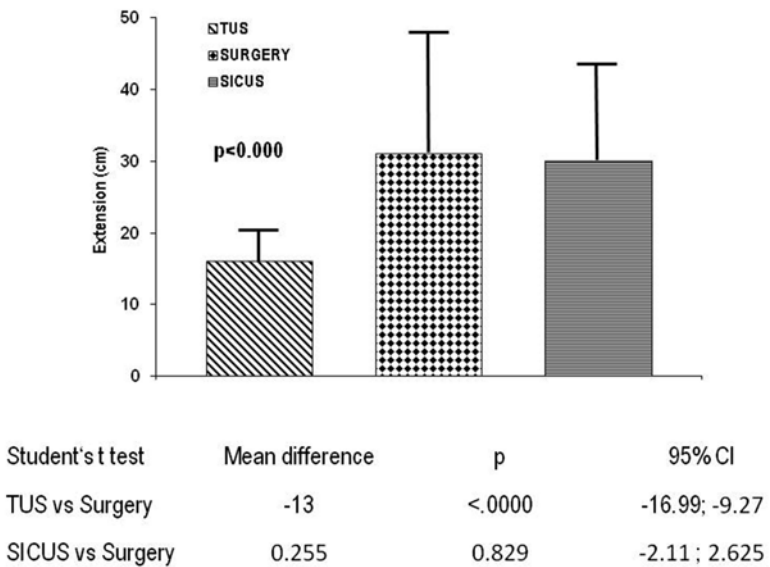
The use of oral contrast improves ultrasound accuracy in assessing extension of small bowel CD lesions in both adults and children independent of the site of lesions (Figs. 2.14 and 2.15).

These findings are of clinical relevance in patients with suspected CD, as well as in those with a previously established diagnosis, to help address follow-up and appropriate management of a progressive disease.

Assessment of Crohn’s Disease Activity

Assessment of inflammatory activity is a central component of the management of Crohn’s disease patients. Measurement of disease activity has traditionally involved a combination of clinical, biochemical (ESR, CRP, α 1-antitrypsin, fecal calprotectin), imaging, and endoscopic methods; although no ideal reference standard

Fig. 2.15 Extension of small bowel CD lesions at TUS, SICUS and surgery. The difference between paired measurements of CD lesion length at SICUS and at TUS and surgery against their mean and statistical difference is also reported



currently exists [38]. Clinical scoring systems such as the CDAI have been shown to have low correlation with mucosal inflammation, poor inter-observer reproducibility and, more relevantly, may not detect asymptomatic inflammation [39]. Laboratory parameters are not specific and endoscopy, including double balloon enteroscopy, is invasive and limited to mucosal assessment. Computed tomography (CT) involves the use of ionizing radiation whereas magnetic resonance (MR) imaging is expensive and time consuming. Several studies evaluated the relationship between CD activity assessed as CDAI and/or with biochemical parameters, and TUS features of the bowel wall with equivocal results [40–42]. Previous studies have shown significant but weak correlation between the degree of bowel wall thickening and its extent and clinical (CDAI) and biochemical parameters (ESR, CRP) [40]. As such, an ultrasound index of intestinal inflammatory activity has been developed based on the wall thickness and stratification of the diseased gut demonstrating a strong correlation with the endoscopic and radiological score but a weak correlation with clinical (CDAI) and biological indices of inflammation [41].

The introduction of second-generation ultrasound contrast agents in combination with low mechanical index harmonic ultrasound allows

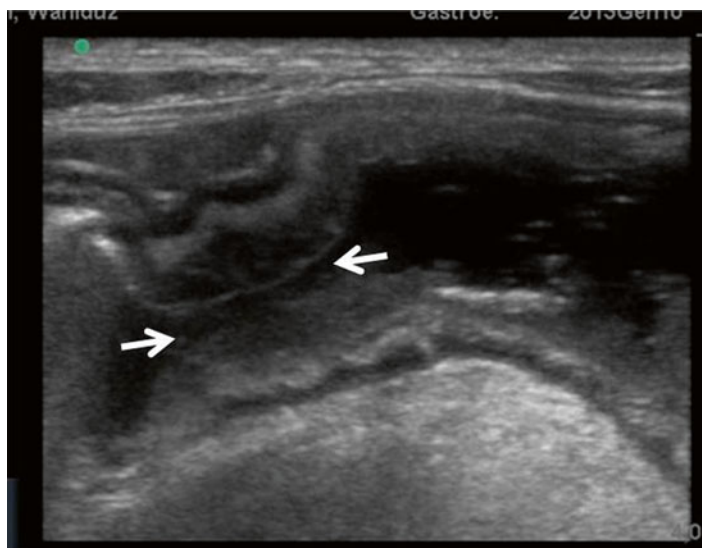
accurate imaging and analysis of bowel wall microvasculature that takes part in the pathogenesis of CD inflammation [43]. Several studies have examined both qualitative and quantitative measures of bowel wall enhancement obtained from CEUS as a means of assessing inflammatory activity in Crohn’s disease with inconsistent results [44–49]. Some studies have demonstrated a significant relationship between measurements obtained from CEUS and clinical or endoscopic indices of disease activity [44, 45] while others have failed to confirm similar results [46, 47], suggesting that mural microvasculature may be variably increased in active disease. Experimental data have previously shown that regional blood flow is, in fact, reduced in Crohn’s disease and associated to microvascular ischaemia [49].

In conclusion ultrasound appears to be of limited value in assessing CD activity.

Assessment of the Abdominal Complications of Crohn’s Disease

Contrast radiology, CT, MRI and TUS have been widely and variably utilized for the diagnosis of Crohn’s disease complications such as strictures, fistulas and abscesses that often develop during the lifelong course of CD [29]. Historically, contrast

Fig. 2.16 SICUS. Crohn's disease of the distal ileum. Short segment of luminal narrowing (arrows) in absence of pre-stenotic dilatation. The presence of oral contrast allows the accurate measurement of luminal diameter and the extension of stricture and of a dynamic assessment of the stenotic bowel loop



radiology was the only diagnostic tool to detect small bowel strictures, but it has been shown to be inaccurate in the detection of fistulas and abscesses and is not indicated in patients with symptoms of obstruction. CT is useful for the detection of shallow abscesses [50] but its diagnostic accuracy for CD strictures and fistulas is low when compared with surgical findings [50, 51]. In any case, radiation-free methods are preferable in CD patients who require repetitive follow-up assessments. MRI is valuable to detect abscesses, but is limited in the identification of low-grade strictures [52] and to discriminate them from muscular bowel wall contractions; finally, its accuracy in the detection of fistulas is not yet fully established [37]. Standard trans-abdominal ultrasound (TUS) has proved to be valuable in detecting small bowel CD strictures and abscesses whereas its sensitivity in detecting entero-enteric fistulas is still debated [15, 50]. Surgery remains an important component of treatment of CD and an accurate preoperative assessment of CD lesions and associated complications is required to plan the surgical approach and intervention [53], more so if a laparoscopic approach is chosen. US being non-invasive, inexpensive, repeatable and accurate is the ideal method to be employed in the follow-up of CD patients for timely and early detection of disease progression.

CD Strictures

The clinical course of Crohn's disease is characterized by the occurrence of intestinal strictures in 21 % of patients with ileal CD and in 8 % of those with ileocolic disease and often requires surgery. A cohort study showed that 22 % of patients with stricturing CD underwent surgery during a 5-year follow-up interval [54]. Although previous small series have suggested a high diagnostic accuracy of contrast radiology for the detection of strictures, a large study by Otterson et al. [55] found that, in comparison to operative findings, small bowel follow-through incorrectly predicted the number of strictures in 30 % of patients. Bowel stricture can be demonstrated by ultrasound as thickened bowel wall associated with a narrowed lumen and increased diameter of the proximal loop greater than 3 cm [15]. Using this definition, TUS correctly detects the presence of at least one stricture in 70–79 % of unselected CD patients and in more than 90 % of those undergoing surgery for severe obstructive symptoms with 7 % false-positive diagnoses [35, 56, 57]. The use of an oral contrast agent (Fig. 2.16 and Fig. 2.17) leads to a significantly greater accuracy of ultrasound in detecting the presence and number of CD strictures (Table 2.6). A recent study that compared surgery to SICUS noted that the latter has a high diagnostic accuracy to detect: (1) the presence of more than two

Fig. 2.17 SICUS. Crohn's disease of the jejunum. Short segment of luminal narrowing (*arrows*) in absence of pre-stenotic dilatation. The presence of oral contrast allows the accurate measurement of luminal diameter and the extension of stricture. The presence of intestinal folds allows to localize the site of stricture



Table 2.6 Comparative results of surgical and SICUS evaluation by k-statistics in the assessment of CD complications

Surgery	SICUS				
	N	N	Sens (95 % CI)	Spec (95 % CI)	k
Patients with strictures	40	39	97.5 % (87–100)	100 % (68–100)	0.93
• Stricture alone	17	16	94 % (74–99)	100 % (67–100)	0.945
• Stricture and fistulas	16	16	100 % (80–100)	100 % (60–100)	1
• Strictures, fistula & abscess	7	7	100 % (61–100)	100 % (44–100)	1
Patients with fistulas	28	27	96 % (82–99)	90.5 % (71–97)	0.88
• Entero-enteric	12	11	100 % (76–100)	82 % (61–93)	0.77
• Entero-mesenteric	9	9	100 % (67–100)	100 % (87–100)	1
• Entero-colic	13	7	54 % (29–77)	100 % (85–100)	0.61
Patients with abscesses	10	10	100 % (72–100)	95 % (83–98.6)	0.89
Patients with MFH	27	26	96 % (82–99)	91 % (72–97.5)	0.88
No SB CD complications	4	3	98 % (88–100)	75 % (30–95)	0.75

strictures, (2) stenoses located in the proximal small bowel, and (3) extension of strictures, independent from the presence of pre-stenotic dilatation and of obstructive symptoms. The presence of the pre-stenotic dilatation has been regarded at imaging techniques as the hallmark of fibrotic strictures [55]; in contrast, in one study a pre-stenotic dilatation was present at surgery and pathology in only one-third of the patients [29].

Further characterization of the stricture is made possible by considering US features of

the intestinal wall. It has been proposed that the loss of stratification is associated with a low degree of fibrosis and a preponderance of inflammation, while the presence of stratification, in turn, correlates with fibrotic tissue apposition. Fibrosis may also lead to decreasing echogenicity of the submucosa and increasing echogenicity of the muscular layer [58]. Finally it has been suggested that contrast-enhanced Doppler US may assess CD inflammatory activity within strictures by evaluating the intramural blood flow

that is increased in inflammatory strictures and reduced in fibrotic ones [59, 60]. A comparable accuracy was shown by CEUS and Doppler US, although the correlation with CDAI was higher for CEUS than for US [61].

Fistulas

Fistulas, which frequently complicate the course of Crohn's disease, are the result of transmural extension of the inflammation and may end blindly in the surrounding mesentery or connect intestinal loops or adjacent organs. According to the site and the organs involved, fistulas are defined as internal, often asymptomatic and unrecognized (enteroenteric, enteromesenteric), external (enterocutaneous, enterovesical, enterovaginal) and perineal—the latter giving rise to symptoms are usually clinically obvious and more easily detected. A cross-sectional study of CD patients evaluated with CT enterography revealed a fistula prevalence of 17 %, of which about half were entero-enteric [62]. At ultrasound, fistulas appear as hypoechoic, duct-shaped peri-intestinal lesions, (Fig. 2.8 and Fig. 2.10) with a cross-sectional lumen diameter less than 2 cm and sometimes displaying echoic spots. The accuracy of TUS in the assessment of intra-abdominal fistulas varies according to the reference standard. So far there is no reliable technique for the diagnosis of this complication and the reference standard for the detection of fistulas in CD is inspection during surgery [63]. Two studies have previously compared surgical findings with the diagnostic performance of TUS [50, 57] and one [50] reported contrast radiology and CT in the detection of internal fistulas reporting a sensitivity of 87 % and 71 %, and specificity of 90 % and 95.8 %, respectively. More recently, the diagnostic accuracy of standard US and SICUS in the assessment of intra-abdominal fistulas has been compared to surgery and pathological findings [29]. This study confirms an excellent specificity (100 %) of standard TUS, but in contrast to previous reports, demonstrated that SICUS has a better sensitivity (96 % versus 55.5 %) than TUS in the detection and characterization of internal, entero-enteric and entero-mesenteric fistulas with a comparable specificity (90.5 %). In the Maconi

et al. study [50] the sensitivity of TUS in the detection of internal fistulas was enhanced up to 97 % by combining it with contrast radiology and CT. Similar diagnostic accuracy has been obtained in our experience with the use of SICUS alone (Table 2.6). It is likely that the oral contrast distending the intestinal lumen allows better visualization with characterization of fistulas. Intravenous contrast-enhanced US and power-Doppler may be used as diagnostic tool in the suspicion of a fistula by detecting increased intramural blood flow in the fistula wall [64].

Finally, a previous report suggests that US may supersede X-ray fistulography in the characterization of external fistulas after the injection of hydrogen peroxide and povidone iodine into the fistula [65].

Intra-abdominal Abscesses

The prevalence of intra-abdominal abscesses in CD patients is about 4 % and usually occurs as a complication of fistulizing disease [62]. Intra-abdominal abscesses are equally detected by MRI, CT and TUS. Even if the diagnostic yield is lower for small, deep, interloop, mesenteric abscesses [50], TUS is considered a first-level procedure in the suspicion of intra-abdominal abscesses. At ultrasound an abscess appears as a hypo-anechoic round shaped lesion with a cross-sectional diameter more than 2 cm, sometimes with internal echoes due the presence of debris or air (Fig. 2.9). Four studies [50, 51, 57, 66] have compared preoperative findings at TUS and CT, and one with SICUS [29] with operative findings in detecting the presence of abscesses. All five studies showed high diagnostic accuracy of US with a mean sensitivity and specificity of 91.5 % and 93 %, respectively, although SICUS appears to be more sensitive than standard US [29].

Mesenteric Fat Hypertrophy

Presence and location of mesenteric fat hypertrophy (MFH) (Fig. 2.8 and Fig. 2.10) may influence the surgical approach [67] and its pre-operative assessment may be important. Recently it has been shown in a cohort of CD patients undergoing surgery for disease complications that MFH was detected in 55 % of patients at

surgery [29]. To date, the presence of mesenteric fat hypertrophy has received little attention in the follow-up of CD patients. MFH has been found at US in about 50 % of CD patients and has been correlated with clinical activity of CD, internal fistulas and increased bowel thickness [68]. The diagnostic accuracy of SICUS for MFH is high with a sensitivity of 96 % and specificity of 91 % (Table 2.6). Notably in this cohort of patients MFH was associated with fistulas but not with strictures, confirming previous surgery findings that MFH is associated with a transmural inflammation [67].

It should be emphasized that the high prevalence of intestinal complications reported in the aforementioned studies is not representative of the CD population at large and may falsely elevate the reported sensitivity of US and SICUS in detecting CD complications. Nevertheless, the use of a luminal contrast agent markedly increases the diagnostic efficacy of TUS in detecting CD complications and SICUS may be appropriate as a noninvasive technique in the follow-up of CD patients to promptly diagnose complications, and plan surgical intervention.

Postoperative Follow-up and Prediction of Crohn's Disease Recurrence

In patients submitted to surgery for ileo-colonic Crohn's disease, recurrence of CD intestinal lesions at the level of ileo-colonic anastomosis and neoterminal ileum is extremely frequent. Indeed, it is now firmly established that surgery, even though apparently radical and despite initial clinical remission, does not offer a definitive cure. A seminal, prospective endoscopic cohort study demonstrated that the postoperative clinical course of Crohn's disease can be predicted by the severity of endoscopic lesions during the first year after resection [69]. Patients with diffuse recurrent lesions in the neoterminal ileum within 1 year of resection present symptoms earlier and are more prone to have complications than patients with no or very mild lesions who more likely have an uneventful postoperative clinical

course. However, even mild recurrent CD lesions such as aphthae have the tendency to progress, often in absence of symptoms, into more severe involvement such as ulcerations and strictures [70]. Based on these observations, and considering that patients are often asymptomatic despite the presence of recurrent CD lesions, it has been proposed that patients with CD have endoscopic evaluation of the neoterminal ileum 6–12 months after surgery to guide therapeutic management [71]. In absence of symptoms, however, patients are not keen to undergo colonoscopy. Because of its invasiveness and need of intestinal preparation, ileocolonoscopy greatly affects patients' compliance. Indeed, in a large survey it has been shown that colonoscopy failed in 25 % because of patients' intolerance and in 35 % for inadequate preparation [72]. A noninvasive method that visualizes the entire small bowel, such as MRI or US performed after the ingestion of oral contrast, is likely to improve patient's compliance to undergo follow-up and can be planned early after surgery and the procedure time adjusted at will. Previous studies have assessed transmural lesions after curative ileal resection in CD patients at the level of neo-terminal ileum with MR and standard TUS [73, 74]. Both MR and TUS did not provide sufficient resolution to differentiate initial lesions in patients with endoscopic scores 1 and 2. Thereafter, two ultrasound studies [75, 76] done after the ingestion of an oral contrast, reported that wall thickness >4 mm at the level of neoterminal ileum had a high sensitivity in detecting severe endoscopic CD recurrence (i.e., score 3 and score 4) as opposed to a low sensitivity in detecting mild lesions (score 1 and score 2). More recently it has been shown [77] that compared to the Rutgeerts score at ileocolonoscopy, the combined evaluation at SICUS of wall thickness at level of the ileocolonic anastomosis (Fig. 2.18), and of the extension of transmural lesions of neoterminal (Fig. 2.19) ileum better discriminate mild (score 1 and score 2) or no recurrence (score 0) from severe (score 3 and score 4) endoscopic recurrence (Table 2.7).

The ROC curve analysis shows that the two combined variables represent an almost perfect tool in discriminating patients with score 0 from

Fig. 2.18 SICUS

assessment of ileo-colonic anastomosis in CD patient without recurrence. Calipers indicate thickness of ileal (up) and colonic (down) limbs (2.8 mm). Neoterminal ileum is shown

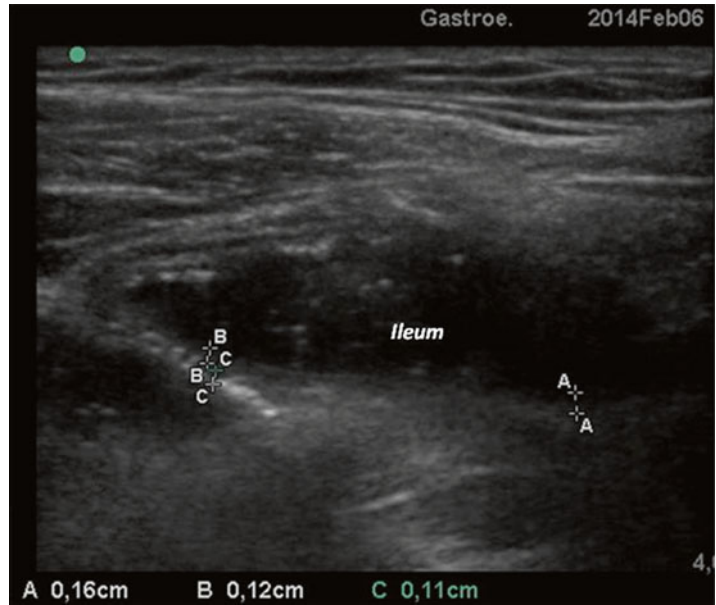
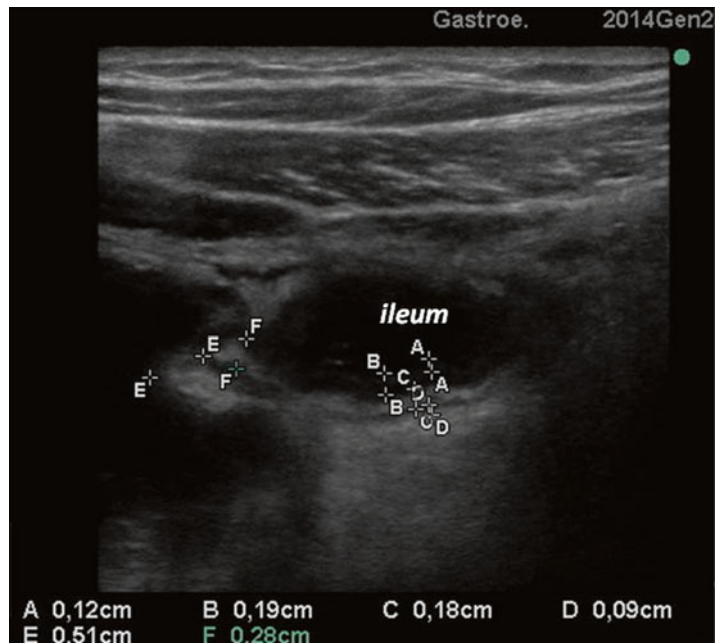


Fig. 2.19 SICUS

assessment of ileo-colonic anastomosis in CD patient with recurrence. CD transmurial involvement of ileo-colonic anastomosis (thickness 7.9 mm E-F) and neoterminal ileum (A-A, extending for 4 cm)



those with score 1–4 and a good tool in discriminating patients with score 0 from those with score 1. In addition, aside from an endoscopic scoring system, this study finds an association between the US grading of transmurial lesions at the level of ileo-colonic anastomosis (ICA) and disease extension along the neoterminal ileum

(Fig. 2.20). Notably in patients with a Rutgeerts score of 1, lesions are confined to anastomosis in half of patients at SICUS whereas in most patients (93 %) substantial transmurial involvement occurs even in the presence of few aphthae and without gross mucosal ulceration at endoscopy. In the Rutgeerts et al. study, patients with no (score 0)

Table 2.7 Estimated adjusted odds ratios (AOR) with 95 % confidence intervals (95 % CI) from two logistic models of having Rutgeerts score 0 versus 1–4 (section A), and 0 versus 1 (section B) on the basis of ICA wall thickness value and extension of increased (>3 mm) neo-terminal ileal wall thickness

	AOR	95 % CI	p value
Score 0 vs. 1–4 (section A)			
ICA wall thickness (for 1 mm increase)	1.96	1.22–3.15	0.01
Extension of increased (>3 mm) neoterminal ileal wall thickness (for 1 cm increase)	1.18	1.08–1.30	<0.01
Score 0 vs. 1 (section B)			
ICA wall thickness (for 1 mm increase)	1.81	1.12–2.93	0.02
Extension of increased (>3 mm) neoterminal ileal wall thickness (for 1 cm increase)	1.15	1.06–1.24	<0.01

or very mild (score 1) and those with severe (score 3 and score 4) lesions at endoscopy were grouped together as they had, respectively, nearly asymptomatic or aggressive disease 1 year after surgery. Patients with intermediate severity of lesions (score 2) had no clear clinical prognosis and they progressed with either mild or aggressive disease. By assessing transmural lesions at the level of the ileocolonic anastomosis as well as the proximal extension in the neoterminal ileum, SICUS has the potential to grade the severity of transmural involvement of recurrent CD lesions in patients who have undergone ileal resection. Given the potential for SICUS to define early extension of transmural lesions, it may be relevant to assess its use in future prospective studies as it is potentially important to define how the degree of transmural involvement may affect the postoperative clinical course.

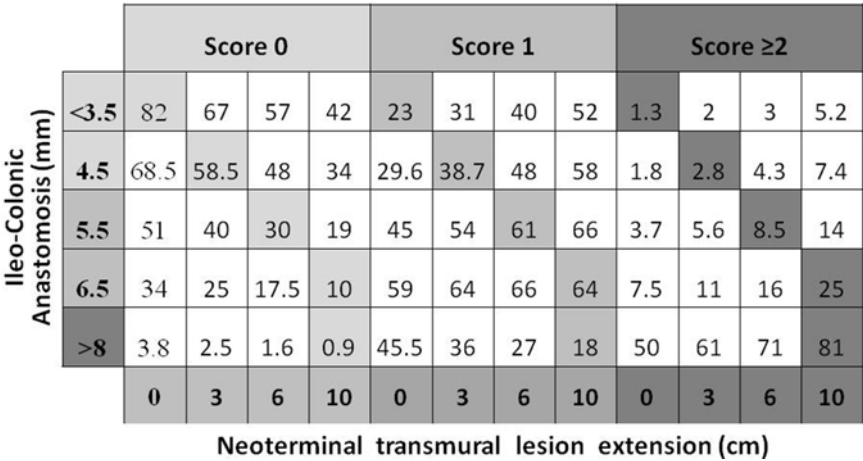


Fig. 2.20 Predicted probabilities of having a score of 0 (pale gray), 1 (gray), and ≥2 (dark gray) from a polychotomous ordinal logistic model with ICA wall thickness and extension of neoterminal intramural lesions as covariates. In absence of transmural lesion (extension 0) of the neoterminal ileum, the predicted probability of having a score of 0 is 82 % when ICA wall thickness is ≤3.5 mm and progressively decreases to 3.8 % for ICA wall thickness ≥8 mm. The probability of having a score of 0 progressively decreases from 67 to 42 % for transmural lesions of the neo-terminal ileum increasing from 3 cm to 10 cm. In absence of transmural lesion (extension 0) of the neoterminal ileum, the predicted probability of having a score of 1, progressively increases from 2 to 45.5 % for wall thickness of ICA increasing from 3.5 mm to 8 mm. In

absence of transmural lesion (extension 0) of the neoterminal ileum, the probability of having a score of 1 with ICA wall thickness >8 mm is low (45.5 %). When the extension of transmural lesions at the level of neo-terminal ileum increases from 3 to 10 cm, the probability of having a score of 1 progressively increases from 23 to 52 %. In absence of transmural lesion (extension 0) of the neoterminal ileum, the predicted probability of having a score of ≥2 is <1.3 % (a) when ICA wall thickness is ≤3.5 mm and progressively increases to 50 % for ICA wall thickness >8 mm. With ICA wall thickness ≥8 mm and with transmural lesions of the neo-terminal ileum increasing from 3 cm to 10 cm, the probability of having a score of ≥2 progressively increases from 50 to >81 %

Ulcerative Colitis

Since the inflammation in UC affects exclusively the recto-colic mucosa, colonoscopy with biopsy is the gold standard for the assessment of disease extent, activity, and severity, thus bowel US has a

limited usefulness in the diagnosis and in the follow-up of patients with UC, except for severe disease or in presence of severe comorbidity. A few studies have assessed the diagnostic accuracy of TUS in diagnosing ulcerative colitis in small numbers of patients with sensitivities ranging from 48 to 100 % and specificities from 82 to 90 % [78] (Fig. 2.21 and Fig. 2.22). Current evidence indicates that in UC diagnostic accuracy of TUS is also related to disease site, as sensitivity is high for sigmoid/descending colonic disease (reaching 97 %) [79] but low for rectal disease [22]. The utility of US for assessing activity of colitis has been assessed in small series of patients showing that the mean colonic wall thickness was higher in moderately or severely inflamed bowel compared to normal segments [23, 80, 81].

Recently Civitelli et al. [82] in a prospective and blind study compared colonoscopy with US in assessing the extent and activity of disease in 60 consecutive pediatric UC patients. The results of the study showed high agreement (90 % concordance) with endoscopy in the assessment of disease extent, with a sensitivity ranging between 75 % at the level of right colon to 96 %



Fig. 2.21 TUS, normal appearance of intestinal wall at the level of sigmoid colon

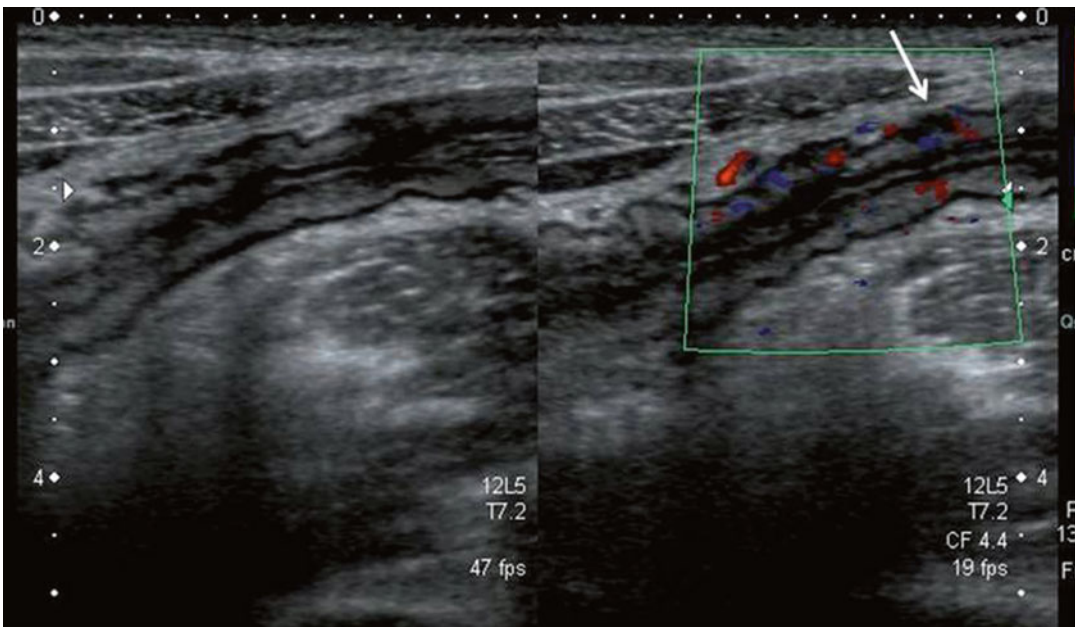


Fig. 2.22 TUS. Ulcerative colitis. Longitudinal scan of descending colon. The wall thickness is increased (>3 mm), with normal multilayered echo-pattern

at the level of left colon as well as a specificity of 100 % for all colonic sites. In addition, a US score ranging from 0 to 4 was assessed based on increased BWT ($p < 0.0008$), vascularity ($p < 0.002$), loss of haustra ($p = 0.031$) and loss of BW stratification ($p = 0.021$). At multiple regression analysis endoscopic severity demonstrated a strong correlation showed ($p < 0.0001$) with the US score as well as Ulcerative Colitis Activity Index (PUCAI) and Mayo endoscopic subscore (MS).

Conclusion

Due to noninvasiveness, low cost, absence of radiation, and widespread availability, ultrasound has been widely used to assess those aspects of the GI tract that are not easily accessible to endoscopic investigations and, in particular, the mural and extramural GI pathology of the small bowel. The greatest advancement in ultrasonographic assessment of the GI tract has been made with Small Intestinal Contrast Ultrasonography (SICUS), which is superior to the standard trans-abdominal US. It has a high sensitivity, and nearly perfect specificity to diagnose Crohn's disease lesions of the small bowel, identifying the site and extension of the inflammatory lesions as well as complications such as strictures, fistulas, and abscesses. Moreover, SICUS has been shown to predict—similar to endoscopy—the severity of postoperative inflammatory recurrence after ileocolonic curative resection for terminal ileocolon Crohn's disease, making its noninvasive nature an attractive alternative for postoperative follow-up.

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