

## Dose Endoscopic Ultrasonography Impact Diagnosis of Intestinal Diseases?

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Substantial development in equipment such as miniprobe endosonography and enteroscopy has made it possible to use endoscopic ultrasonography (EUS) to detect any part of the digestive tract. EUS plays a vital role in evaluating a lower intestinal malignancy, particularly rectal cancer, to determine whether the disease is localized (T1-2, N0) and appropriate for surgery or locally advanced (T any, N1-2) and would benefit from preoperative neoadjuvant chemoradiation. Moreover, follow-up by EUS may contribute to early recognition of focal tumor recurrence, particularly for lesions that cannot be detected by other imaging modalities. EUS is also an invaluable modality for diagnosing intestinal submucosal tumors, such as gastrointestinal stromal tumors, lipomas, lymphangiomas, leiomyomas, carcinoids, and others such as intestinal endometriosis. Although a definite diagnosis of a submucosal tumor is generally confirmed by cytology or histology results, EUS-guided fine needle aspiration or core biopsy is a fairly helpful practice. EUS is also useful for discriminating between Crohn's disease and ulcerative colitis as well as assessing disease severity. Moreover, it has emerged as a powerful imaging tool to manage perianorectal diseases. EUS also has the potential to be useful for intra-small intestinal ultrasonography for the diagnosis of small bowel diseases in the future. (**Intest Res 2011;9:179-188**)

**Key Words:** Endosonography; Diagnosis; Intestinal Disease

### INTRODUCTION

The diagnostic value of endoscopic ultrasonography (EUS) has been clearly demonstrated in the upper gastrointestinal disease.<sup>1</sup> Relatively, it has not gained such widespread utilization in lower intestine except in anorectum. With the development in equipments such as high-frequency miniprobe endoscopic ultrasound and enteroscopy, EUS can be applied to detect any part of lower intestinal tract. In addition to the well established role in local staging of rectal cancer, EUS has also developed versatile roles in other intestinal disorders, such as differential diagnosis of submucosal tumors, assessment of inflammatory bowel disease,

evaluation of perianal and perirectal sepsis, and diagnosis of small bowel diseases. Here, we will review current usefulness of EUS in various intestinal diseases.

### TUMOR IN LOWER GASTROINTESTINAL TRACT

#### 1. Rectal Cancer

Accurate preoperative staging of rectal cancer is important in tailoring the most optimal treatment for the patient. Early tumors (T0 to T1) may be suitable for local excision therapy. More advanced lesions, such as T3 to T4, should be treated with neoadjuvant chemoradiation before surgery because it has been shown to reduce local recurrence and improve outcomes.

EUS has been proven to be most favorable in assessing T staging of local-regional rectal cancer. The overall accuracy ranges from 62% to 92%, with over-staging rate up to 18% and understaging rate up to 16%.<sup>2,3</sup> A recent study including 7,096 patients detailed

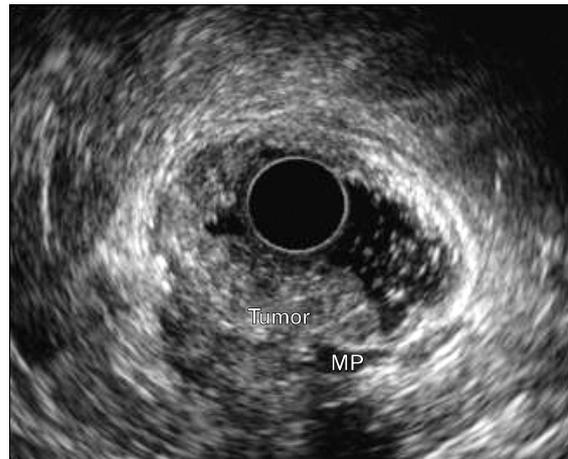
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the correspondence between the EUS assessment of tumor depth and that determined by histology in different T stage, the kappa coefficient was greatest in the category T1 ( $\kappa=0.591$ ), followed by T3 tumors ( $\kappa=0.468$ ), the poorest correspondence was found for T2 and T4 tumors ( $\kappa=0.367$  and  $0.321$ , respectively).<sup>4</sup> EUS appears to be particularly useful in identification of early rectal lesions suitable to local excision and advanced lesions that could benefit from neoadjuvant treatments. Accuracy in staging T2 tumors is generally lowest, which may be overstaged as T3 lesions (Fig. 1).<sup>5</sup> EUS tends to overstage cancers because interfaces between stages (T2-T3 and T3-T4) are complicated by fibrous and inflammatory reaction in the vicinity of the tumor involving the next layer of the rectal wall.<sup>6</sup> In addition, impact of experience and expertise of the endosonographers on the accuracy of tumor staging was confirmed in one study,<sup>4</sup> which showed that the correspondence between ultrasonographic T and pathologic T was 63.2% for hospitals undertaking  $\leq 10$  EUS/year, 64.6% for those doing 11-30 EUS/year, and 73.1% for those performing  $>30$  EUS/year. On the contrary, another study didn't find that experience accumulation impacted accuracy of T staging on rectal cancer.<sup>7</sup>

Endosonographically, lymph nodes appear as round or oval structures that are hypoechoic compared with the surrounding perirectal fatty tissue. Correctly differentiating benign from malignant perirectal lymph nodes by EUS is difficult, because inflammatory nodes may be present in the setting of rectal cancer. EUS features predictive of malignant lymph nodes include size  $>1$  cm, hypoechoic and homogeneous echo pattern, round shape, and well-defined borders.<sup>8,9</sup> If a lymph node is measured greater than 5 mm in diameter on EUS, there is a 45-70% chance from metastasis.<sup>10</sup> Although no single feature is diagnostic, the likelihood of malignancy increases in the presence of multiple features. The overall accuracy of nodal staging ranges from 66% to 83%, with a false-positive rate from 16% to 22% and false-negative rate from 12% to 14%.<sup>3,7,11-13</sup>

Recent studies reported that three-dimension (3D) EUS showed greater accuracy than conventional two-dimension (2D) EUS, the overall accuracy of conventional 2D EUS and 3D EUS in T staging was



**Fig. 1.** Endoscopic ultrasonography image of a rectal adenocarcinoma (T3). The tumor invades through the muscularis propria (MP) into serosa.

84-88% and 88-91%, respectively, that in N staging was 66.7-76% and 84.8-90%, correspondingly.<sup>14-16</sup> The accuracy of 3D EUS in local rectal cancer staging was 100% in T1 stage, 72-91% in T2 stage, 85% in T3 stage and 92% in T4 stage, respectively.<sup>6,16</sup>

Locally advanced rectal cancer patients commonly need preoperative chemoradiotherapy which can down-stage rectal cancer and improve long-term survival and reduce recurrence. Evaluating tumor response to neoadjuvant therapy and restaging are essential for next-term management. The accuracy of EUS after chemoradiation for pathologic T stage varied from 27% to 75% with overstaging rate up to 18% and understaging rate up to 7%. The EUS accuracy for N stage was 65-72.6%.<sup>17-19</sup> Since neoadjuvant therapy of rectal cancer results in sonographically indistinguishable image from focal necrosis and inflammatory or fibrotic changes, EUS has a limited role as a true predictor of rectal cancer response to preoperative therapy.

Local recurrence following surgical treatment for rectal cancer is a major cause of mortality. It is assumed that an early detection of local recurrence, thereby permitting attempts at curative resection, would improve survival, although it has yet to be established. Some EUS findings for rectal cancer before treatment have been reported to be predictive of tumor recurrence. Tumors classified by EUS as minimally invasive (invasion over 2 mm beyond muscularis propria) have

a higher recurrence rate of 39.3% than tumors classified as advanced T3 disease (invasion of less than or equal to 2 mm beyond muscularis propria) with a recurrence rate of 14.3%.<sup>20</sup> Another study demonstrated that the preoperative maximum tumor thickness measured by EUS in T3 rectal cancer was an independent prognostic factor for local and overall recurrence, maximum tumor thickness over 19 mm was related to a significantly increased risk of local recurrence.<sup>21</sup> For these rectal cancers with high risk in tumor recurrence, a routine surveillance may be useful for early detection of recurrent local tumor. In this respect, EUS may help the detection of suspected local recurrence when no mucosal lesion is seen during surveillance endoscopy. Several studies suggested that EUS was highly sensitive of 90-100% for the detection of local rectal tumor recurrence.<sup>22-24</sup> However, the postoperative and postradiation inflammatory and fibrotic changes have similar sonographic imaging to locally recurrent tumors, in these cases, extraluminal local recurrence suspected by EUS can be confirmed by EUS-fine needle aspiration (FNA) or biopsy.<sup>25</sup>

## 2. Colon Cancer

Application of EUS in colon cancer staging is much less than that in rectal cancer. Traditional treatment of both early and locally advanced colonic cancer is open surgery. Recently, laparoscopic colectomy is a therapeutic alternative to open surgery when patient presents with no locally advanced disease.<sup>26</sup> EUS may offer information of tumor infiltration depth and lymph node involvement for the decision whether laparoscopy is an adequate option. The accuracy of miniprobe EUS in colon cancer T staging in various studies ranged from 87% to 94%, that in N staging ranged from 80% to 84%.<sup>27-29</sup> The treatment decisions based on the findings of colonic EUS were correct in 90% of patients.<sup>29</sup>

## 3. Anal Squamous Cancer

Anal squamous cell carcinoma (SCC) is the most common malignancy of the anal canal. The primary treatment for this disease is combined chemoradiotherapy rather than surgery. On EUS examination,

SCC usually appears as vascular hypoechoic central mass that may involve the sphincters and invade deeply.<sup>30</sup> Evaluation of lymph node involvement is also important in staging of the SCC, whereas EUS is not a preferred modality when compared with MRI and CT.<sup>31</sup> A recent study, however, showed a high concordance in the assessment of node status between EUS and MRI with kappa index of 0.77.<sup>32</sup>

Evaluation of tumor response to chemoradiotherapy treatment is essential to following management, but it is difficult to be determined by EUS due to edema and scar tissue that may present with the residual or recurrent tumor. It was suggested that 16-20 weeks after radiation was sufficient time frame to allow for discriminating between postradiation fibrosis, residual tumor and local recurrence.<sup>33-35</sup> Meanwhile, a recent study also showed that 3D EUS could improve sensitivity in the evaluation of patients with suspicion of local recurrence of anal cancer, the sensitivity of 3D EUS and 2D EUS was 86%, 57%, respectively.<sup>36</sup> Furthermore, Color Doppler can increase the specificity of EUS in distinction between fibrosis and tumor as vascularity is more likely within tumor relapse rather than fibrosis.<sup>37</sup>

## SUBMUCOSAL LESIONS

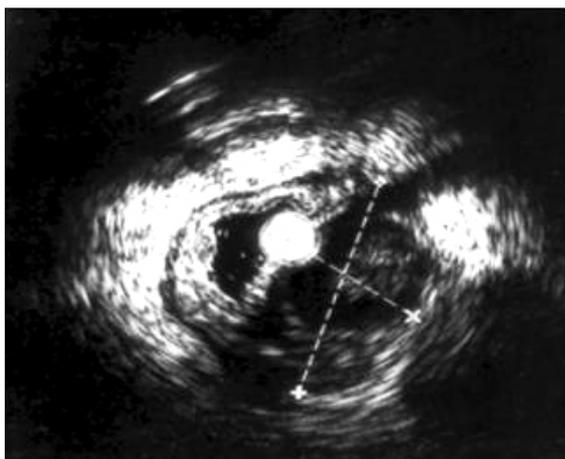
EUS with or without FNA has been applied extensively for investigating submucosal lesion of the upper gastrointestinal tract and the actual cause of a submucosal lesion. Recently, several studies have evaluated the usefulness of EUS in the diagnosis of lesions either within or adjacent to the wall of the lower intestine, especially in the diagnosis of submucosal tumors.

### 1. Gastrointestinal Stromal Tumor (GIST)

GISTs are a subset of mesenchymal tumors and account for 80% of all mesenchymal neoplasms of gastrointestinal tract. It has become clear that GISTs arise from the multi-potential mesenchymal stem cells with immunohistochemical characteristics of positive staining for Kit protein (CD117). The most common location of GISTs is stomach (50-60%) and small

intestine (30-40%). Five to ten percent of GISTs arise from the colon and rectum, and 5% are located in the esophagus. Other less common locations are those outside of the gastrointestinal tract such as mesentery, retroperitoneum and omentum.<sup>38</sup>

Under EUS investigation, GISTs typically arise within the muscularis propria layer of intestinal wall with heterogenous hypoechoic echogenicity (Fig. 2). However, these findings are not unique to GISTs. The prognosis of GISTs varies widely ranging from benign to frankly malignant, thus, correctly discriminating malignant from benign is essential for further management. Although EUS imaging criteria is helpful in identifying GISTs which should be resected, the key to preoperatively determining malignant potential lies on cytology, histology and immunohistochemistry. Tissue specimens can be obtained by EUS-guided FNA or core biopsy. The diagnostic yield for EUS-FNA ranged from 61.6% to 91%.<sup>39,40</sup> EUS-FNA with immunohistochemical analysis could increase the accuracy rate for GISTs to 97%.<sup>41</sup> A novel sonographic technique known as contrast-enhanced harmonic EUS (CEH-EUS) was also reported recently in a single center to have promisingly important role in predicting the malignancy risk of GISTs. CEH-EUS could identify irregular intratumoral vessels with a sensitivity of 100% and thereby predict malignancy of GISTs with



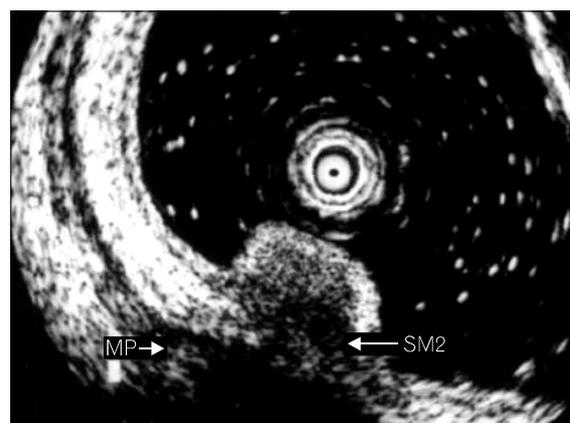
**Fig. 2.** Endoscopic ultrasonography image of a rectal gastrointestinal stromal tumor. The tumor arises from the muscularis propria layer of intestinal wall with heterogenous hypoechoic echogenicity.

sensitivity, specificity and accuracy of 100%, 63% and 83% respectively, while compared with 63%, 92% and 81% respectively by EUS-guided FNA.<sup>42</sup>

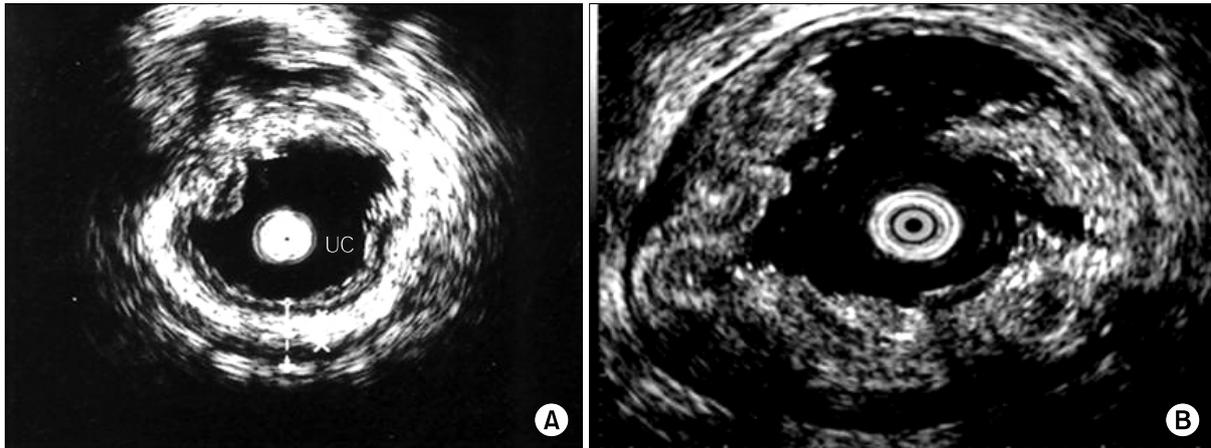
## 2. Carcinoid Tumors

Carcinoid tumors are primary malignant neoplasms that originate from neuroendocrine cells throughout the body. Most carcinoids are located in the gastrointestinal tract and bronchopulmonary system.<sup>43</sup> Within the gastrointestinal tract, most carcinoids arise in the small intestine, followed by rectum, appendix, colon, and stomach.

The common EUS features of carcinoid tumor include distinct margin, homogeneous hypoechoic lesion and deep mucosa to submucosal origination (Fig. 3). EUS is highly useful in the evaluation of local-regional rectal carcinoid tumor to assess tumor size, depth of invasion, and lymph node involvement.<sup>44,45</sup> By focusing on the submucosa, which is the hyperechoic third layer of the rectum, tumors as small as 2 mm in diameter can be detected.<sup>43</sup> Thus, EUS can accurately provide preoperative assessment and then determine the appropriateness of endoscopic submucosal dissection versus transanal excision or radical surgery.<sup>46</sup>



**Fig. 3.** Endoscopic ultrasonography image of a rectal carcinoid. The tumor arises from the deep mucosa with distinct margin and homogeneous hypoechoic echogenicity. MP, muscularis propria; SM2, submucosa 2 or middle 1/3 layer of submucosa.



**Fig. 4.** Endoscopic ultrasonography images of ulcerative colitis (A) and Crohn's disease (B). (A) Significant thickening of the submucosa. (B) Thickening of total intestinal wall.

## INFLAMMATORY BOWEL DISEASE

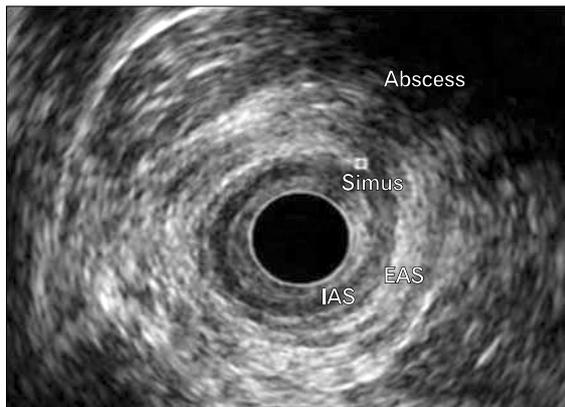
### 1. Ulcerative Colitis (UC)

UC is a chronic intractable inflammatory bowel disease with repeated flare-ups and remission. Diagnosis of this disease largely depends on clinical and endoscopic findings, however, all the findings at initial presentation and during exacerbations are nonspecific. As a result, great attempts to correctly categorize UC and CD by EUS have been made. Based upon the fact that CD is a transmural disease and UC is mostly limited to the mucosa and submucosa, thus total wall thickness of intestine as a differential parameter on EUS has been assessed in several studies. Unfortunately, previous studies have yielded inconsistent results.<sup>47,48</sup> While, our practical experience characterized thickening of submucosa in active UC patients and disappearance of layer structure with total wall thickening in CD patients (Fig. 4). Additional paracolic echopoor lymph nodes were found to be present in 14/19 patients (73.7%) with acute CD but in none with UC, although this result was opponent to an early study which showed a greater number of pathological lymph nodes for acute UC than CD.<sup>49</sup> Besides, the number of enlarged vessels which was increased in acute CD may also be helpful to distinguish acute UC from CD.<sup>49</sup>

Severity assessment of UC plays an important role in the selection of treatment. The severity of UC is

generally assessed on the basis of clinical variables and findings with colonoscopy and contrast barium enema which are limited to the mucosal surface. Several studies have assessed the association of changes in the structure and the thickness of the bowel wall on EUS with conventional endoscopic findings and the clinical severity of UC. A recent study showed EUS could accurately and objectively estimate the degree of vertical spread of intestinal inflammation in UC with greatest concordance (100%) for sites consisting primarily of open ulcers. This study also showed a close relationship between the degree of vertical spread of intestinal inflammation on EUS and endoscopic severity classified according to Matts's classification, while such relationship was not found between EUS and clinical severity.<sup>50</sup>

Furthermore, EUS has been found to be predictive of response to medical treatment and relapse in UC. Intestinal inflammation that extends to the muscularis propria or deeper showed a poor response to medical treatment.<sup>51</sup> A more recent study reported that thickness of the rectal mucosal layer before cyclosporine. A treatment was significantly greater in responders than in non-responders, which may predict and evaluate the efficacy of cyclosporin. A treatment in severe UC patients who did not respond to high-doses of corticosteroids.<sup>52</sup>



**Fig. 5.** Endoscopic ultrasonography image of Crohn's perianal fistula and abscess. Fistula appears as hypoechoic round to oval structure and abscess is visible sonographically as a hypoechoic mass. IAS, internal anal sphincter; EAS, external anal sphincter.

## 2. Crohn's Disease (CD)

CD is a chronic inflammatory disease of the gastrointestinal tract with a variable clinical course characterized by segmental transmural inflammation and granulomatous changes.<sup>53</sup> The most common involved gastrointestinal tract of CD is small bowel, and approximately 40% have disease involving both the ileum and colon.<sup>54</sup> On EUS, acute CD is characterized by significant total wall thickening and disappearance of layer structure (Fig. 4).

Fistulas and abscesses are common complications of CD, it has been known that up to 50% of patients develop fistulas after 20 years.<sup>55</sup> Fistulas usually require surgical treatment, especially given complex fistulas account for a large proportion in CD, thus accurate diagnosis and classification of fistulas is crucial before treatment to plan an optimal and sufficient therapy for each patient and to reduce the risk of postoperative fecal incontinence and recurrence. On EUS, fistulas are usually identified as small, hypoechoic, round to oval structures, while there may be internally hyperechoic as a result of air within fistulas between anal canal or rectum and vagina (Fig. 5).<sup>56</sup> Injection of contrast agents like hydrogen peroxide through the external fistula opening can provide visualization of entire course of the echogenic fistula, including its relation with the internal and external

sphincters. 3D EUS has proven to be useful in improving the reliability of ultrasound imaging of fistulas.<sup>57-59</sup> An abscess is visible sonographically as a mass which is either anechoic without internal echoes or hypoechoic with internal echoes secondary to cellular debris.<sup>60</sup> Currently, the main imaging modalities for evaluation of perianorectal fistulas are EUS and MRI, the comparison between these two modalities has been conducted in several studies. EUS has been demonstrated to be equal to or superior to MRI.<sup>61-64</sup> A previous study compared EUS, MRI, and examination under anesthesia (EUA) in 34 patients with suspected Crohn's perianal fistulas,<sup>61</sup> the accuracy was 91% for EUS with 95% confidence interval (CI) of 75-98%, 87% for MRI with 95% CI of 69-96%, and 91% for EUA with 95% CI of 75-98%, respectively. This study also showed that the accuracy was 100% when any two modalities were combined.

EUS can also be a useful tool to monitor the outcome of fistula treatment.<sup>65,66</sup> One retrospective study of 21 patients demonstrated that using EUS to guide surgical therapy for perianal fistulas with infliximab, immunosuppressant and antibiotic, was associated with a high and long-term response rate. Moreover, EUS may also identify patients who can discontinue infliximab without recurrence of fistula drainage.<sup>67</sup>

## INTESTINAL ENDOMETRIOSIS

Endometriosis is a gynecologic disorder defined as the presence of endometrial glands and stroma outside the endometrial cavity and the uterine musculature. Although the most common location of ectopic endometriosis is in the pelvis, the rectosigmoid colon is the most common site of extrapelvic endometriosis.<sup>68</sup> The diagnosis of intestinal endometriosis is difficult to make on colonoscopy alone because of the subepithelial location of the endometriotic implants.

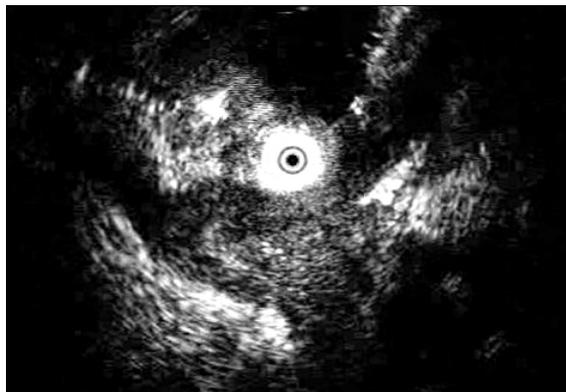
Most common presenting features of intestinal endometriosis are dysmenorrhea, abdominal mass, rectal bleeding and abdominal pain,<sup>69</sup> while a majority of intestinal endometriosis is asymptomatic and is incidentally diagnosed during surgery or laparoscopy for pelvic endometriosis. Under EUS examination, the

endometriotic implants are hypoechoic and heterogeneous crescent-shaped lesions, involving the serosa and the muscularis propria layers of the rectal wall (Fig. 6).<sup>70-72</sup>

EUS is a noninvasive technique with a high sensitivity of 88.9-96% and specificity of 66-100% for the diagnosis of intestinal endometriosis.<sup>73-76</sup> Making a diagnosis of intestinal endometriosis by EUS preoperatively may allow for less invasive surgical approaches and better patient outcomes, but a differential diagnosis of a malignant disease can be missed. A further EUS-FNA can confirm the diagnosis, differentiation of endometriosis as well as help the treatment decision.<sup>71</sup>

### SMALL BOWEL DISEASE

Administrated EUS in small intestine is rare because of difficulties in approaching the small bowel



**Fig. 6.** Endoscopic ultrasonography image of intestinal endometriosis. Hypoechoic crescent-shaped lesion involves serosa and muscularis propria layer of the intestinal wall.

endoscopically. Although new development in endoscopic techniques such as capsule endoscopy or double-balloon enteroscopy (DBE) permits examination of the entire small bowel, both modalities have limits in visualization of submucosal condition. Given this situation, DBE guided intra small intestinal ultrasonography can provide precise ultrasonographic imaging diagnosis of small bowel diseases.

The diagnostic performance of EUS with DBE in small bowel has been evaluated in a few explorative studies and case reports.<sup>77-80</sup> EUS with DBE was shown to be useful for diagnosis of submucosal tumor by determining the echogenicity, layer of origin or depth of invasion of small intestinal neoplasms.<sup>77</sup> Small bowel ulcers may exhibit a typical EUS pattern that consists of three separate elements: the ulcer crater, the echo-rich ulcer base, and frequently an echo-poor inflammation zone, which can extend beyond the thickness of the wall and more wide than the endoscopic changes.<sup>81</sup> DBE with EUS may be particularly useful for confirming variceal or angiogenic lesions of the small bowel to avoid unsafe biopsies.<sup>82</sup> All these studies suggested an accurate modality for EUS in diagnosis of small bowel diseases such as GIST, staging primary small intestinal cancer, guiding stricture dilation and helping endoscopic treatment, although these utilities need to be further confirmed by more and larger studies.

### CONCLUSION

Although EUS embarked gastrointestinal endoscopy for more than thirty years, the majority of its application is still focused on upper gastrointestinal di-

**Table 1.** Endoscopic Ultrasonography Characteristics of Common Lesions in Lower Intestine

	Shape	Border	Involved layer	Echogenicity	Internal echo
Colorectal cancer	Irregular	Irregular	First to fifth	Hypoechoic	Heterogeneous
Gastrointestinal stromal tumor	Round/oval	Smooth	Fourth	Hypoechoic	Homogeneous/heterogeneous
Carcinoid tumor	Round/oval	Regular	Second to third	Hypoechoic	Homogeneous
Ulcerative colitis	-	-	First to third	Thickened third layer	-
Crohn's disease	-	-	First to fifth	Disappearance layer structure	-
Endometriosis	Crescent-shaped	Irregular	Fourth to fifth	Hypoechoic	Heterogeneous

seases as well as pancreaticobiliary diseases. A series of investigations have already demonstrated the diagnostic role of EUS in the lower intestinal tract by the EUS image features of various kinds of lesions (Table 1), while much more evidence and convincing studies are still needed.

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