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LATEST INTESTINAL ULTRASOUND ADVANCEMENTS IN INFLAMMATORY BOWEL DISEASE

Introduction

Inflammatory bowel disease (IBD) treatment has evolved from monitoring clinical symptoms to targeting objective measurements of mucosal healing with endoscopic and radiologic imaging. It is well known that clinical symptoms do not match disease severity. Frequent evaluation with radiologic imaging is now the standard of care. Although Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) recommendations do not list radiographic targets as an endpoint due to the "limited ability of the currently available treatments to achieve transmural healing," this will likely evolve over time particularly with the rapidly growing uptake of intestinal ultrasound (IUS) in clinical trials.[1] For the time being, imaging is considered as an "adjuvant assessment rather than a formal treatment target."[1]

While endoscopy is the current reference standard technique for examining the bowel in IBD, the feasibility of repeating these invasive examinations for monitoring is limited. One of the greatest limitations of endoscopy in the context of IBD is its inability to evaluate the extent of transmural involvement and peri-enteric disease complications. Furthermore, assessing the proximal disease extent in Crohn's disease (CD) is impossible when there is a failure to intubate a strictured ileum. Consequently, computed tomography (CT), magnetic resonance imaging (MRI), and IUS are all valuable diagnostic imaging modalities for fully monitoring disease extent, severity, and progression. IUS has been shown in reviews and meta-analyses to be equally sensitive and specific as CT and MRI in diagnosing and monitoring CD,[2,3] and has high accuracy for disease activity when compared to endoscopy in diagnosing and monitoring ulcerative colitis (UC).[4,5] IUS is advantageous for its accuracy, non-invasiveness, and easy repeatability due to excellent patient tolerability. Overall, gastroenterologist-performed IUS has revolutionized the ability to visualize inflammation and complications in the bowel. This overview will discuss the availability of IUS, its current use in CD and UC, and future directions.

Current Use of Gastroenterologist-Led IUS in Canada

A. IUS in Canada

The University of Calgary IBD Unit was the first in North America to establish an innovative clinic that uses IUS at the bedside to safely evaluate the bowel. Currently, IUS clinics led by gastroenterologists are present in all but three provinces in Canada. The interest in IUS is experiencing rapid growth globally.

Studies evaluating patient experiences and preferences for disease monitoring in CD has repeatedly shown a desire among patients to have access to IUS for varying reasons, including education of disease severity in real-time and increased engagement.[6,7] Its ease of use for patients by physicians has made IUS a repeatable choice for routine surveillance and urgent imaging. The use of IUS by gastroenterologists for timely decision making has been shown to improve disease control and limit invasive testing.[8]

B. IUS Training

The International Bowel Ultrasound Group (IBUS), based in Germany, has established the only credentialed training program for IBD-focused IUS monitoring in the world. In Canada, the majority of gastroenterologists have either been trained in IUS from radiologists experienced in IUS, or from IBUS. At present, eight IBUS-certified Canadian training centres in pediatric and adult IUS are available (Kelowna, Edmonton [pediatric and adult], Calgary [pediatric and adult], Saskatoon, Hamilton, and Bridgewater). Other centres that are either developing or have established IUS programs include Vancouver, Lethbridge (Alberta), Grand Prairie (Alberta), Winnipeg, Toronto, London, Montreal, Sherbrooke, and Halifax.

Most recently, studies have assessed the accuracy of IUS performed by gastroenterologists by taking into account their abdominal ultrasound experience.[9] IBUS mandates a minimum of 40 observed examinations for a gastroenterologist to be certified for basic competence in IUS. A study by Bezzio et al. observed that trainees with limited abdominal ultrasound experience (<50 exams) required a minimum of 84 exams to achieve concordance with the expert sonographer for detecting findings such as increased bowel wall thickness.[9] To achieve advanced IUS competence, a minimum of 97 examinations is required to obtain concordance with an expert sonographer for identifying intra-abdominal complications.

C. IUS Application in Clinic and Limitations

Hallmark Features of IBD Activity

Four key features on IUS allow for grading of CD and UC activity. These include bowel wall thickness, colour doppler signal (CDS), presence of inflammatory fat, and loss of wall stratification **(Table 1)**. Bowel wall thickness is the most specific objective measure for inflammatory activity with a thickness of > 3mm in the small bowel and colon indicating abnormality.[10] Other adjunct activity parameters include lymphadenopathy. Scoring indices have been devised and the IBUS-SAS (Segmental Activity Score) is one of the most widely used tool that incorporates the four aforementioned parameters.[10] Real-time interpretation of these parameters including complications such as strictures and penetrating disease for CD, and use during UC flares in clinic allows for immediate decision making and reduces reliance on other imaging modalities and endoscopy. Validated scoring indices for CD (Simple Ultrasound Score[11]) and UC (Milan Ultrasound Criteria[12] and UC-Ultrasound Index[4,13]) have been established using endoscopy as the comparator. However, a robustly validated, reliable and responsive index remains unavailable to monitor treatment response.

Obstacles to Implementation

Although IUS offers considerable value, barriers for IUS implementation remain present. Obtaining an IUS machine at a Canadian centre requires a financial investment of typically approximately $100 000 to 150 000 CAD. Additional costs for maintenance and service contracts have to also be factored in. Secondly, physicians interested in obtaining certification from IBUS require the completion of three modules (Module 1; intensive introductory hands-on workshop, Module 2; four-week hands-on training module at a certified IBUS training centre, Module 3; advanced workshop and final exam). This is a competitive process and examinations have been typically only offered annually at ECCO (European Crohn's and Colitis Organization) congress. Most gastroenterologists are unable to leave their practice for 4 weeks at a time, and

Intestinal Ultrasound Parameter*	Cut-Offs
Bowel Wall Thickness	>3mm
Colour Doppler Signal (Hyperemia)**	**Modified Limberg Score** 0 – absent 1 - small spots (single vessels) within the wall 2 - long stretches within the wall 3 - longer stretches within the wall extending into the mesentery.
Inflammatory Fat	Present or Absent
Wall Stratification	Focal loss (<3cm) Extensive loss (>/= 3cm)

Table 1. Four Key Inflammatory Bowel Disease Activity Parameters on Intestinal Ultrasound
Adapted from Novak et al. J Crohns Colitis. 2021 Apr 6;15(4):609–16.
*Other parameters such as motility abnormalities, lymphadenopathy, submucosa echogenicity, stricture measurements, and penetrating complications are also evaluated when evaluating activity, but are not in formal intestinal ultrasound activity scoring.
**Other scoring systems for hyperemia are available: Limberg score and International Bowel Ultrasound Color Doppler Signal score.

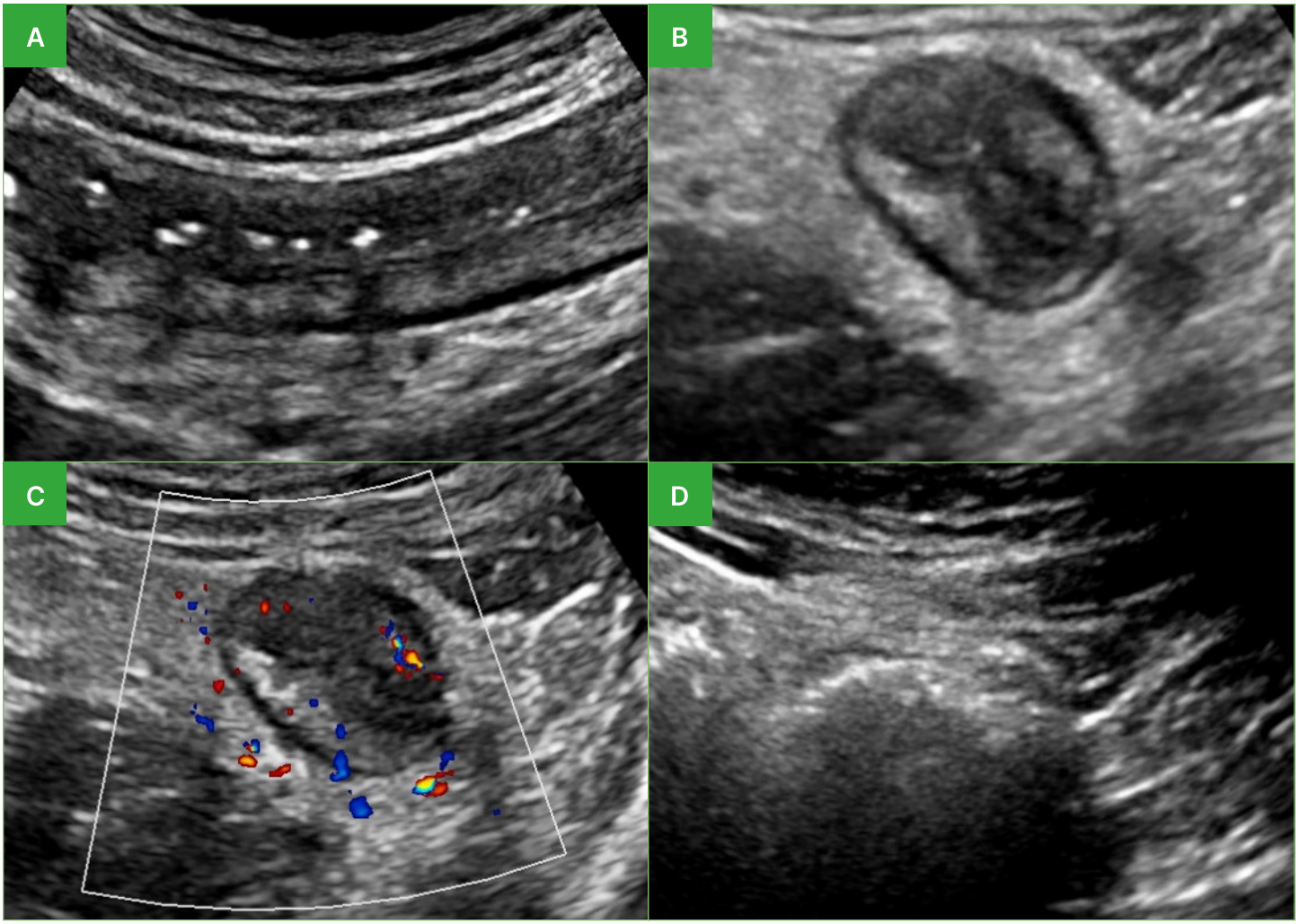

Figure 1. 21 year old male with new diagnosis of left sided ulcerative colitis. Loss of normal descending colon haustration with thickened bowel and loss of stratification in longitudinal view **A**. Ample inflammatory fat seen as echogenic (white) wrapping around descending colon in axial view **B**. Hyperemia graded as modified Limberg 3 with vascular signal in bowel walls and surrounding inflammatory fat **C**. Normal haustration in cross-sectional view of transverse colon unaffected by ulcerative colitis in same patient; *courtesy of Cathy Lu, MD, MSc*

training is typically completed over 1-to-2-week blocks. Training at Canadian centres is organized by IBUS with preference for training of Canadian nationals. Thirdly, gastroenterologist-led IUS during clinic visits generally requires 10 to 15 minutes for straightforward examinations and may take 30 minutes or greater for complex scans such as those with peri-enteric complications, or long segment disease with multi-focal structuring. Allotting time for IUS evaluation, image capture, and documentation may favour academic centres due to the lack of current remuneration and fee codes in the majority of Canadian centres. Achieving competence and maintaining competency in IUS are also areas of current study with comparisons to endoscopy and echocardiography frequently cited.[14,15]

Limitations of IUS include its inability along with CT and MR to detect mild mucosal disease such as a simple endoscopic score of 3 in the ileum or colonic segment. Proctitis is often also difficult to evaluate as examination of the rectum using transabdominal IUS may be limited visually; the transperineal approach is typically favoured in this situation. Similarly, very deep structures of bowel may be missed. Detection of proximal CD such as in the duodenum may also be limited. Abdominal obesity is reported as a limitation of IUS. However, bowel visualization may actually be minimally hampered by central adiposity and body habitus does not predict failure of ultrasound.[16] A criticism of ultrasound is that accuracy is dependent on examining experience of the sonographer. Good reproducibility of assessing bowel thickness and complications has been described between gastroentoerlogists alone, and between gastroenterologists and radiologists from six IBD referral centres.[17,18]

Efficacy of IUS and Comparison with Other Imaging Modalities

IUS is comparable to MR enterography (MRE) in diagnosing CD with a sensitivity of 94%, a specificity of 97%, a positive-predictive value of 97% and a negative predictive value of 94%.[19] Regarding the diagnostic performance of IUS for CD, the ileum, sigmoid, and descending colon have the highest diagnostic performance; however, a lower predictive accuracy has

been reported for the duodenum, proximal jejunum and rectum.[20]

A landmark prospective, multicentre trial, MR Enterography or ulTRasound In Crohn's disease, (METRIC), was conducted in the United Kingdom. The trial evaluated the diagnostic accuracy of MRE and IUS for the extent and activity of newly diagnosed and relapsed CD. This trial's findings have confirmed that both MRE and IUS are accurate and have a high sensitivity for detecting terminal ileal CD, with a sensitivity of 97% (95% confidence interval (CI) 91–99) for MRE, and a sensitivity of 91% (95% CI 79–97), for IUS.[21] This trial has observed that detecting colonic disease on cross-sectional imaging is more challenging. There were no significant differences in detecting colonic disease, with an MRE sensitivity of 64%, and an IUS sensitivity of 73%.[21] Overall, IUS is comparable to MRE and CT enterography (CTE) in identifying the location and activity of IBD.

Post-operative recurrence of CD can be confidently predicted when combining IUS with fecal calprotectin levels.[22] The role of IUS in diagnosing post-operative recurrence of CD has been evaluated in multiple studies.[23–27] More specifically, a recent prospective study has shown that bowel wall thickening of >3 mm and the presence of lymphadenopathy with a fecal calprotectin level of >50 mcg/g is reliable at predicting endoscopic disease recurrence, with less than 5% of patients being falsely classified.[22] Overall, non-invasive techniques such as IUS and fecal calprotectin levels allow for adequate CD evaluation post-surgery, although future studies are necessary to determine whether the changes that can be made to medical therapy without the requirement for endoscopy are appropriate.

Transmural Healing and Response; Definitions on CT, MR, and IUS

Concepts such as transmural healing, transmural remission, and transmural response are evolving and are currently based on expert consensus. However, ongoing studies are working on a prospective validation of these terms. Research has shown that achieving deeper control, particularly in CD, is associated with better long-term outcomes, specifically, with lower rates of surgery, hospitalization, and therapy escalation.[28,29]

Transmural healing refers to the healing of all layers of the bowel in both CD and UC, recognizing that UC does involve layers beyond the mucosal surface **(Figure 1)**. Proposed definitions of transmural response and remission have been described for CT, MRI, and IUS **(Table 1)**.[30] In a systematic review by Geyl et al, transmural remission for any modality was proposed as the improvement of bowel wall thickness to <3 mm for the small bowel and <4 mm for the colon.[30] The authors suggest that the definition of transmural remission should consider both imaging for full thickness assessment and endoscopic evaluation in order to confirm the achievement of transmural remission. Furthermore, the optimal timing for evaluating transmural healing has been found to be at week 26 or 52 for CD, and at week 12 or 14 for UC, also recognizing that some patients will obtain a much quicker response.

Treatment response has been evaluated and in CD it is described as a reduction in bowel wall thickness by >25%, or >2.0 mm, or >1.0 mm, along with one reduction in the colour Doppler signal grade.[31] Transmural remission is defined as normalization of bowel wall thickness, and normalization of all IUS parameters (increased blood flow, loss of bowel wall stratification, and inflammatory mesenteric fat).[32]

For UC, definitions of transmural remission utilized a bowel wall thickness cut off of <3 mm for the colon and an absent colour Doppler signal.[31] Transmural healing data is evolving in UC, particularly as it is being recognized that wall layers other than the inner mucosa are involved. Colectomy for refractory UC is associated with thickening of the muscularis mucosae and increased fibrosis, while submucosal fibrosis is related to the severity of intestinal inflammation.[33] Given that endoscopic biopsies of the mucosa are unable to predict the quantity of fibrosis or muscularis mucosae thickening,[33] IUS is an excellent modality to further understand the composition of the colon, and to study the definitions of transmural remission. IUS is the only imaging modality that is able to detect the five distinct layers of the bowel **(Figure 2)**. Therefore, IUS offers sizable advantages over CT and MR for both clinical evaluation and research.

Current Evidence for Therapies Achieving Transmural Healing on IUS

Emerging data suggests that successful therapies should be able to achieve endoscopic remission and achieve transmural improvement. STARDUST, a randomized controlled trial evaluating a treat-to-target approach for ustekinumab in CD, has utilized IUS to assess the efficacy of treatment.[32] The trial has shown that a transmural response was present as early as week 4 after treatment initiation, and that 46.3% of patients had a progressive IUS response, and 24.1% had achieved transmural remission at week 48.[32]

A prospective study using IUS at baseline and at 6 months, with at least 12 months of follow up after starting a new medication, has shown that transmural healing can predict more favourable long-term outcomes than those of mucosal healing in CD.[34] Furthermore, 32% patients achieved transmural healing (bowel wall thickness <3 mm with normalization of stratification, absent hypervascularization, inflammatory fat, and abscesses/fistula) while 40% achieved mucosal healing; notably, both parameters showed poor correlation with each other (Cohen's $\kappa = 0.387$; $p<0.05$).[34] Transmural healing was an independent predictor of being steroid-free, requiring less drug escalation, and fewer hospitalizations.[34]

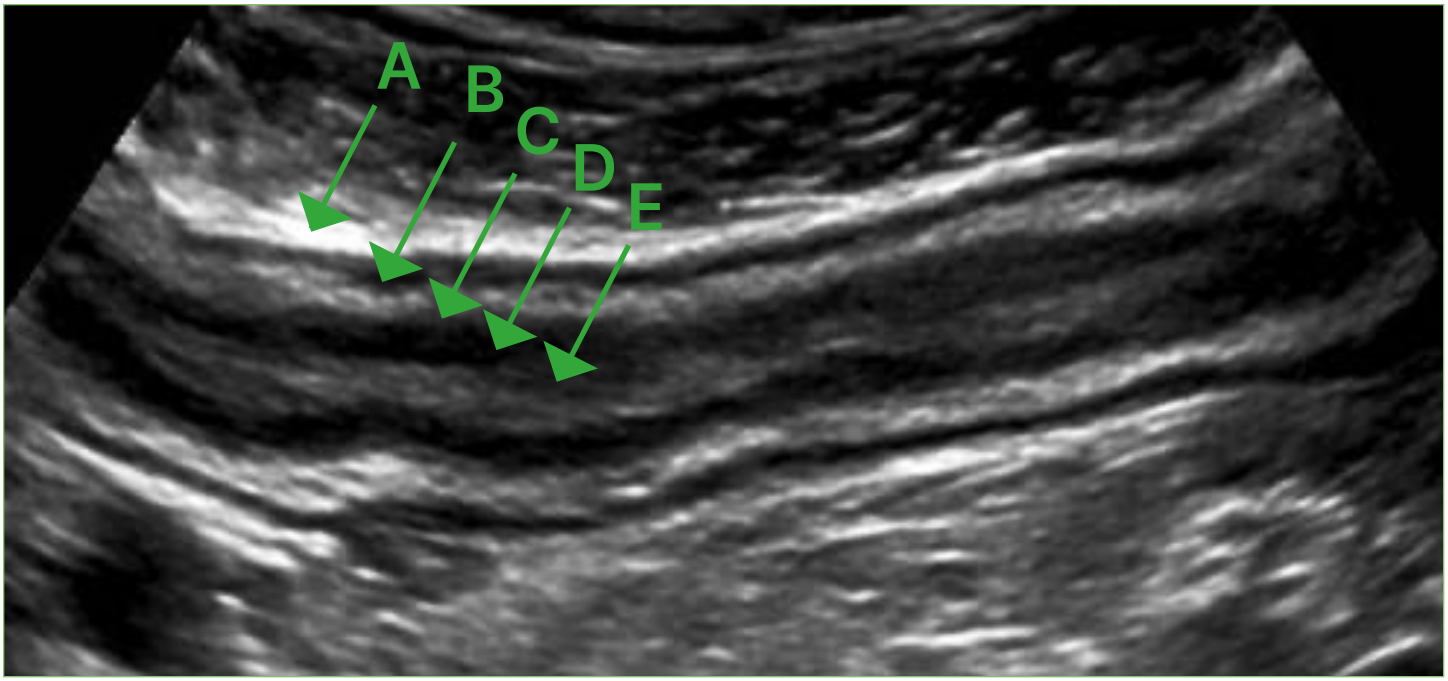

Figure 2. Normal terminal ileum with five wall layers in longitudinal view. Layers alternate in echogenicity. **A.** serosa, **B.** muscularis propria (hypoechoic), **C.** submucosa (echogenic), **D.** muscularis mucosa (hypoechoic), and **E.** mucosa interface; *courtesy of Cathy Lu, MD, MSc*

In UC, a recent prospective cohort study conducted in 2022 has demonstrated that IUS is accurate for determining endoscopic response and remission in patients with moderate-to-severe UC who started treatment with tofacitinib.[5] Patients received IUS and endoscopy at baseline and at week 8. A bowel wall thickness of 2.8 mm (area under curve [AUC] of 0.87) matched endoscopic remission (endoscopic mayo score and Robarts Histopathologic Index), and a decrease of 32% (AUC of 0.87) was able to detect an endoscopic response.[5]

A recent study conducted in 2022 was the first to predict disease progression in UC using the Milan Ultrasound Criteria (MUC), which is a validated transmural IUS score. The study findings suggest that a baseline transmural assessment using MUC could predict a negative disease course, hospitalization, and colectomy.[35]

Although a deeper level of disease control in the form of transmural healing may be optimal, questions remain regarding the following: the appropriate timing of transmural healing; acceptable ranges of healing, with some patients experiencing slower healing; whether an overall improvement in bowel wall thickness along with residual thickness of certain layers, such as the submucosae is meaningful; and whether transmural healing of the small bowel and colon are different. Furthermore, whether strictures can achieve remodelling and transmural healing is an area of interest. Notably, the first anti-fibrotic agent, Agomab-129, is currently available in Canada for Crohn's Disease, and is being evaluated in a phase 2a global clinical trial. Overall, bowel wall thickness is the most frequently described parameter for assessing transmural healing. Future research is required to develop standardized and validated definitions of transmural healing in diagnostic imaging to gain an understanding of the true impact on patient disease control.

Future Frontiers of IUS

A. Artificial Intelligence

The field of artificial intelligence is rapidly growing across all types of cross-sectional imaging. In IUS, machine-learning models have been validated to distinguish between IUS images of normal bowel wall and bowel wall thickening, which is the best surrogate for active disease and inflammation.[36] This machine learning module was trained on a dataset of 1008 images (50% abnormal images, 50% normal images). The model demonstrated high accuracy, sensitivity, and specificity for detection of bowel wall thickening at 90.1%, 86.4%, and 94%, respectively. In addition, the network exhibited an average area under the receiver operating characteristic curve of 0.9777.[36]

B. Future Directions and IUS Advancements in CD Complications

IUS easily detects the morphologic alterations of CD strictures **(Figure 3)**. An expert consensus panel has provided definitions, diagnosis, and treatment targets for anti-fibrotic stricture therapies in CD using CTE and MRE.[37] The three key parameters for small bowel strictures on CT and MR are bowel wall thickness, luminal apposition, and pre-stenotic diameter. Recently, these same parameters for IUS have been evaluated in an international consensus using a modified RAND/University of California Los Angeles process led by the Stenosis Therapy and Anti-Fibrotic Therapy (STAR) consortium. These statements

Figure 3. Longitudinal view of neo-terminal ileal stricture with bowel wall thickness 8.9mm, luminal apposition of 1.1mm, and pre-stenotic dilation of 4.5cm; *courtesy of Cathy Lu, MD, MSc*

will lead to the formation of an imminent IUS index for validation and use in clinical trials.

An emerging area of interest in fibrostenotic CD is the relationship of IUS parameters and each individual bowel layer in comparison with histopathology obtained from small bowel resection samples.[38,39] Considering that strictures contain varying degrees of inflammation and fibrosis, understanding the imaging correlates with stricture composition may be of use to assess who can benefit most when considering resection. Studies have shown that distinct IUS findings such as the submucosal layer brightness/echogenicity,[39] mucosal layer thickness,[39] and submucosa spiculates extending toward the mesentery are associated with fibrosis in small bowel CD strictures.[38]

Regarding peri-enteric complications, a recent systematic review, which analyzed 60 of 1498 identified studies, demonstrated that IUS is accurate for diagnosing inflammatory masses and fistulas, with a sensitivity of 0.90 and 0.87, respectively and a specificity of 0.67 and 0.95, respectively.[40]

Conclusions

Timely and accurate measures of inflammation in IBD during routine follow-up are essential to inform clinical decision-making to ensure patients reach therapeutic targets. IUS offers physicians timely information on the structure and function of the bowel including bowel motility, while for the patient, it offers a patient-centred, safe, alternative means of routine monitoring in the clinic. The progress of IUS is rapidly advancing in several areas. These include the development of validated indices, understanding its use in transmural healing and response to therapy, its correlation with histopathology, its integration with artificial intelligence, and its expanding role in training and education. IUS is currently playing a prominent role and is being interpreted centrally, similar to endoscopy, in multi-centre international studies involving both approved and anticipated biologic therapies, and small molecules. This points to a future for IUS that is both exciting and incredibly bright.

Key Takeaways:

1. Gastroenterologist-led intestinal ultrasound improves patients' knowledge of their disease and provides accurate real-time measures of activity in IBD.
2. Validated intestinal ultrasound scoring systems in both UC and CD are available.
3. Intestinal ultrasound utilization is rapidly growing in Canada and the United States, as more gastroenterologists are training and becoming certified in the skill.
4. As intestinal ultrasound provides reproducible and repeatable point-of-care assessment of IBD activity and response to therapy, its use has expanded into clinical trials.

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