Role of Endoscopic Ultrasound in the Diagnosis and Management of Complications of Inflammatory Bowel Disease

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KEYWORDS

• Endoscopic ultrasound • IBD • Ulcerative colitis • Crohn's disease • EUS

KEY POINTS

- Inflammatory bowel disease-related complications such as abscesses, fistulae, and dysplasia are associated with a decreased quality of life, requirement for surgery, and increased morbidity.
- Endoscopic ultrasound (EUS) can provide mucosal as well as transmural evaluation of the bowel wall, and it plays a role in the diagnosis as well as management of inflammatory bowel disease-related complications.
- EUS can accurately characterize fistulae and abscesses and can guide treatment planning.
- EUS can assess for depth of inflammation helping differentiate ulcerative colitis from Crohn's disease as well as helping assess treatment response.
- Interventional EUS paves the path for EUS-guided treatment of Crohn's-related abscesses and strictures thereby avoiding surgery.

INTRODUCTION

Inflammatory bowel disease (IBD) is an autoimmune disease that results in chronic inflammation of the gastrointestinal (GI) tract and is subdivided into Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis.[1] IBD-related complications can occur in up to 60% of patients, and up to 80% patients with CD will undergo surgery during their disease course as a result of these complications.[2–4]

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An accurate diagnosis of IBD can be challenging and requires the corroboration of clinical, endoscopic, radiologic, and histopathological findings. Symptoms usually suggest a diagnosis of IBD; however, this is commonly followed by a colonoscopy. A colonoscopy allows the visual and histopathological examination of the mucosal surface. However, it is limited by its inability to assess layers deeper to the mucosa, which is important to identify a transmural process as seen in CD as opposed to an isolated mucosal involvement of UC.[5] As a result of transmural inflammation, abdomino-pelvic abscesses can occur in 10% to 30% of patients.[6] Patients with inflammatory bowel are also at a higher risk of developing dysplasia and malignancy within the inflamed areas.[7,8]

Computed tomography (CT), MRI, and intestinal ultrasound (IUS) are cross-sectional techniques that can assess the outer layers of the GI tract and have been used to diagnose such complications beyond the mucosa in IBD.[9] However, these modalities have certain limitations. The image quality obtained by IUS can be influenced by abdominal circumference, presence of intestinal gas, and motion artifacts.[10] CT scans carry the limitation of exposure to ionizing radiation limiting its use for younger individuals and during pregnancy. Optimized colonic evaluation by magnetic resonance enterography (MRE) requires purgation and luminal distention, which are omitted from routine MRE protocols. Thus, accuracy of MRE for evaluating colonic disease is inferior as compared to colonoscopy.[11] Endoscopic ultrasound (EUS) is a minimally invasive technique that combines endoscopy and ultrasound to visualize the layers of the GI wall and adjacent structures. It provides high-resolution images of the GI wall layers and helps to assess for transmural inflammation, fibrosis, and complications associated with IBD such as fistulae, strictures, and abscesses.[12] Additionally, evolution of therapeutic EUS has allowed minimally invasive therapies for these complications such as EUS-guided drainage of pelvic abscesses and EUS-guided creation of anastomosis to bypass strictures.

This review focuses on the role of EUS in the diagnosis, prognosis, and management of IBD-related complications. We also review the technical and clinical considerations of the applicability of EUS in individuals with IBD. We aim to summarize the pivotal literature that has emerged in this field.

ENDOSCOPIC ULTRASOUND TECHNICAL ASPECTS

Colorectal EUS is typically performed using a radial or linear echoendoscope or using EUS miniprobes passed through conventional colonoscopes. Previously, echoendoscopes were side-viewing instruments. Their application in the lower GI tract was limited to the rectum and anal canal.[13] With the advent of forward-viewing linear echoendoscope, EUS-guided diagnostics and therapeutics are possible throughout the entire colon.[14] Echoendoscopes typically use frequencies of 7.5 and 12 MHz, and the frequency used in miniprobes can reach up to 20 MHz allowing for a detailed examination of the bowel wall in a 5 layer pattern[15] (**Fig. 1**).

EUS appearance of these layers from inner to outermost is as follows: layer 1—hyperechoic mucosa, layer 2—hypoechoic muscularis mucosae, layer 3—hyperechoic submucosa, layer 4—hypoechoic muscularis propria, and layer 5—hyperechoic serosa. The circular fibers of muscularis propria get thicker around 4 cm from the anal verge and continue as the thick hypoechoic internal anal sphincter (IAS). The intersphincteric space appears as alternating hypoechoic and hyperechoic areas and separates the IAS from the hyperechoic external anal sphincter (EAS; see **Fig. 1**). While performing EUS examination in the rectum, anatomic landmarks seen in male and female individuals differ. In the midrectum, the urinary bladder, seminal vesicles, and

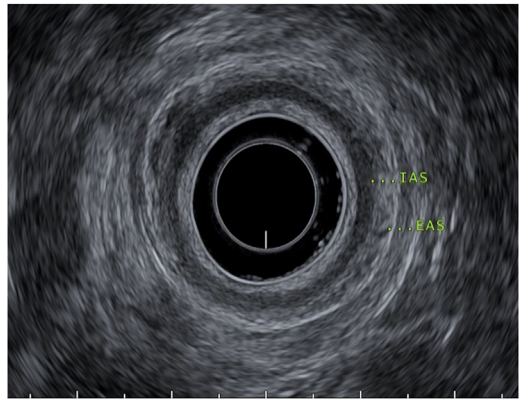

Fig. 1. Endosonographic appearance of the normal internal and external anal sphincters.

uterus are seen as landmarks at around 6 to 7 cm from the anal verge. The lower part of the rectum is identified by the prostate in male individuals and vagina in female individuals. At the level of the anus, the IAS and EAS are imaged as landmarks. The conventional EUS system is preferred while examining a large colonic lumen, whereas to examine a smaller lumen, the use of a EUS miniprobe can be a practical and effective alternative.

ROLE OF ENDOSCOPIC ULTRASOUND IN MONITORING ACTIVITY OF INFLAMMATORY BOWEL DISEASE

EUS has the capability to characterize the layers of the GI wall and assess local lymphadenopathy, which allows simultaneous assessment of the mucosa as well as the deeper layers of the bowel wall during endoscopy. IBD is currently treated not only to achieve endoscopic remission but also to achieve transmural control of inflammation, which can be measured by either cross-sectional imaging or EUS.[16] EUS allows for simultaneous evaluation of the mucosal surface along with the thickness of the various layers of the bowel wall achieving a transmural assessment efficiently. It can also assess loss of bowel wall stratification, vascularity of the bowel wall, extramural inflammatory fat, and adjacent lymph nodes. Recently, contrast-enhanced EUS has been shown to predict early response to therapy and long-term success.[17] Thus, EUS has emerged and has been described as a useful tool in assessing disease activity in IBD.

Role of Endoscopic Ultrasound in Crohn's Disease

Transmural healing has been recognized as a crucial measure of disease activity especially in CD.[16] Majority of studies describe wall thickness as a measure of ongoing disease activity with increased wall thickness corresponding to active inflammation. Soweid and colleagues described EUS findings in 11 patients with CD and found that patients with active disease had a higher total wall thickness (TWT) than healthy controls ($P < .001$). In CD, loss of endosonographic layer structure correlated with disease activity score ($r = -0.8$, $P = .003$), and TWT correlated with the severity of histologic changes ($r = 0.62$, $P = .04$).[18] Ellrichmann and colleagues reported on 37 patients with CD and found that patients with active inflammation had a significantly higher TWT as compared to healthy controls and patients with IBD in remission. Active CD was seen to cause thickening of the submucosa with a nearly normal mucosa and

muscularis propria. Notably, echo-poor paracolonic lymph nodes were present in 74% patients with CD and none in patients with UC.[19] Recently, the role of through-the-scope EUS catheter (Olympus UM-3R-3, Olympus Surgical Technologies America & Olympus America Inc., Westborough, MA) was evaluated in a prospective observational study. This study also demonstrated the correlation of increased TWT with active disease (3.7 mm vs 2.1 mm, $P < .01$). In CD, the increased thickness was observed mostly in the submucosa. The most notable advantage of through-the-scope miniprobes is their utility among patients with strictures where standard echoendoscopes may not be useful. Their 20 MHz frequency also provides great detail and resolution of the bowel wall layers at the cost of depth of visualization.[20]

Role of endoscopic ultrasound in complications of Crohn's disease

Development of fistulas, strictures, and abscesses is an established complication of CD and can lead to significant morbidity and impaired quality of life. Long-standing Crohn's colitis has a 2 to 3 times higher risk of colorectal cancer as compared to the general population.[21] EUS has emerged as a crucial tool in the diagnosis, staging, and management of these complications. Key studies investigating the role of EUS in CD are summarized in **Table 1**.

Endoscopic ultrasound for fistulizing Crohn's disease. Patients with CD may develop fistulas between 2 bowel segments, between a bowel segment and skin, or between a bowel segment and an adjacent organ such as vagina, bladder, or uterus. The incidence of fistulizing disease can range from 17% to 50%.[22–24] Over half of these fistulas are perianal in location that cause significant discomfort and impairment in quality of life.[23] Optimal anatomic characterization, understanding relationship with neighboring anatomic structures, accurately classifying them into simple or complex fistulas is crucial to plan treatment and prevent recurrence.[25]

Both linear and radial probes can be used for EUS in the anorectal region. The radial probe may work well in the anorectal area for better characterization of sphincter anatomy, whereas a linear probe can help facilitate obtaining biopsies and performing therapeutic interventions.[26,27] Whenever possible linear and radial EUS should be performed in conjunction for optimal inspection of the area of interest. Fistulas on EUS are seen as a continuous linear hypoechoic structure in the subepithelial area, a defect in the IAS, and a hypoechoic area in the intersphincteric space. Gas bubbles may be seen as small hyperechoic foci within these hypoechoic structures. The internal opening can be identified as the hypoechoic focus that abuts the internal sphincter (**Fig. 2**).

The use of contrast agents such as hydrogen peroxide can improve identification and delineation of fistulae on EUS. Contrast agents can be injected during the EUS procedure through the external fistulous opening, which creates hyperechoic bubbles facilitating fistula visualization. The use of contrast also improves the assessment of location of fistula in relation with the anal lumen and sphincters.[28] In a prospective study of 80 patients with anal fistula, hydrogen peroxide-enhanced EUS identified the internal opening of the fistula in 94% cases and whether the fistulous tract was linear or curvilinear in 95% cases. The level of fistula by EUS correlated with surgical findings in 85% of patients.[29]

EUS has shown excellent performance for the assessment of fistulas and is well tolerated by patients.[30] It has the advantage that it can assess the endoscopic mucosal pattern and internal fistulous orifice during the examination. MRI and examination under anesthesia (EUA) are other commonly used modalities for fistula evaluation. However, EUA can be inaccurate in up to 10% of cases due to the scarring and induration associated with perianal CD and MRI has economic considerations.[31,32] Orsoni and colleagues[33] compared rectal EUS, MRI of pelvis, and EUA among 22

Table 1
Key studies summarizing role of endoscopic ultrasound in Crohn's disease

Study	Primary Objective	Key Findings
Schwartz et al,[32] 2001	EUS compared with MRI and EUA for the evaluation of perianal fistulae	The accuracy of EUS was 91%, (95% CI 75%–98%), for MRI was 87% (95% CI 69%–96%), and for EUA was 91% (95% CI 75%–98%). Accuracy reached up to 100% when 2 modalities were used in conjunction
Schwartz et al,[40] 2005	Role of EUS to guide medical and surgical therapy in fistulizing CD	EUS identified persistent fistula activity (even after cessation of drainage) in 48% patients preventing premature seton removal. Among patients with fistula in-activity, 64% were able to discontinue infliximab without fistula recurrence
Spradlin et al,[38] 2008	EUS used to guide medical and surgical decision-making in fistulizing perianal CD (RCT)	Patients divided in 2 groups based on whether decisions (seton removal, need for repeat surgery) will be based on EUS findings or surgeons' discretion. Complete cessation of fistula drainage achieved in 80% (EUS group) vs 20% (control). 30% (control) vs 10% (EUS) patients had persistent/recurrent fistula and/or abscess leading to surgical failure
Ellrichmann et al,[19] 2014	EUS to differentiate between CD and UC	Increased TWT had a high-positive predictive value for active inflammation. Active CD had significant thickening of submucosa with near normal mucosa and muscularis propria. Paracolonic LNs were detected in active CD
Wiese et al,[37] 2015	EUS to guide medical therapy in perianal CD (RCT)	Patients getting EUS-guided fistula assessment had more rapid escalation of ADA dosing. At 24 wk, drainage cessation was achieved in 78% in EUS group vs 27% in control group ($P<.05$)
Nguyen et al,[20] 2023	TTS EUS miniprobes to differentiate active from inactive colonic CD	Rectal submucosal thickness cutoff of 1.1 mm was 100% sensitive and specific to identify active CD

Abbreviations: ADA, adalimumab; CD, Crohn's disease; EUA, examination under anesthesia; EUS, endoscopic ultrasound; LN, lymph node; TTS, Through-the-scope.

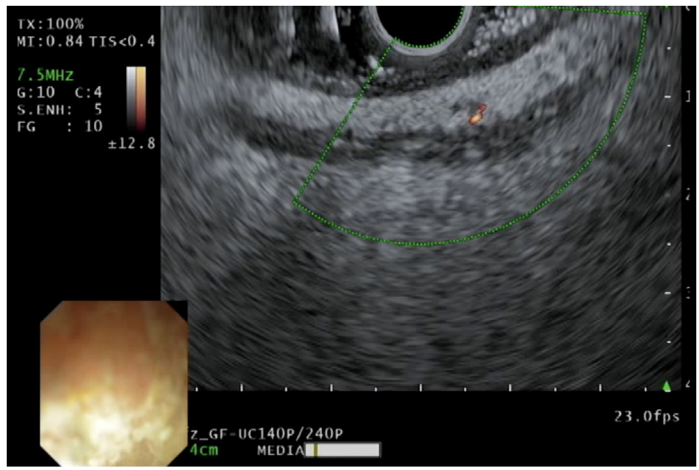

Fig. 2. Endosonographic appearance of transmural thickening of rectal wall in active ulcerative colitis.

patients with CD perianal fistulae and found that rectal EUS was the most sensitive imaging modality for perianal fistulae. EUS and MRI findings corroborated with surgical findings 82% and 50% of times, respectively. In a landmark study by Schwartz and colleagues,[32] EUS, MRI, and EUA were compared for the evaluation of perianal fistulas in patients with CD. The accuracy of EUS was 91% (95% CI 75%–98%), for MRI was 87% (95% CI 69%–96%), and for EUA was 91% (95% CI 75%–98%). Accuracy reached up to 100% when 2 modalities were used in conjunction.

A meta-analysis of 4 studies comparing EUS and MRI in assessing perianal fistulas revealed comparable sensitivities for both imaging techniques, standing at 87%. However, the findings indicate that both EUS (with 43% specificity) and MRI (with 69% specificity) exhibit relatively low specificity when it comes to confirming the diagnosis and imaging modalities should be used in conjunction with EUA for accurate treatment planning.[34,35] A limitation of EUS is that it cannot be used in the presence of anorectal strictures, and it is mainly helpful to evaluate low fistulae. Thus, more than one diagnostic modality should be used as each of them has its own drawbacks and are complementary when used together. Transperineal ultrasound (TPUS) is a simple, noninvasive, and cost-effective investigation can be performed using convex or high-resolution lineal probes to evaluate for fistulae and abscesses. In a study of 46 patients with confirmed or suspected perianal CD, TPUS was able to assess 45 out of 53 fistulae and all perianal abscesses (2 horseshoe, 4 deep, and 4 superficial) that were confirmed by EUS. TPUS is, thus, an effective investigation modality especially when MRI and EUS are either not available or contraindicated.[36]

Studies have demonstrated that the applicability of EUS for the evaluation of perianal penetrating CD was technically feasible and well tolerated in most patients. EUS performed accurate characterization of fistula morphology, was used to guide treatment decisions, and helped identify patients who might benefit from additional surgical interventions and/or anti-tumor necrosis factor (TNF) dose escalation.[37] The use of EUS to guide medical and surgical therapy for perianal CD has shown improved rates of cessation of fistula drainage.[37,38] Spradlin and colleagues[38] in their randomized controlled trial (RCT) found that among 10 patients with fistulizing perianal CD after maximizing medical therapy and initial surgical intervention, rates of fistula drainage were lower (20% vs 80%) when EUS findings were used to guide decisions regarding surgical reinterventions.

Wiese and colleagues[37] in their RCT found that when patients had their medical therapy adjusted based on EUS findings, they more rapid escalation of adalimumab therapy and led to faster healing of fistulae. In a retrospective analysis of 21 patients, Schwartz and colleagues used EUS to monitor fistula activity among patients undergoing either medical or surgical therapy. Serial EUS examinations were performed, and findings were used to guide therapy such as Seton removal, discontinuation of infliximab, and/or antibiotics. They found that EUS could identify a subset of patients with negligible fistula activity who could safely discontinue infliximab with a very low risk of recurrence of fistula drainage. EUS to monitor healing after seton placement has shown to improve outcomes even among pediatric patients. Rosen and colleagues[39] demonstrated that when EUS was able to identify peri-seton inflammation and identified patients who required continued seton drainage and also who needed step-up medical therapy. EUS also identified fistulous tracts that were superficial enough that the risk of inadequate drainage and/or abscess formation was low and were treated with medical therapy alone avoiding surgery.[40] EUS, however, can present limitations to identify suprasphinteric and posterior fistulous openings and trajectories and is unable to be performed in patients with tight strictures of the anorectum.[25]

Newer ultrasonographic techniques allow 3 dimensional reconstruction of the anal region during EUS. Zawadzki and colleagues reported in patients with perianal CD, fistulae have a characteristic EUS appearance, resembling hypoechogenic tract encompassed by hyperechogenic area with a thin hypoechogenic margin—"Crohn's Ultrasound Fistula Sign" (CUFS). CUFS was identified among 20 out of 29 patients with fistulizing CD. CUFS had a positive and negative predictive value of 87% and 93%, respectively, for CD-associated fistulae.[41] Lahat and colleagues[42] demonstrated that EUS helped in medical and surgical decision-making in 86% of patients with perianal CD. However, EUS has a few limitations such as interobserver variability, complex learning curve and anatomic challenges such as anorectal strictures that may hinder the examination.[43]

Role of endoscopic ultrasound in Crohn's disease-associated abscesses. Pelvic and abdominal abscesses arise spontaneously in approximately 10% to 30% of patients with CD during the course of their illness.[44] Anorectal abscesses include perianal and perirectal abscesses. Perianal abscesses are superficial and can be diagnosed on physical examination as painful, tender, and fluctuant swellings near the anal orifice. Perirectal abscesses, in contrast, are deep and form a tract that extends from the rectum into the pelvis. They can be found in various locations in the pelvis. Perianal and perirectal abscesses associated with CD are diagnosed based on imaging (**Fig. 3**A). They are strongly associated with fistula formation and studies have shown that abscess drainage while overlooking the associated fistula leads to a high risk of abscess recurrence.[45]

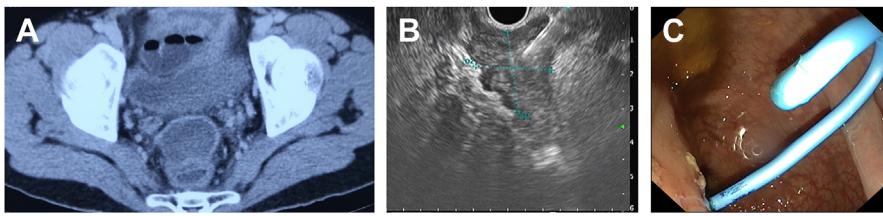

Fig. 3. (*A*) Computed tomography pelvis revealing perianal abscess in a patient with Crohn's disease. (*B*) Endosonographic appearance of needle puncture of pelvic abscess. (*C*) Endoscopic ultrasound-guided abscess drainage using plastic stent.

EUS-guided drainage using plastic and metal stents has been shown to a safe and effective modality for drainage of abdomino-pelvic abscesses, pancreatic fluid collections, gallbladder, as well as the biliary tract.[46–48] EUS has been used to assist endoscopic diagnosis and drainage of abdominopelvic abscesses among patients with CD. EUS helps with an accurate delineation of abscess anatomy and relation with colon wall. EUS-guided puncture with aspiration or drain placement leads to an effective and adequate abscess drainage (**Fig. 3**).

A handful of case reports have so far been published outlining the use of EUS for abscess drainage in patients with CD. Mohy-ud-din and colleagues[49] described a case of a 44 year old man with a history of ileocolonic CD since 2015 and B-cell lymphoma of the skull who underwent a laparoscopic colectomy and end ileostomy complicated by small bowel perforation requiring small bowel resection and placement of biomesh. Postoperative imaging revealed large perigastric abscess not amenable to percutaneous drainage. EUS-guided drainage using a lumen-apposing metal stent (LAMS) was performed and resulted near-total resolution of the abscess.

Teoh and colleagues[50] described a case of 40 year old woman with a known history of CD and 5 years previously had undergone total colectomy and end ileostomy. She was admitted for acute urinary retention and was found to have a large rectal-stump mucocele. EUS-guided transrectal drainage using 2 plastic stents was performed with complete resolution of the mucocele 1 month later. Simons-Linares and colleagues[51] published a case of a persistent left subdiaphragmatic abscess in a patient with CD complicated by pneumothorax after failed CT-guided drainage that was successfully and uneventfully drained endosonographically using a LAMS. Hadithi and colleagues[52] and Zator and colleagues[53] in their case-series describe one patient with CD who underwent successful EUS-guided perirectal abscess drainage each.

Role of endoscopic ultrasound in Crohn's disease-associated strictures/stenosis. Patients with CD are known to be at risk of developing strictures throughout their GI tract. Up to 20% of patients with CD present with stricturing disease and over 50% patients can develop strictures during their lifetime.[54,55] These can be treated medically in case of inflammatory strictures or need endoscopic or surgical therapy for fibro-stenotic strictures. EUS has an emerging role in stricturing CD and there have been reports of EUS-guided interventions to treat Crohn's-related strictures. Monino and colleagues[56] reported a case where the patient had undergone multiple surgeries for stricturing CD and presented with a duodenal stricture. EUS-guided gastro-jejunostomy was performed using a LAMS where the patient was able to resume modified diet in 48 hours after the procedure.

Another report by Manski and colleagues[57] describes the use of a 20 $\times$ 10 mm LAMS to create a gastro-jejunostomy to treat a duodenal CD-related stricture. Even this patient had severe disease requiring multiple previous surgeries for strictures leading to short gut syndrome. EUS-GJ is technically feasible to bypass the strictured bowel segment in poor surgical candidates with stricturing CD; however, more data are needed prior to its adoption as a treatment modality.

Role of Endoscopic Ultrasound in Ulcerative Colitis

UC is generally considered to be limited to the mucosal layer of the colon. However, more severe inflammation extends to deeper layers of the bowel wall and can cause submucosal fibrosis that cannot be evaluated by endoscopy alone. EUS provides accurate measurement of thickness of the mucosal and submucosal layer along with thickness of the total intestinal wall, which has shown to assess the presence of transmural inflammation. Experience with EUS in UC is quite limited but studies have

explored its utility in assessing and monitoring disease activity, assessing prognosis, predicting response to therapy, and so on. Key studies investigating the role of EUS in UC are summarized in **Table 2**.

Endoscopic ultrasound for monitoring disease activity in ulcerative colitis

Similar to patients with CD, the role of EUS in assessing the disease activity in UC has been investigated. A consistent finding across all studies is that increased TWT correlated with active inflammation.[18–20] In active UC, EUS reveals hypoechoic changes along with wall thickening, which are not seen during times of remission. These changes in UC have been classified based on severity of disease as follows: UC-M, thickening of whole wall with preserved structure; UC-SM, hypoechoic changes reach superficial part of third layer with increased TWT; UC-SM deep, hypoechoic changes reach deep part of third layer with increased TWT; UC-MP, hypoechoic changes reach fourth layer with increased TWT; and UC-SS/SE, hypoechoic changes penetrate through the fourth layer with increased TWT. The authors suggest close monitoring for patients exhibiting changes indicative of UC-SM deep, UC-MP, or UC-SS/SE, as a significant number of those who underwent surgery were in these stages[58] (**Fig. 4**).

Studies have showed that in active UC, the greatest increase in wall thickness was observed in the mucosal layer and not in the submucosa as observed with CD.[19,20] Dagli and colleagues[59] observed the presence of arterial or venous capillary flow in the submucosal layer among patients with active UC as opposed to patients in remission. Cutoff values of TWT of 5.36 mm, mucosal thickness of 2.23 mm, and submucosal thickness of 2.34 mm were effective in differentiating active disease from patients in remission. In the study by Rana and colleagues,[60] 48 patients with UC were prospectively studied. They found that mean TWT as measured by EUS was significantly higher in patients with moderate–severe UC as compared to patients with mild disease or those in remission. They found that EUS-guided measurement of TWT, mucosal and submucosal wall thickness, and loss of intestinal wall stratification correlated with clinical and endoscopic severity of patients with UC.

Through-the-scope EUS miniprobes have been studied and a cutoff value of rectal mucosal thickness of 1.1 mm and TWT of 3 mm have been shown to be effective to differentiate active from inactive UC.[20] Several other studies have demonstrated that EUS findings such as increased wall thickness, loss of bowel wall stratification, and the presence of arterial or venous blood flow in the submucosal layer have been used to differentiate active from inactive disease.[18,61]

Endoscopic ultrasound for dysplasia surveillance in ulcerative colitis

Patients with long-term UC are known to be at an increased risk for UC-associated neoplasia arising from inflamed mucosa.[62] Dysplasia and intraepithelial neoplasia are frequently missed during routine white-light endoscopic examinations and at the same time, random biopsies have a low yield for dysplasia detection.[63] Studies have explored the utility of EUS in detecting dysplasia among patients with UC. Shimizu and colleagues[7] reported the first case report that described the use of EUS to diagnose an invasive rectal carcinoma in a patient with ulcerative pancolitis. Elrabat and colleagues[64] conducted a cross-sectional analysis to evaluate the value of EUS in prediction of dysplasia in UC. In their study of 57 patients with UC, they evaluated how well could TWT predict severe UC and dysplasia. They demonstrated a 75% sensitivity and 94% specificity for detecting dysplasia at 10 cm from the anal verge by using a TWT cutoff of greater than 5.05 mm. However, these studies have been limited by small sample sizes, inadequate control groups, and thus their generalized applicability has been limited.

Table 2
Key studies summarizing role of endoscopic ultrasound in ulcerative colitis

Study	Primary Objective	Key Findings
Higaki et al,[66] 2002	EUS to predict relapse in UC	Patients without relapse for 1 mo studied and followed for 1 y; rectal wall thickness (1st–3rd layer) was 2.73 mm in patients who relapsed vs 1.79 in nonrelapse group, $P = .0001$
Ellrichmann et al,[19] 2014	EUS to differentiate between CD and UC	Increased TWT had a high-positive predictive value for active inflammation. Active UC had significant thickening of mucosa with near normal submucosa and muscularis propria. Paracolonic LNs were not detected in active UC
Kobayashi et al,[65] 2015	Role of EUS to assess depth of UC-associated tumors	Accuracy of EUS to ascertain depth of tumor was 94%, downstaged one tumor as ImCa instead of Ca with SMI
Rana et al,[60] 2021	48 patients prospectively studied to identify role of EUS in UC	TWT and endoscopic severity had a strong correlation, $P = .001$, correlation coefficient 0.55. Loss of intestinal wall stratification correlated with endoscopic severity ($P < .05$; $r = 0.342$)
Jin et al,[71] 2022	Validation of EUS-UC score (consisting of TWT, depth of inflammation, hyperemia), each component scored from 0 to 3 with 3 being highest	Among 79 patients with UC, the EUS-UC score positively correlated with disease severity as measured by the modified Truelove and Witts score and Mayo score ($P<.05$). EUS-UC score also decreased significantly at 2 and 6 mo after treatment
Ellrichman et al,[17] 2024	CE-EUS in UC	CE-EUS used to quantify vascularity by using "rise time" and "time to peak" parameters. Patients responding to therapy had a significant decrease in TWT at 2-wk ($P = .04$) from baseline whereas nonresponders had no significant change in TWT. Time to peak had significantly normalized in responders ($P = .001$) and showed no alterations among nonresponders ($P = .9$). CE-EUS changes were measured at just 2 wk when endoscopic mayo score did not exhibit significant changes

Abbreviations: CD, Crohn's disease; ImCa, intramucosal carcinoma; LN, lymph node; SMI, submucosal invasion; TWT, total wall thickness; UC, ulcerative colitis.

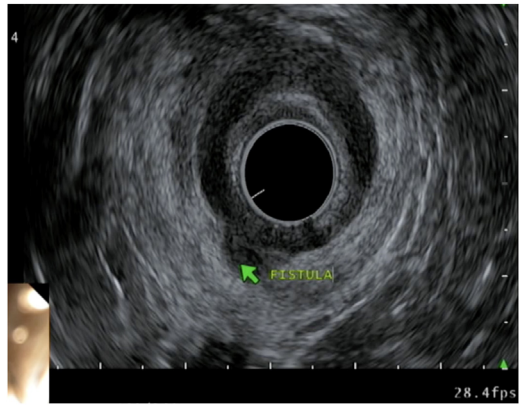

Fig. 4. Endosonographic appearance of a low intersphincteric fistula.

Kobayashi and colleagues[65] evaluated the role of EUS to determine the depth of invasion and extent of UC-associated tumors. In their small study of 13 patients with 16 UC-associated tumors, EUS was able to accurately estimate depth of invasion in 94% (15 out of 16) tumors, and 1 tumor was understaged as intramucosal carcinoma when it was carcinoma with submucosal invasion. This helps identify patients who may benefit from minimally invasive endoscopic resection of tumors as compared to those patients who will need surgery.

Role of endoscopic ultrasound in monitoring treatment response

EUS features have been studied to predict treatment response and prognosis among patients with UC. Higaki and colleagues[66] reported that EUS-assisted measurement of rectal wall thickness could predict relapse in UC. Patients who had relapse at 1 year had a significantly higher rectal wall (first to third layer) thickness at the beginning of the study (2.73 vs 1.79 mm, $P = .0001$). Watanabe and colleagues[67] reported that when patients with steroid refractory disease were treated with cyclosporine A, the patients who responded to therapy had a higher rectal mucosal layer thickness prior to treatment as compared to nonresponders ($P < .05$). Thus, it is unclear whether pretreatment increased TWT portends a favorable prognosis or not. Yoshizawa and colleagues[58] demonstrated that when the inflammation affected the muscularis propria or deeper as per EUS, there was an increased risk of colectomy. Among patients who failed corticosteroid therapy, 67% patients had inflammation to muscularis propria or beyond, whereas among patients who responded to medical management, only 19% showed deep inflammation.

To standardize EUS-assisted evaluation of patients with UC, scores such as the Tsuga score and EUS-UC score have been developed and validated in studies.[68,69] This score assigns a value from 0 to 3 based on the EUS features of total wall thickening, hyperemia, and depth of inflammation, and the sum of these 3 numbers gives the total EUS-UC score. The Tsuga score consisted of the presence of wall thickening and regularity of the mucosa–submucosa and submucosa–muscularis propria interface.[68,70] Substantial intrarater agreement (0.85) and fair interrater agreement (0.36) were found for the Tsuga score. The EUS-UC score performance was studied in a cohort of 79 patients and was shown to be higher among patients with moderate and severe disease compared to mild disease ($P < .05$). The EUS-UC score positively

correlated with the Truelove and Witts score and the Mayo score ($P < .05$) and reduced significantly after 6 months of treatment showing its efficacy to monitor treatment response.[71] Thus EUS may provide additional prognostic information beyond other modalities. Newer advances such as contrast-enhanced EUS (CE-EUS) can precisely quantify bowel wall thickness and microvascular circulation, which could enable quantification of inflammation. A recent prospective study followed 45 patients receiving anti-TNF agents for active UC using CE-EUS in the rectum. CE-EUS was used to quantify vascularity by using "rise time" and "time to peak" parameters. Patients responding to therapy had a significant decrease in TWT at 2 weeks ($P = .04$) from baseline, whereas nonresponders had no significant change in TWT. Time to peak had significantly normalized in responders ($P = .001$) and showed no alterations among nonresponders ($P = .9$). Importantly, endoscopic mayo score did not exhibit significant changes at 2 weeks in both groups thus failing to predict long-term response.[17]

Role of Endoscopic Ultrasound to Differentiate Between Crohn's Disease and Ulcerative Colitis

The principle that inflammation in UC is limited to the mucosa and CD is a transmural disease process is applied with EUS to aid in differentiating between UC and CD. Several studies have shown that EUS in UC demonstrates mucosa predominant bowel wall thickening and in CD, submucosal thickening is prominent.[19,72] Ellrichmann and colleagues[19] in their prospective study reported that those with active UC had a mean mucosal thickness of 2.08 ± 0.11 mm compared to those with active CD who had a mucosal thickness of 1.32 ± 0.17 mm, $P = .0001$. Whereas mean submucosal thickness in active CD was 2.01 ± 0.22 mm compared to 1.01 ± 0.08 mm in active UC, $P = .0001$. They found that using the criteria of increased TWT, increased mucosal and submucosal thickness, and the presence of paracolonic lymph nodes they were able to differentiate active UC from CD with a sensitivity of 92.3%. Nguyen and colleagues[20] studied 40 patients with IBD (20 UC, 20 CD) with the through-the-scope EUS catheter and by setting a cutoff value of rectal submucosal thickness of 1.1 mm, they were able to differentiate all cases of CD from UC based on EUS findings (100% sensitivity and specificity). There are conflicting data on the presence of prominent paracolonic lymph nodes among patients with IBD. Gast and colleagues[73] reported pathologic lymph nodes to be more prevalent among patients with active UC, whereas Ellrichmann and colleagues[19] found pathologic lymphadenopathy in 74% of patients with CD and in none of the patients with UC.

Transrectal ultrasound with elastography is a recent technique reported by Rustemovic and colleagues[74] to differentiate UC and CD. EUS elastography can be used to differentiate the stiffness of normal and pathologic tissue by ultrasound. In their pilot study, patients with active CD had a higher strain ratio in the rectal wall and surrounding tissue as compared to those with active UC. There was a significant difference in rectal wall thickness between CD patients without rectal involvement and control group suggesting that TRUS could potentially identify patients with CD who may develop rectal or perianal disease during their course.[74] IUS was found to be effective at measuring tissue strain to determine fibrosis in CD and predicting therapeutic outcomes in those treated with anti-TNF agents.[75] Similarly, future studies on EUS elastography should be directed toward assessing whether the strain ratio correlates with response to therapy.

CD, primary intestinal lymphoma (PIL) and intestinal tuberculosis (ITB) can have similar clinical and radiographic features. Qiu and colleagues[76] reviewed 272 patients with these pathologies and studied their EUS characteristics. EUS features of CD

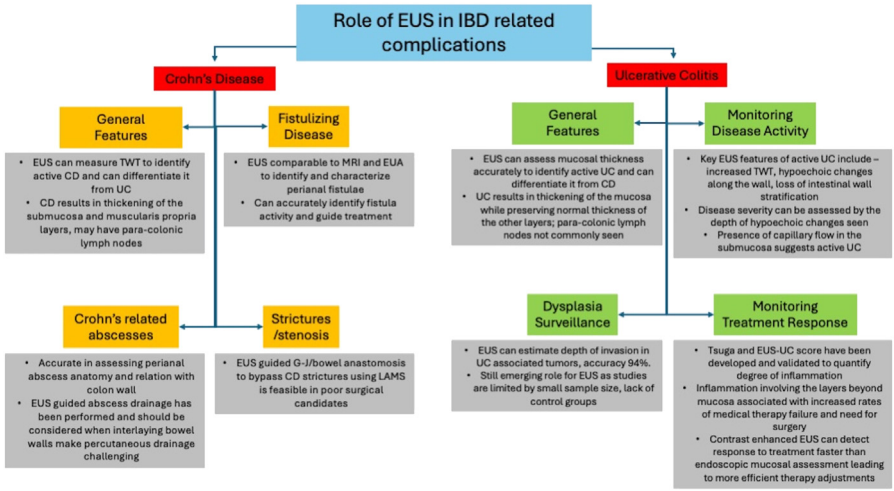

Fig. 5. The role of EUS in IBD-related complications. CD, Crohn's disease; EUA, examination under anesthesia; G-J, gastro-jejunostomy; LAMS, lumen apposing metal stents; TWT, total wall thickness; UC, ulcerative colitis.

included thickened submucosa, visible layer borders, and isohyperechoic submucosa. Features for PIL included invisible layer borders (thus, layer thickening was unable to be identified) and diffusely hypoechoic layers. ITB had hyperechoic thickening of the mucosal layer with visible layer borders with a normal to thinned out submucosa.

ROLE OF ENDOSCOPIC ULTRASOUND IN EXTRAINTESTINAL FEATURES OF INFLAMMATORY BOWEL DISEASE

IBD can be associated with several extraintestinal manifestations including primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH), and autoimmune pancreatitis (AIP).[77–79] Limited data suggest that EUS can be a feasible and safe approach to diagnose extrahepatic PSC when MRCP has been inconclusive.[80] Endosonographic features of duct wall thickening greater than 1.5 mm, irregular CBD wall/caliber (change of wall thickness by greater than 1 mm over 5 mm ductal length and caliber >2 mm over 5 mm ductal length), and the presence of perihilar lymph nodes at least 1 cm in diameter were suggestive of PSC, and the presence of 2 or more criteria gave an EUS diagnosis of PSC.[81] EUS-fine needle aspiration of the bile duct is not recommended in a patient with suspected cholangiocarcinoma especially if they are candidates for liver transplantation as there is a risk of tumor seeding.[82]

Patients with IBD can present with PSC-AIH overlap or can have isolated AIH as well.[79] EUS-guided liver biopsy is a safe and accurate modality to effectively diagnose and classify these conditions.[83,84] EUS-guided fine needle biopsy has been performed in cases when AIP has been diagnosed among patients with IBD to determine the type of AIP and assess for worrisome features such as pancreatic cancer. However, a definitive histologic diagnosis of lymphoplasmacytic sclerosing pancreatitis or idiopathic duct-centric pancreatitis was rare even after a biopsy. Due to the lack of surrogate markers for AIP in patients with IBD, histologic assessment could be necessary and thus these cases should be discussed at multidisciplinary conferences.[77]

SUMMARY

The role of EUS in the diagnosis, staging, monitoring, and treatment of IBD is still emerging and has not been widely adopted as standard practice yet. The main advantage of EUS is the simultaneous and efficient assessment of the endoscopic mucosal assessment of disease activity and ultrasonographic transmural assessment. The potential applications of EUS in IBD have a wide spectrum (**Fig. 5**). Current literature is limited but quite promising. The strongest data support the applicability of EUS in perianal CD. EUS has established its role in the accurate delineation of penetrating CD and perianal abscesses. Emerging data suggest that EUS could be a complementary modality in diagnosing active versus quiescent IBD, differentiating UC from CD, staging colonic dysplasia and neoplasia, and monitoring response to therapy. EUS is also gaining traction as its application expands to therapeutic interventions among patients with IBD such as abscess drainage and bypassing strictures. Future research should aim at fortifying available evidence with the help of larger and well-designed studies.

CLINICS CARE POINTS

- Rectal EUS is complementary to MRI and EUA to correctly delineate fistula anatomy and help plan surgical procedures.
- EUS can be used to monitor fistula healing and determine optimal timing of seton removal or consider surgery in a medically treated patient with inadequate healing.
- EUS-guided pelvic abscess drainage should be considered in CD, especially when overlying bowel loops preclude interventional radiology-guided drainage.
- EUS can be used to identify dysplasia in patients with UC.
- Through-the-scope EUS probes can expand the utility of EUS in evaluating the more proximal colon in IBD.

DISCLOSURE

J. Bapaye, S. Chandan have nothing to disclose. G.S. Kochhar is a Speaker, Lilly Pharma; Advisor Board: GIE Medical, Lilly Pharma, CorEvitas Research foundation, Pharmacocosmos; Consultant: Pentax endoscopy, Boston Scientific Endoscopy, Olympus Endoscopy, Takeda Pharamceuticals, Exact Sciences; Stock Options: Digbi Health.

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