Recent Developments in the Role of Endoscopic Ultrasonography in Diseases of the Colon and Rectum

Manoop S. Bhutani

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Abstract and Introduction

Abstract

Purpose of Review: Endoscopic ultrasound has evolved as a useful technique for imaging and intervention in a variety of gastrointestinal and extraintestinal diseases including diseases of the colon and rectum. This paper will review recent developments in endoscopic ultrasound for colorectal diseases.
Recent Findings: Recent studies have shown significant clinical impact of endoscopic ultrasound in rectal cancer staging. Iliac lymph node evaluation by endoscopic ultrasound-guided fine needle aspiration may further expand the role of endoscopic ultrasound in rectal cancer. Three-dimensional endoscopic ultrasound may help decrease some of the errors of staging with two-dimensional endoscopic ultrasound and may further improve staging accuracy. Recent studies have confirmed continued problems with re-staging rectal cancer after chemoradiation. Endoscopic ultrasound-fine needle aspiration can be helpful in detecting local recurrence of rectal cancer and has been shown to be useful in evaluation of subepithelial masses of the colon and rectum and evaluation of rectosigmoid endometriosis.
Summary: Endoscopic ultrasound continues to be useful for a variety of conditions of the colon and rectum with recent studies confirming its clinical impact as well as expanding its role into newer indications. Assessment for residual cancer after chemoradiation is still problematic and hopefully technological developments in ultrasound in the future may help in improving the accuracy of endoscopic ultrasound in this situation.

Introduction

Endoscopic ultrasound (EUS) has evolved as a useful technique for imaging, intervention and therapy for a variety of gastrointestinal and extraintestinal diseases including diseases of the colon and rectum. This paper will review recent developments in EUS for colorectal diseases. The focus of the paper will be primarily on rectal cancer, which has the greatest application of EUS in the colorectal area, but recent developments in some other colorectal applications of EUS will be briefly discussed as well. Instruments (made by a variety of manufacturers) for imaging in the colorectal area include radial (cross-sectional) and linear (longitudinal) flexible endoscopic ultrasound echoendoscopes, endorectal/anal probes, and high frequency catheter miniprobes that can be passed through the biopsy channel of conventional endoscopes. Interventional EUS procedures require use of the linear array echoendoscopes that allow visualization of a needle along its length.

Endoanal ultrasound is an established technique for anal sphincter imaging. The utility of endoanal ultrasound for mapping out anal sphincter defects has been shown in multiple studies[1-3] and will not be described in detail in this review. Similarly, endo-anorectal ultrasound is a very useful technique for imaging of perianal fistulas that will not be discussed in detail but I would like to mention a recent study[4] comparing EUS, magnetic resonance imaging (MRI) and examination under anesthesia (EUA) in 34 patients with suspected perianal fistulas in Crohn's disease that demonstrated good agreement for all three methods: EUS 91%, MRI 87%, EUA 91%. Combination of EUS or MRI with EUA provided 100% accuracy.

Endoscopic Ultrasound in Rectal Cancer

EUS is a highly useful technique for local staging of rectal cancer as preoperative staging determines the type of surgery performed and whether preoperative neoadjuvant chemoradiation is needed. Savides *et al.*[5] recently summarized the indications for EUS in rectal cancer in a concise way after review of the literature and potential impact based on tumor stage. Indications for EUS in rectal cancer include the following situations: (1) in a large polyp or small rectal cancer to

determine suitability for endoscopic mucosal resection or transanal excision (if the lesion is T1 by EUS); (2) in a large, rectal cancer to determine whether preoperative chemotherapy and radiation is needed (T2: radical resection (Figure 1), T3-4 or N1, preoperative chemoradiation followed by radical resection; (3) surveillance after surgery for rectal cancer.

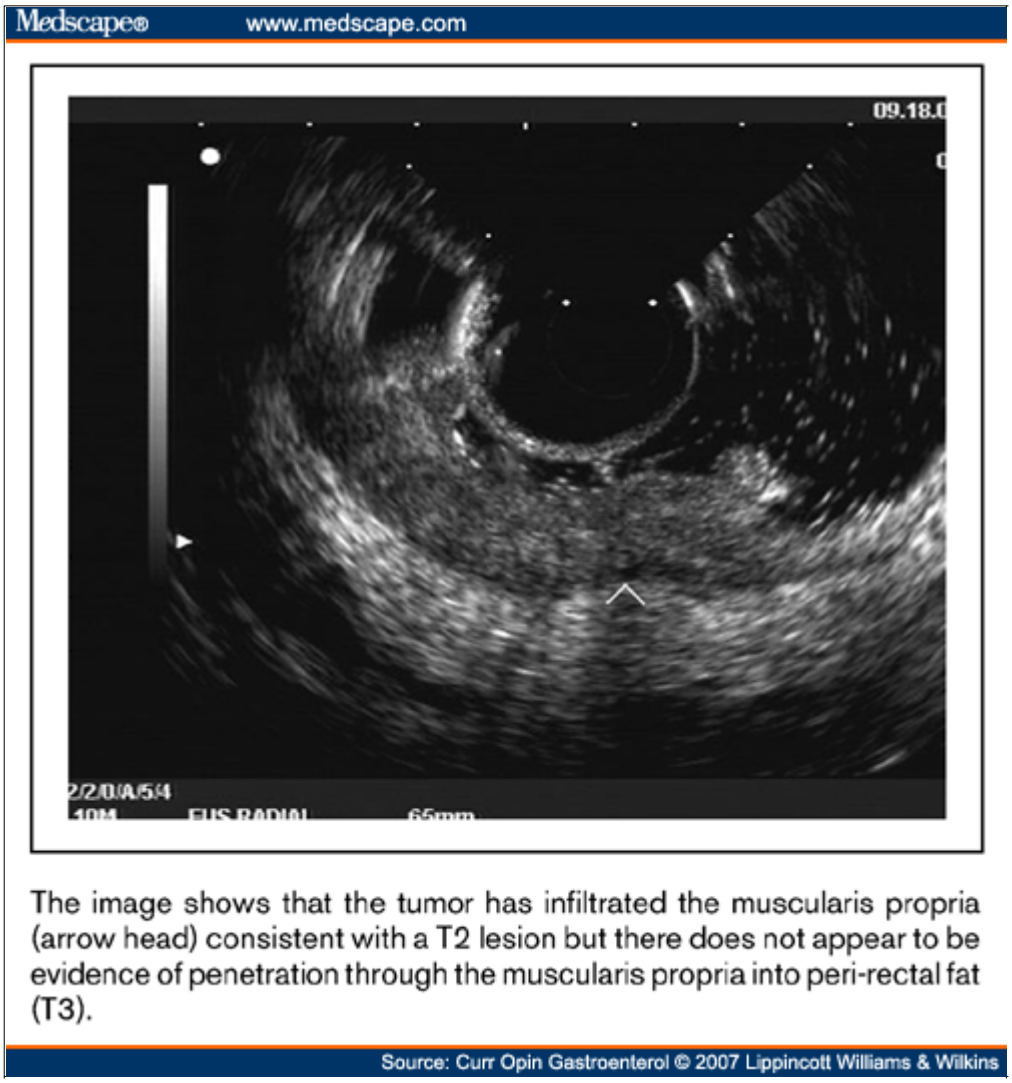

Figure 1.

Radial endoscopic ultrasound of a rectal adenocarcinoma.

The accuracy of EUS for assessing local depth of invasion of rectal carcinoma (T stage) ranges from 80 to 95%[5-7] compared to 65-75% for computed tomography (CT) and 75-85% for MRI.[8-12] Concerning T stage, the major limitation with EUS is overstaging of T2 tumors[13] as peritumorous inflammation cannot be distinguished from malignant tissue by ultrasound. On the other hand, inability to detect microscopic malignant infiltration can lead to understaging. Stenotic tumors in a subset of patients with rectal cancer may have suboptimal staging by EUS due to inability of the echoendoscope to traverse the stenosis[13,14] but usually stenotic tumors represent advanced lesions. Catheter ultrasound probes that can be passed through a conventional endoscope may provide some assistance with regard to this situation.

The accuracy of EUS for lymph node staging is less than for T-staging and ranges from 70 to 75%, with CT and MRI accuracies being about 55-65% and 60-65% respectively.[7] Round, echo-poor or hypoechoic lymph nodes that are more than 5 mm are generally considered suspicious for metastases in rectal cancer.[5,15] Lymph node staging by EUS is less accurate than T-staging as there is an overlap between the echo features of benign/inflammatory and malignant lymph nodes. EUS-guided fine needle aspiration (FNA) can be attempted to improve the accuracy of lymph node staging but this can only be done for lymph nodes that are not in the immediate vicinity of the primary tumor (Figure 2), since traversing of the EUS-FNA needle through the primary will obviously lead to spurious results and false positives.

Figure 2.

Linear endoscopic ultrasound-guided fine needle aspiration of a perirectal lymph node through normal proximal rectal mucosa.

With technical developments in cross-sectional imaging modalities the comparison of EUS with MRI and other imaging modalities continues to be investigated and is in evolution. A recent study compared the ability of EUS and two MRI coils to locally stage rectal carcinoma before surgery.[14] Forty-nine patients with rectal carcinoma were staged by EUS and either body coil MRI or phased-array coil MRI. The EUS and MRI findings were compared with histologic findings on the surgical specimen. For local T-staging the accuracy of EUS was 70%, 43% for body coil MRI and 71% for phased-array coil MRI. For N stage, accuracy of EUS, body coil MRI and phased-array coil MRI was 63%, 64% and 76% respectively. For T staging, EUS had the best sensitivity (80%) and the same specificity (67%) as phased-array coil MRI. For N stage, phased-array coil MRI had the best sensitivity (63%) and the same specificity (80%) as the other methods. In this study, EUS and phased-array coil MRI provided similar results for assessing T stage. No method provided satisfactory assessments of local N stage, although phased-array coil MRI was marginally better in assessing this important parameter. It is clear that none of the imaging modalities for rectal cancer staging are perfect and there is room for improvement.

Parallel with technical improvements in cross-sectional imaging techniques such as MRI, technical advances for improving the ability of transrectal EUS for rectal cancer staging are also being actively investigated. Planar two-dimensional EUS provides limited spatial information. Three-dimensional EUS image reconstruction may improve the accuracy of EUS and may help decrease errors in staging. Kim *et al.*[16] recently published a study to compare the efficacy of three-dimensional EUS with that of two-dimensional EUS and CT for staging of rectal cancer. Eighty-six rectal cancer patients prior to surgery were evaluated by two-dimensional EUS, three-dimensional EUS, and CT scan. EUS imaging was performed with rigid rectal probes. The accuracy for T-staging was 78% for three-dimensional EUS, 69% for two-dimensional EUS, and 57% for CT, with accuracy for lymph node metastases being 65, 56, and 53%, respectively. Examiner errors were the most frequent cause of misinterpretation, occurring in 47% of two-dimensional EUS examinations and in 65% of three-dimensional EUS examinations. By eliminating examiner errors, the accuracy rates in T-staging and lymph node evaluation could be improved to 88 and 76%, respectively, for two-dimensional EUS, and to 91 and 90%, respectively, for three-dimensional EUS. Poorly differentiated or mucinous rectal tumors with adverse prognostic factors were closely associated with infiltration grade by three-dimensional EUS in the study by Kim *et al.*[16] The three-dimensional reconstruction of rectal tumors revealed conical protrusions along the deep margins with the number of cones correlating closely with infiltration grade, advanced local T stage and presence of lymph node metastases.

Clinical Impact and Cost Effectiveness of Endoscopic Ultrasound in Rectal Cancer

Harewood and colleagues[7,17-20] have done a number of studies on the clinical impact of EUS in rectal cancer. In a study on cost effectiveness[17] for rectal tumors, evaluation with abdominal CT plus EUS was found to be the most cost-effective approach ($24 468/year) compared with abdominal CT plus pelvic MRI ($24 870) and CT alone ($26 076). In a study[18] on clinical impact in rectal cancer, EUS staging information changed the surgeon's original treatment plan based on CT alone in 31% of patients. T staging accuracy was 71% for CT and 91% for EUS (*P* = 0.02). N staging accuracy was 76% (CT), 82% (EUS), and 76% (EUS-FNA) (*P,* NS). The authors showed that preoperative staging with EUS results in more frequent use of preoperative neoadjuvant therapy than if staging was performed with CT alone. The addition of FNA of lymph nodes only changed the management of one patient. The authors opined that FNA seems to offer the most potential for impacting management in those patients with early T stage disease, and its use should be confined to this subgroup of patients. In another study by the same group, outcomes of 68 (non-EUS control group) and 73 (EUS group) patients with nonmetastatic rectal cancer were compared. In patients with advanced T or N stage, preoperative adjuvant therapy was administered to 58.5% versus 14.9% patients in the non-EUS group. EUS staging of rectal cancer appeared to facilitate appropriate employment of preoperative neoadjuvant therapy in patients with advanced disease with EUS use associated with a recurrence-free survival advantage in patients. Another way of making an impact of EUS in rectal cancer is to classify T3 tumors into early T3 lesions (Figure 3) versus advanced T3.[20] In this study of 42 patients[20] with T3 rectal tumors who had surgical resection without receiving preoperative neoadjuvant therapy (with 14 minimally invasive T3 and 28 advanced T3 by preoperative EUS), tumor recurrence rates in minimally invasive and advanced T3 tumors were 14.3% and 39.3%, respectively, *P* = 0.02 (log-rank test). Advanced T3 disease by EUS provided important prognostic information that may help improve selection of patients for neoadjuvant therapy.

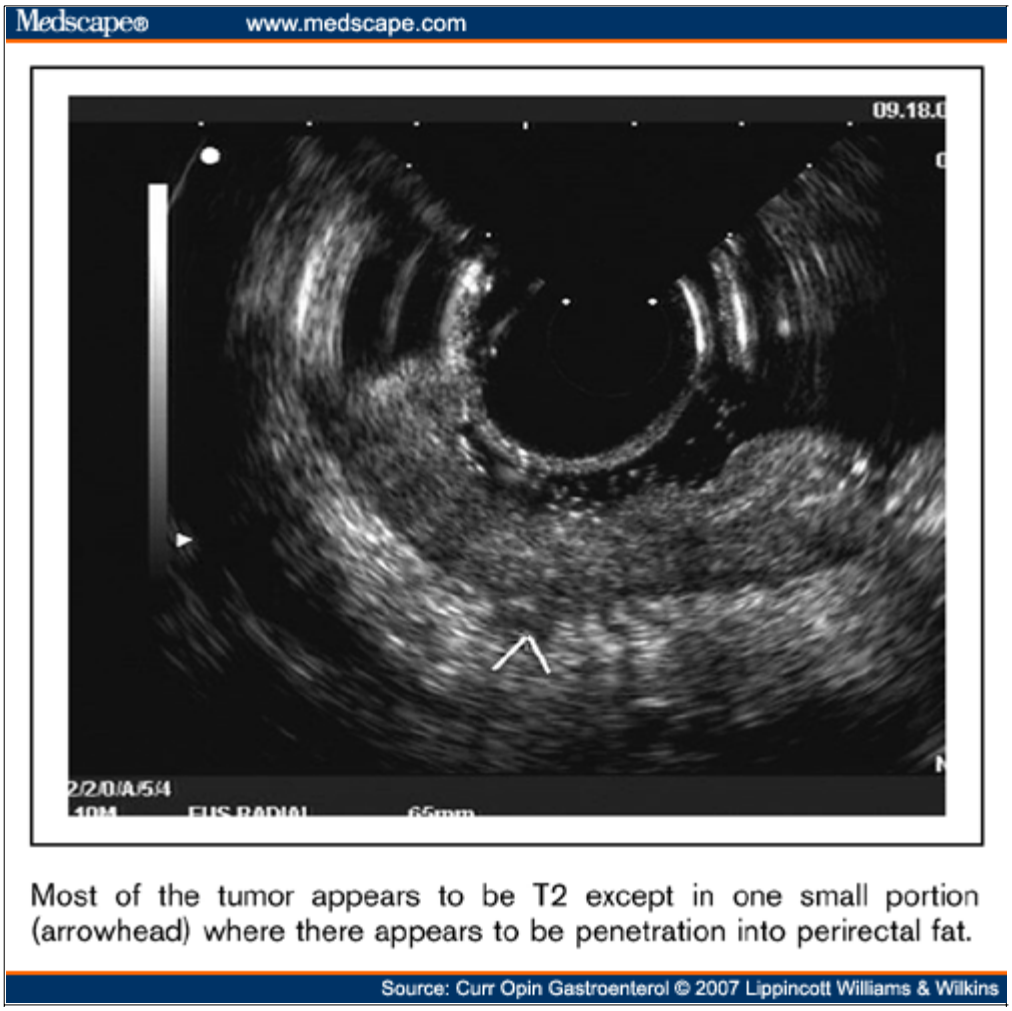

Figure 3.

Radial endoscopic ultrasound showing an early T3 rectal carcinoma.

Harewood[7] recently conducted a *Medline* search for all published estimates of EUS accuracy in staging rectal cancer between 1985 and 2003 in the English literature. Published studies were analyzed for accuracy of EUS, year of publication, number of subjects studied, impact factor of journal, and type of journal. EUS T-staging accuracy was reported in 40 studies while EUS N-staging accuracy was reported in 27 studies. The experience of 4118 participants was reported with an overall mean T-staging accuracy of 85.2% (median, 87.5%) and N-staging accuracy of 75.0% (median, 76.0%). Both T-staging and N-staging accuracy rates declined over time with the lowest rates reported in more

recent literature. The author concluded that the performance of EUS in staging rectal cancer may be overestimated in the literature due to a publication bias and an inflated estimate of the capability of EUS may lead to unrealistic expectations of this technology.

Even though in the study by Harewood *et al.*,[18] in 2002, EUS-FNA was considered to have a negligible role in the initial management of rectal cancer, a recent study from the same institution by Levy *et al.*[21] seeks to expand the role of EUS-FNA in staging of rectal cancer. The presence of malignant iliac lymph nodes (ILNs) designated M1 stage in rectal cancer alters patient management in relation to surgical candidacy, extent of resection or radiation therapy field. Traditionally rectal EUS studies have not included evaluation of the iliac area for lymph nodes although this is an area accessible to flexible EUS probes in contrast to the rigid endoultrasound instruments. In this prospective study, 457 rectal cancer patients underwent T, N, and M staging by EUS. Suspicious nonperitumoral lymph nodes were sampled by FNA. EUS visualized suspicious ILNs in 32 of 457 rectal cancer patients (7.0%) of which 15 of 32 (47%) were found to be malignant ILNs by EUS-FNA. In contrast, CT detected iliac lymph nodes in only seven of 15 (47%) patients with confirmed malignant ILN. Discovery of malignant ILNs by EUS-FNA indicated the need for expansion of the radiation field and extended lymphadenectomy in four patients, and expanded radiation field and palliative nonoperative therapy in 11 patients. The authors concluded that these data support the routine assessment of ILN status among rectal cancer patients who undergo EUS. If these results are confirmed at other centers and clear impact of ILN imaging and FNA is shown by EUS in future studies, then flexible echoendoscopes with FNA capability may have a definite advantage and preference (for rectal cancer staging) over rigid rectal probes that cannot be advanced in the colon to the level of the iliac lymph nodes.

Restaging Rectal Cancer After Chemoradiation

Accuracy of EUS for staging rectal cancer after radiation therapy is decreased because of postradiation edema, inflammation, necrosis, and fibrosis [5,22,23]. A recent study by Vanagunas *et al.*[24] aimed to verify the accuracy of EUS in staging rectal cancer after neoadjuvant chemoradiation in a large cohort of patients. EUS staging was performed before and after concurrent 5-fluorouracil and radiotherapy in 82 patients with recently diagnosed locally advanced rectal cancer. All patients underwent subsequent surgical resection and complete pathologic staging. After chemoradiation, 16 patients (20%) had no residual disease at pathologic staging (T0N0). The overall accuracy of EUS after chemoradiation for pathologic T-stage was only 48%. Fourteen percent were understaged and 38% overstaged. EUS accuracy for N-stage was 77%. The T-category was correctly staged before surgery in 23 of the 56 responders (41%) and in 16 of 24 nonresponders (67%). EUS was unable to accurately distinguish postradiation changes from residual tumor. Similarly another recent study[25] tried to compare the accuracy of EUS staging for rectal cancer before (group I) and following chemoradiation (group II). The accuracy of the T staging for group I was 86% (57/66). Inaccurate staging was mainly associated with overstaging EUS T2 tumors. In group II, following chemoradiation, overstaging EUS T3 tumors accounted for most inaccurate staging. The EUS staging predicted postchemoradiation T0N0 stage correctly in only 50% of cases. Thus, in my opinion re-staging with EUS after chemoradiation, if undertaken, should be done with caution with understanding of limitations/pitfalls as well communication of the same to oncologists and surgeons using the EUS information for possible therapeutic decisions.

Another study by Romagnuolo *et al.*[26] using a novel brachytherapy protocol for downstaging and achieving high tumor sterilization rates in rectal cancer showed that the sensitivity, specificity, and positive and negative predictive values of post-brachytherapy EUS in predicting residual tumor were 82, 29, 64 and 50%, respectively. The post-brachytherapy EUS accurately predicted the T-stage in eight (44%) patients. Most of the errors were due to overstaging. The authors concluded that EUS appears sensitive in predicting the presence or absence of residual tumor in rectal adenocarcinoma after preoperative brachytherapy, but the low predictive values in this setting limit its utility at this time.

Endoscopic Ultrasound for Detection of Recurrent Rectal Cancer

The risk of recurrence after surgery for rectal cancer is greatest in the first 2 years after surgery. Detection of recurrent local tumor may lead to further treatment and improved survival. A number of studies have shown EUS to be very accurate in detecting recurrent rectal cancer at or near the anastomotic site, with EUS-FNA being able to provide tissue confirmation.[27-30,31] The optimal interval for repeating EUS after surgical treatment of rectal cancer is uncertain. A recent joint update by Rex *et al.*[32] of guidelines by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer addresses endoscopic (colonoscopy and EUS) surveillance of these patients. The details of follow-up colonoscopy intervals are discussed in this joint statement and will not be elaborated further in this review. Specifically for EUS, however, the statement does state that patients undergoing low anterior resection of rectal cancer generally have higher rates of local cancer recurrence than those with colon cancer. Although effectiveness is not proven, the joint update states that performance of endoscopic ultrasound or flexible sigmoidoscopy at 3-6-month intervals for the first 2 years after resection can be considered for the purpose of detecting a surgically curable recurrence of the original rectal cancer.

Endoscopic Ultrasound for Colorectal Subepithelial Lesions

The differential diagnosis of a subepithelial compression of the gastrointestinal tract is broad and may include intramural lesions or extramural compression from a pathologic process or an anatomic aberration causing subepithelial

compression without true pathology. EUS with or without FNA has been applied extensively for investigating subepithelial compression of the upper gastrointestinal tract and is clearly the investigation of choice for delineating the actual cause of a subepithelial compression. Similar subepithelial lesions do occur in the rectum and the colon which can be investigated with flexible echoendoscopes that can be advanced not only into the rectum (like rigid nonoptical rectal probes) but also higher up in the rectum.[33] The high frequency through the scope catheter EUS miniprobes provide an additional method for investigating subepithelial lesions anywhere in the colon.[34]

Sasaki *et al.*[31] recently presented their results on the use of EUS-guided FNA for investigation of submucosal and extrinsic masses of the colon and rectum. The aim of this study was to evaluate the use of EUS-FNA for the diagnosis of lesions either within or adjacent to the wall of the colon and rectum (Figures 4 and 5). Sufficient tissue for evaluation was obtained from 21 of the 22 patients (95.5%). The overall rate of detection of malignant and benign masses was 95.5% (21/22) for EUS-FNA and 81.8% (18/22) for pre-EUS-FNA imaging investigations. There were no complications related to the EUS-FNA procedure. Some of the lesions that were diagnosed by EUS with FNA in this series included gastrointestinal stromal tumor, hemangioma, lymphoma, neuroendocrine carcinoma, lipoma, carcinoid tumor, recurrence of rectal carcinoma and recurrence of other distant malignancies such as gastric and ovarian carcinoma. Please also see the section below on EUS for rectosigmoid endometriosis that may also present as a subepithelial compression or mass in the rectosigmoid region.

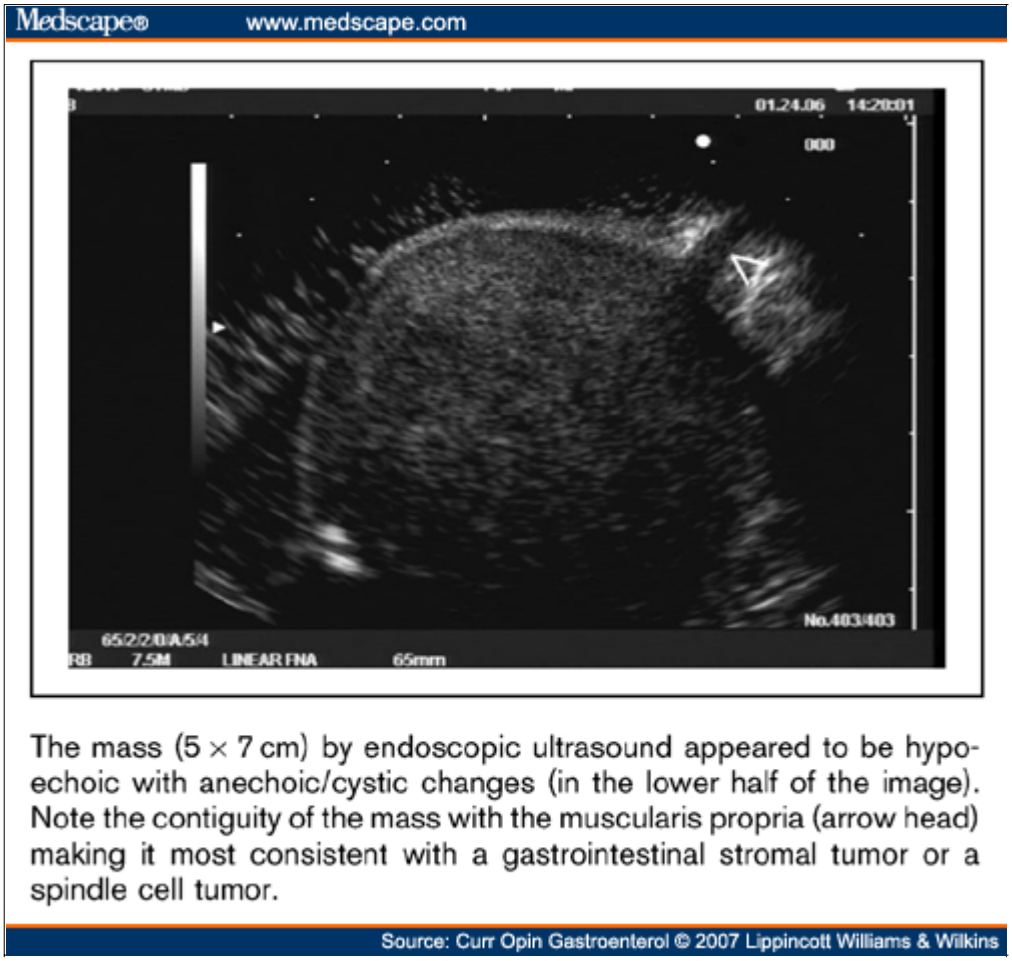

Figure 4.

Linear endoscopic ultrasound of a subepithelial compression of the rectum with smooth overlying mucosa.

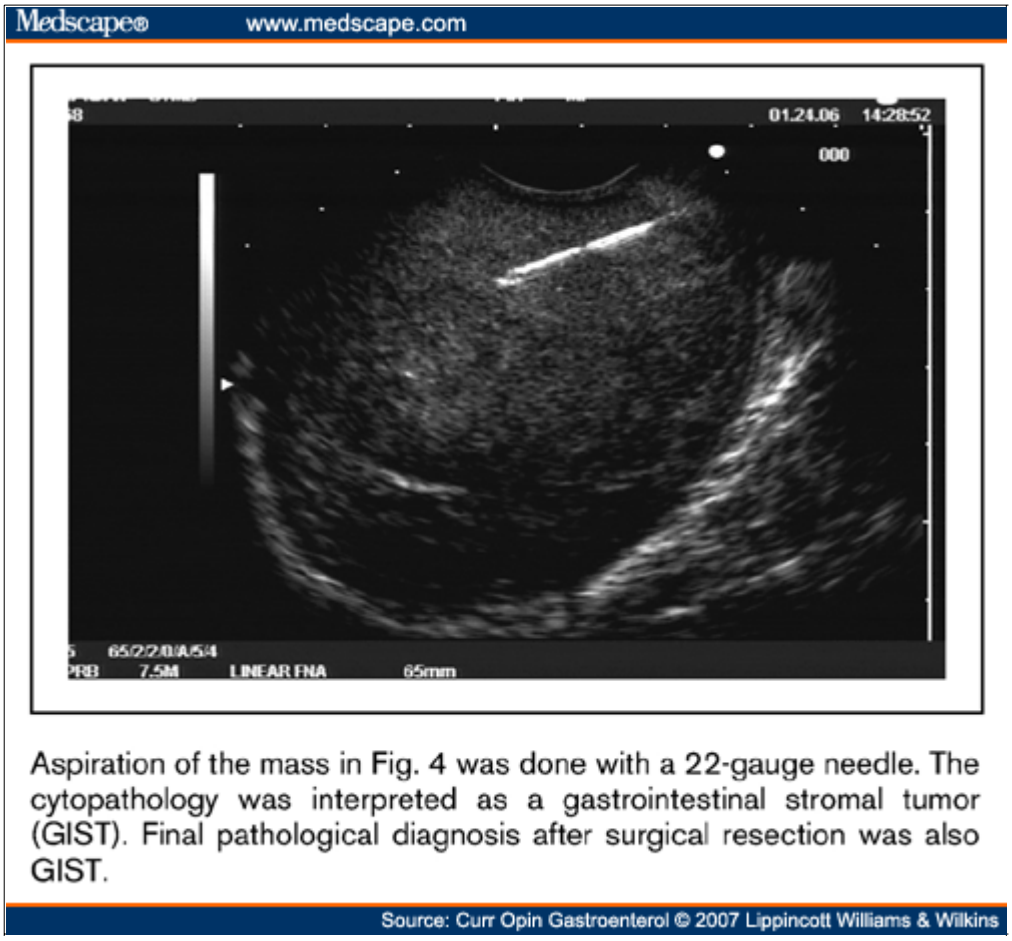

Figure 5.

Endoscopic ultrasound-guided fine needle aspiration of a subepithelial compression of the rectum with smooth overlying mucosa.

Endoscopic Ultrasound for Rectosigmoid Endometriosis

There have been two recent reports[35,36] that suggest that EUS may have an important role in assessing rectosigmoid involvement in patients with endometriosis. EUS has not been extensively used for this condition in the past. Delpy *et al.*[35] wanted to assess the value of EUS in diagnosing rectal wall involvement by pelvic endometriosis. A prospective study was done in 30 patients who presented with suspected rectovaginal septal endometriosis and underwent anorectal EUS that showed the presence of endometriosis in the rectovaginal septum in 26 patients (88%), in the uterosacral ligaments in 10 patients (33%), and in the ovaries in two patients (6%). The sensitivity, specificity, and positive and negative predictive value of anorectal endoscopic ultrasonography as a means of diagnosing endometriosis of the rectovaginal septum and infiltration of the rectal wall were high and found to be 96, 100, 100 and 83%, and 92, 66, 64 and 92%, respectively. EUS was somewhat less accurate for nodules located away from the EUS probe such as endometriosis in uterosacral ligaments and ovaries. The accuracy for detecting nodules in the uterosacral ligaments or in the ovaries was 56 and 53%, respectively.

In another recent series, the role of EUS and EUS-guided FNA in the diagnosis of rectosigmoid endometriosis in symptomatic patients was studied.[36] Five women with nonspecific gastrointestinal complaints underwent EUS examination of a rectosigmoid subepithelial mass found on colonoscopy. EUS revealed a hypoechoic lesion infiltrating the muscularis propria and the serosa of the rectal wall, and extending outside the rectal wall. These findings were consistent with rectosigmoid endometriosis. This diagnosis was confirmed in these patients by EUS-FNA, surgical exploration, or the patient's clinical course.

Endoscopic Ultrasound Guided Drainage of Perirectal Abscesses

There are two reports of EUS guided drainage of perirectal pelvic abscesses.[37,38] Attwell *et al.*[38] reported a case of EUS guided drainage of diverticular abscess as an adjunct to surgical therapy. In a larger series by Giovannini and colleagues,[37] clinical efficacy of EUS-guided transrectal aspiration and drainage by plastic prosthesis of deep pelvic abscesses using a therapeutic echoendoscope was studied in 12 patients. No major complication occurred during this study. Transrectal stent insertion succeeded in nine patients. In three patients, only aspiration was possible without

ability to insert a stent for drainage. Of the nine patients in whom a stent was successfully introduced into the fluid collection, complete drainage without relapse was achieved in eight patients at a mean follow-up of 10.6 months. The stent was removed via endoscopic means after 3-6 months. Drainage was incomplete in one patient who subsequently needed surgical drainage. Two of the three patients in whom aspiration alone was performed developed a recurrence of the abscess and required surgical treatment. The above studies in a limited number of patients showed that EUS-guided drainage of deep pelvic abscesses could be considered in carefully selected patients as adjunctive or alternative treatment to surgery. These techniques may be even more suited for patients who are at increased surgical risk due to comorbidities. Hopefully larger studies on this technique will be available by these[37,38] and other investigators in the future.

Conclusion

In conclusion, EUS is a very versatile technique that continues to be useful for a variety of conditions of the colon and rectum. Recent studies and developments on this technique in the colorectal area have been on confirming and assessing the clinical impact of staging of rectal carcinoma, technological improvements (e.g. three-dimensional EUS), assessing recurrence of rectal carcinoma with EUS becoming part of postrectal cancer surgery surveillance guidelines, evaluation of rectocolonic subepithelial lesions and development of techniques for EUS-guided therapy. Assessment for residual cancer after chemoradiation is still problematic and hopefully technological developments in ultrasound in the future may help in improve the accuracy of EUS in this situation.

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Abbreviation Notes

CT: computed tomography; EUA: examination under anesthesia; EUS: endoscopic ultrasound; FNA: fine needle aspiration; ILN: iliac lymph node; MRI: magnetic resonance imaging.

Reprint Address

Manoop S. Bhutani, MD, FASGE, FACG, FACP, Professor of Medicine, Co-Director, CERTAIN (Center for Endoscopic Research, Training and Innovation), Director, Center for Endoscopic Ultrasound, University of Texas Medical Branch, 301 University Boulevard, Route 0764, Galveston, Texas, TX 77555-0764, USA. Tel: +1 409 772 1501; fax: +1 409 772 4789; e-mail: msbhutan@utmb.edu .

Manoop S. Bhutani, Center for Endoscopic Ultrasound, University of Texas Medical Branch, Galveston, Texas