Current Gastroenterology Reports (2019) 21: 18
https://doi.org/10.1007/s11894-019-0682-9

LARGE INTESTINE (B CASH AND R CHOKSHI, SECTION EDITORS)

Rectal Endoscopic Ultrasound in Clinical Practice

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Published online: 12 April 2019

Abstract

Purpose of Review Endoscopic ultrasound (EUS) is routinely utilized for evaluation of disorders of the lower gastrointestinal tract. In this review, we summarize the current status of rectal EUS in clinical practice and describe recent developments in diagnostic and therapeutic rectal EUS.

Recent Findings Recent guidelines recommend rectal EUS for rectal cancer staging as a second line modality in cases where MRI is contraindicated. Forward-viewing echoendoscopes and through the scope EUS miniprobes allow for EUS imaging of lesions through the entire colon and for evaluation beyond stenoses or luminal narrowings. EUS can be used to assess perianal disease and drain pelvic abscess associated with IBD, along with newer applications currently under investigation. For rectal varices, EUS can confirm the diagnosis, assess the optimal site for banding, guide therapy placement with sclerotherapy and/or coils, and assess response to treatment by confirming absence of flow. Therapeutic rectal EUS is emerging as a promising modality for drainage of pelvic fluid collection drainage and fiducial placement for rectal or prostatic cancer. Drug delivery mechanisms and substances that may increase the scope of therapy with rectal EUS are in varying stages of development.

Summary Rectal EUS continues to be an important modality for evaluation of benign and malignant disorders of the lower gastrointestinal tract, although its use as a cancer staging modality has declined due to improvements in MRI technology. Various technologies to enhance ultrasound imaging and for therapeutics have been developed that have or may contribute to expanded indications for rectal EUS.

Keywords Endoscopic ultrasound · Rectal cancer · Subepithelial lesions · Fiducials

Introduction

Endoscopic ultrasound (EUS) allows for detailed imaging of the gastrointestinal (GI) tract and adjacent structures using sound waves and allows for sampling of tissue with fine needle aspiration (FNA) or fine needle biopsy (FNB).

The two primary types of echoendoscopes are radial and linear devices [1]. Radial EUS allows 360° viewing, while linear EUS provides longitudinal imaging, which allows for tracking of EUS-guided interventions in real time [1]. A balloon attached to the tip of the endoscope allows for a better view of the mucosa. Historically, endoscopic ultrasound of the lower GI tract was limited to the anal canal and rectum as the liner and radial echoendoscopes are side-viewing instruments. The recently introduced forward-viewing linear echoendoscopes allow for ultrasound evaluation of the entire colon as they can be advanced under direct vision and have the capacity for tissue acquisition via FNA or FNB [2]. With the EUS miniprobe, ultrasound can be performed with standard colonoscopy through the instrument channel, allowing for biopsy and 360-degree EUS views throughout the colon with one scope insertion [2].

Rectal EUS is indicated to stage rectal cancer by clarifying depth of invasion, involvement of adjacent structures, and presence of lymph nodes, but magnetic resonance imaging (MRI) is the recommended modality unless there is a contraindication [3••]. Throughout the colon, EUS with FNA or FNB of pericolonic lymph nodes is useful if tissue acquisition will change cancer stage. FNB allows for core samples to be sent for molecular testing. EUS characteristics and tissue acquisition can clarify the identity of subepithelial or pericolonic lesions. EUS is also used to assess for vascular lesions, primarily rectal varices. Anal EUS can be used to clarify the extent of anal sphincter injury. Finally, EUS is used to assess

This article is part of the Topical Collection on *Large Intestine*

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for perianal, perirectal, and pelvic disease in IBD and can be used to follow response to therapy.

EUS-guided therapeutics including abdominopelvic fluid collection drainage, fiducial placement, rectal varix treatment, and targeted microbubble drug delivery are available in varying degrees and have been evaluated in retrospective case series.

This review will discuss the indications for lower GI EUS with respective yields in each indication compared to other diagnostic modalities, newer technologies to augment EUS, and current and potential therapeutic uses of lower GI EUS.

Rectal Cancer

Accurate staging of rectal cancer is critical for deciding on appropriate therapy as prognosis is related to T and N stages at the time of diagnosis [3••]. EUS was initially a mainstay for preoperative staging, but with advances in MRI the role for EUS has diminished. In fact, the NCCN clinical practice guidelines for rectal cancer suggest EUS for staging only if MRI is contraindicated, such as when a patient has an MRI-incompatible pacemaker [3••]. MRI is preferred because EUS cannot assess the relationship of the tumor to the mesorectal fascia or the circumferential resection margin, which are vital in determining the need for neoadjuvant chemotherapy [3••](Table 1). However, both imaging modalities are still commonly used, and in a recent survey of radiation oncologists, EUS was the most commonly utilized imaging modality [15]. In general, EUS performs well for local T staging. A 2004 meta-analysis demonstrated similar sensitivities of EUS and MRI for T1 and T2 lesions, but EUS specificity was higher than MRI (86% vs. 69%, $p = 0.02$) [16]. For T3 lesions, EUS was more sensitive (90% vs. 82%, $p = 0.003$) [16]. However, a more recent study showed that EUS in "real world practice" was inaccurate in 44.8% of tumors, when surgical pathology is used as the gold standard [17]. Evaluation with EUS is limited when the rectal tumor is large, bulky, high, and stricturing [4]. The ultrasound field of view limits the assessment of tumor relationship to the circumferential resection margin [4].

EUS accuracy for nodal staging of rectal cancer is 65–75% [2]. Overall assessment of the extent of disease beyond the immediate vicinity of the primary tumor is limited, and EUS can miss discontinuous tumor deposits, mesorectal fascia involvement, and other pelvic tumor deposits [4]. Older reports of similar performance of MRI and EUS do not take into account depth of extramural spread, involvement of mesorectal fascia, and extramural vascular invasion [16]. Moreover, recent studies have demonstrated that EUS does not change the management of rectal cancer, when compared to MRI results combined with clinical features [6]. Compared to computed tomography (CT), EUS is associated with higher utilization of neoadjuvant chemoradiation without a significant difference in overall survival [18].

Table 1 Comparison of EUS and MRI for rectal cancer staging

Indication	EUS	MRI
Differentiating polyps from invasive adenocarcinoma	Elastography may be useful/promising [4, 5•]	No data, unable to assess small polyps [5•]
Early T stage (T1/T2)	Good resolution of tissue layers; precise level of mural infiltration, may perform better 63–93% vs 75–85% for MRI, but does not change management when compared to MRI and clinical data [6–8]	Good resolution of rectal wall anatomy to assess for tumor invasion within wall layers and into mesorectum [4]
Locally advanced T3/T4	Poorer performance for T4 > T3 compared to MRI, smaller field of view limits visualization of local spread, mesorectal fascial involvement, and discontinuous invasion (67% accurate for T4) [4, 8]	Better resolution and able to subclassify T3 stage, [4, 9] better predictor of disease recurrence [4]
N stage	65–75% accurate [2], allows for tissue acquisition if needed, unable to visualize upper mesorectum and pelvic side wall [4], may be more accurate for excluding rather than diagnosing nodal invasion [8]	Able to visualize entire mesorectum
Circumferential margin	Unable to accurately assess the involvement of mesorectal fascia [10]	Test of choice as able to assess distance from the tumor to mesorectal fascia—92% accurate, predicts local recurrence, disease-free survival and overall survival [10, 11]
Treatment response	Not accurate in restaging after neoadjuvant chemoradiation due to inflammation, edema, necrosis, and fibrosis with accuracy < 50% [8, 12]	MR-tumor regression grade (TRG) predicts disease-free and overall survival [13, 14]
Recurrence	Useful to differentiate recurrence from postoperative changes or radiation with high sensitivity but poor specificity; this increases with FNA (57% vs 97%) [8]	Useful in defining extent of disease [4]

EUS is also operator-dependent [16]. However, with more experience and training, interobserver agreement has improved, with agreement between endosonographers regarding T staging ($\kappa = 0.61$) better than agreement with N staging ($\kappa = 0.45$) [19•]. To date, there is a paucity of data on learning curves for lower EUS. In 2001, the ASGE suggested that 75 cases of mucosal tumors (including esophageal, stomach, and rectal cancer) should be performed before competency is assessed [20]. More recently, a Canadian group proposed 25 rectal cancer EUS cases as a minimum for credentialing [21•]. In general, individuals reach procedural competence variably, but at this point clear outcomes to determine competence in lower EUS have not been formally defined or studied [22••].

EUS with FNA provides the benefit of confirming metastases with cytology. Despite good accuracy, the negative predictive value is moderate at 77%, meaning there is some degree of sampling error [23]. EUS-guided FNA offers the most benefit in management strategy for T1–2 disease where perirectal lymph nodes modify the strategy [7]. FNB offers better tissue acquisition and allows for immunohistochemical studies but has not been extensively studied for use in rectal cancer staging. It is standard practice to administer antibiotics when transrectal sampling is performed, but the benefit of this practice has not been well studied.

Rectal EUS has been evaluated as a modality for re-staging following neoadjuvant chemotherapy for locally advanced rectal cancer with disappointing results [24]. The overall accuracy in this setting for T stage was 48%, with 14% understaging and 38% overstaging [12].

Proximal Colon Cancer

For staging of colon cancers proximal to the rectum, EUS is not part of the standard evaluation, and the results of evaluation of EUS do not alter treatment based on the current paradigms. Proximal colon cancer staging with EUS was not possible until the development of EUS miniprobes and forward viewing echoendoscopes, but these modalities are feasible and moderately accurate [25]. In a recent report by Castro-Pocas et al., colon cancer staging with EUS miniprobes was feasible in 98%, with accurate T staging in 88% and accurate N staging in 82% using endoscopic or surgical pathology as a reference standard [26].

Anal Cancer

Staging for squamous cell carcinoma of the anal canal involves evaluation for locoregional and metastatic disease. EUS can be used for initial locoregional staging and to monitor response to therapy, but MRI is currently the locoregional imaging modality of choice [27, 28]. MRI provides accurate, high-resolution imaging of location, size, local invasion, and nodal spread [28]. On the other hand, EUS may be superior to MRI for detection of small, superficial tumors [28]. In general, both EUS and MRI are accurate in the local staging of anal cancer, including precise assessment of depth of infiltration, sphincter involvement, tumor spread into adjacent tissue, and perirectal lymph node involvement, with one head-to-head comparison showing similar results [29, 30]. Despite similar performance in locoregional staging, MRI is the test of choice because regional nodes higher in the pelvis are outside the field of view of EUS, discomfort and technical difficulties limit EUS use in stenotic tumors, and EUS is operator-dependent [16, 28]. Finally, EUS may be beneficial in diagnosing recurrent anal cancer if standard biopsy is unable to differentiate tumor recurrence from radiation-induced changes [31].

Other Neoplasms of the Lower Gastrointestinal Tract

EUS can be used for tissue acquisition adjacent to the GI tract and can therefore assist with the diagnosis of pathologic lesions of nearby organs. EUS defines morphology of mucosal lesions and can differentiate primary colon tumors from other lesions. EUS characteristics of primary or secondary rectal linitis plastica and metastatic transitional cell bladder cancer have been described [32, 33]. Primary anorectal melanoma can be diagnosed with colonoscopy and biopsy, but EUS can accurately determine depth of infiltration with 100% concordance with pathologic results [34].

There are other mimics of rectal cancer that can be clarified with EUS. One example is infiltrative mucosal-associated lymphoid tissue (MALT) lymphoma, where depth of invasion by EUS can guide therapy, as it does in the stomach. In one report of three patients with colonic MALTomas, EUS depth of invasion was evaluated and response to triple antibiotic therapy was evaluated by EUS [35]. Rectal teratoma has also been diagnosed by EUS [36].

For prostate cancer, EUS has been evaluated for staging with sensitivities of 100% and specificities greater than 90% for T2 and T3 lesions. Performance for T1 lesions and N staging was worse [37].

Solitary Rectal Ulcer Syndrome

Solitary rectal ulcer syndrome can manifest in many ways, including as a malignant-appearing mass. In this situation, EUS in combination with histopathology can clarify the diagnosis and should be considered a part of the evaluation if the diagnosis is in doubt [38].

Rectal Polyps

Biopsies of rectal tumors can miss focal carcinoma in up to 24%, which is important to know when considering EMR and ESD [39]. EUS reduces the rate of missed carcinomas from 21 to 3% and correctly establishes a cancer diagnosis in 81% of misdiagnosed lesions [40, 41]. A meta-analysis concluded that improved diagnosis with EUS decreased the need for additional surgery and other associated problems from 24 to 5% [40]. When evaluating for residual polyp in the rectal wall or peritumoral adenopathy, a recent retrospective cohort found no additional benefit of EUS ± FNA following endoscopic polypectomy of high-risk rectosigmoid lesions [42].

EUS with elastography is a recent advance that is potentially useful for detecting malignant transformation in rectal adenomas. Elastography measures tissue strain, tissue elastic properties, and hardness, which can help differentiate benign from malignant tumors [43]. One study showed that elastography could assess tissue hardness to distinguish benign adenomas from invasive adenocarcinomas with sensitivity of 0.96, specificity of 0.86, and accuracy of 0.94 compared to pathology [5•].

Subepithelial Lesions

A common indication for rectal EUS is the evaluation of subepithelial lesions, which may be seen on colonoscopy as intraluminal lesions or extrinsic compressions. In the rectum, standard EUS can be used, but for lesions seen in the proximal colon, miniprobes or forward viewing echoendoscopes can be used for evaluation [25, 44]. EUS features such as originating layer and echostructure can suggest the nature of the lesion [2](Table 2). In an earlier prospective study, the diagnostic accuracy of EUS image findings for subepithelial lesions throughout the GI tract, including the rectum, was 48% when compared to histologic diagnosis [48]. The accuracy was worst for lesions in the third and fourth EUS layers [48]. With more experience, the accuracy of EUS for this indication has improved. In a larger study of subepithelial lesions throughout the colon, EUS miniprobe evaluation was 88% accurate using imaging, pathology, and clinical follow-up as the reference standard [44]. In a more recent study evaluating the accuracy of rectal EUS for differentiating rectal neuroendocrine neoplasms from other subepithelial lesions, 94.4% of neuroendocrine neoplasms and 74.2% of other subepithelial lesions were diagnosed correctly [49]. The positive predictive value of EUS for rectal neuroendocrine lesions was 80.9%, while the negative predictive value was 92.0% [49]. EUS is very accurate (90%) at distinguishing intramural lesions from extramural compression, which cannot be easily distinguished on standard endoscopy [48].

Despite the benefits of EUS imaging, tissue acquisition is often needed for confirmation of subepithelial lesion diagnosis. Biopsy forceps are often unsuccessful at obtaining sufficient tissue, so FNA or FNB is used for histologic confirmation if needed [50]. Both FNA and FNB can be utilized to sample subepithelial lesions [51]. However, as in other areas of the gastrointestinal tract, FNB is superior to FNA with respect to diagnostic yield (86.7% vs. 52.7%, $p = 0.01$) [52•]. FNB is technically similar to and as safe as FNA, yet with better tissue acquisition, fewer needle passes, and improved diagnostic yield [52•]. In our center, we use FNB.

Findings on EUS, including size and layer of origin, guide the method of tissue acquisition and endoscopic resectability or need for surgical resection [53, 54]. These same EUS findings also determine the optimal method of endoscopic resection, which are varied and growing in number [51]. In addition to treatment, the intent of endoscopic resection is often tissue diagnosis [51].

EUS of the rectum and sigmoid may be useful for staging of endometriosis (Table 2), but these lesions can be difficult to differentiate from rectal cancer in certain locations. Also, the specific patients that will benefit from EUS for evaluation of endometriosis are unknown [47].

EUS in Inflammatory Bowel Disease (IBD)

Pelvic MRI is routinely used for evaluation of perianal and perirectal complications of Crohn's disease (CD), but EUS performs well if there are contraindications to MRI and the EUS operator has adequate experience. In many centers, colorectal surgeons perform endoanal EUS with rigid EUS as perioperative assessment. Fistulae can be complex, and in order to maximize therapeutic success, accurate anatomical assessment is needed. The data show that rectal EUS performs better than CT and fistulogram, with similar sensitivity to MRI, but lower specificity [2, 55]. The benefit of MRI is visualization of the entire pelvis with detection of fistulae to other structures. The benefit of EUS is visualization of the rectal mucosa. The use of hydrogen peroxide and 3D reconstruction are tools to improve visualization of fistulae and relationship to the sphincteric apparatus [56, 57]. EUS may be more easily repeated and used to follow up response to therapy. A small study of EUS performed during medical and surgical treatment for perianal CD showed EUS was associated with better outcomes and reduced the need for additional surgery [58, 59]. EUS can also diagnose and potentially drain pelvic abscesses related to CD with good technical and clinical success [60•].

Beyond perianal disease assessment, EUS may be an adjunctive diagnostic tool for IBD. For example, a forward viewing echoendoscope can be used to assess sigmoid wall thickness and for pericolonic lymph nodes. The total

Table 2 Lower GI subepithelial lesions and EUS features

Lesion	EUS layer	Tissue layer	Echogenicity	Other features	Cell of origin
GI stromal tumor (GIST)	Fourth ≫ second	Muscularis propria ≫ muscularis mucosa	Hypoechoic, but heterogeneous or anechoic when malignant [45]	Calcification is rarely seen, malignant GIST appear cystic, FNA to differentiate from leiomyoma and schwanomma [45]	Interstitial cells of Cajal C-Kit+, CD34 [45]
Carcinoid-(neuroendocrine tumor)	Second➔third	Muscularis Mucosa➔Submucosa	Hypoechoic	Usually < 2 cm; central depression; well-differentiated to poorly differentiated and infiltrative	Epithelial neoplasm with neuroendocrine differentiation
Lipoma	Third	Submucosa	Hyperechoic	Smooth margins; soft, yellow, pillow or cushion sign when pressed with biopsy forceps on endoscopy; no FNA is needed	Adipocyte
Leiomyoma	Second or fourth	Muscularis mucosa or muscularis propria	Hypoechoic	Round or oval; well demarcated; can appear as multilobulated, echogenic dots from calcification [45], FNA to differentiate from GIST; leiomyosarcoma appears irregular and invasive	Smooth muscle; desmin +, C-kit -, CD34-[45]
Fibroma	Third	Submucosa	Hypoechoic		Mesenchyma
Lymphangioma	Third	Submucosa	Anechoic	Can be septated [46]	Lymph
Cyst	Third, but can be any layer	Submucosa but can be any layer	Anechoic	Compressible, round, or oval	Duplication cysts, congenital
Ectopic pancreas	Third>fourth	Submucosa>muscularis propria	Heterogeneous	Poorly demarcated, ductal structures and cystic components [45], central dimpling on endoscopy	Pancreatic
Glomus	Fourth>Third	Muscularis propria>submucosa	Hypoechoic or isoechoic	Hypervascular on contrast EUS	Mesenchyme-glomus body, ckit-, cd34+/−, SMA+ [45]
Granular cell tumor	Second, third	Muscularis mucosa, submucosa	Hypoechoic	Well demarcated, small, sessile, yellow white on endoscopy	Neural
Schwannoma	Fourth	Muscularis propria	Hypoechoic	Rare calcification, FNA to differentiate from GIST and leiomyoma	Spindle cell, Schwann cell, S100+, Ckit-, CD34-[45]
Varix	Third	Submucosa	Anechoic	Linear or serpiginous, can visualize collaterals, can appear as thickened folds on endoscopy	Portosystemic collateral veins
Metastatic deposit or lymphoma	All	All	Hypoechoic	Heterogeneous mass	Primary tumor
Endometriosis	Fourth	Muscularis propria	Hypoechoic	Rectum and sigmoid, in-homogenous; invades submucosa in 40% [47]	Endometrial gland

thickness is greater in patients with active IBD compared to controls [61•]. In ulcerative colitis (UC) the mucosa is thickened compared to the submucosa and muscularis propria, whereas in CD the submucosa is thickened compared to the mucosa and muscularis propria [61•]. One study showed that pericolonic lymph nodes were detected in 73.7% of patients with active CD, but there were none in UC. Combined wall thickness measurements and lymph node assessment resulted in a 92.3% sensitivity for differentiating CD from UC [61•]. Other technologies have been used with EUS for evaluation of IBD including contrast-enhanced EUS to assess disease activity based on bowel wall vascularization. This can be followed to assess response to therapy and to differentiate fibrotic from inflammatory strictures [62, 63]. Contrast-enhanced EUS is not currently available in the USA. EUS with elastography can help differentiate inflammatory stenoses from fibrotic ones and can classify IBD phenotypes, as strain is noted to be higher in CD compared to UC patients [64, 65].

Rectal Varices

Rectal varices are dilated submucosal portosystemic veins that extend from the mid-rectum to the anorectal junction, are distinct from internal hemorrhoids, and can occur in the setting of cirrhosis or extrahepatic portal vein obstruction [66, 67]. On EUS, rectal varices appear as rounded, oval, or longitudinal echo-free structures (Figs. 1, 2, and 3). EUS is superior to endoscopy in detecting rectal varices, irrespective of size, especially because bleeding can occur from endoscopically inevident rectal varices [68, 69]. EUS is also useful in differentiating varices from congestive rectopathy, in which EUS will show multiple, small dilated veins in the submucosa [68].

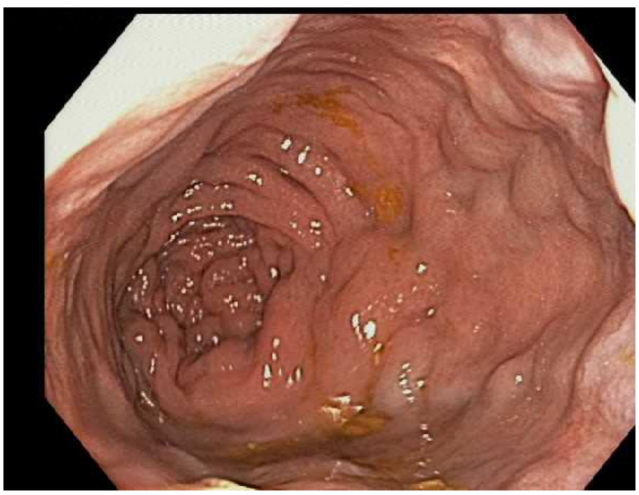

Fig. 1 Standard endoscopic view of rectal varices as multiple, submucosal, blueish hued, serpiginous lesions extending proximally in the rectum and originating proximal to the anal verge

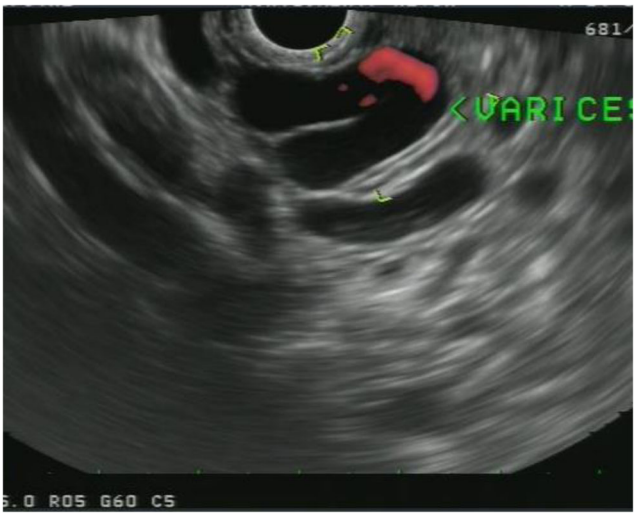

Fig. 2 EUS appearance of rectal varices as rounded, oval, or longitudinal echo-free structures in the submucosa

Hemodynamic evaluation through EUS can clarify the diagnosis of rectal varices and can also be used to aid in the selection of specific varices to treat and which intervention to choose as initial therapy [69, 70]. Theoretically, EUS can be used to diagnose and treat varices in the proximal colon, but these are less common, so available data are limited to case reports [71].

Benign Anorectal Disorders

In the evaluation of fecal incontinence, initial diagnostic testing includes anorectal manometry and defecography. Based on the results, further imaging of the anal sphincter with endoanal ultrasound or MRI is needed preoperatively if surgery is indicated. Each of these modalities has strengths [72•]. Endoanal ultrasound is better at visualizing the internal anal sphincter, and MRI is better at differentiating tissue planes, distinguishing external anal sphincter tears from scars, and

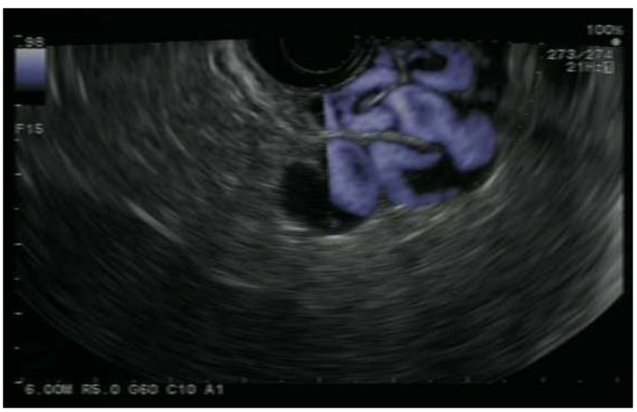

Fig. 3 EUS with color Doppler appearance of flow in the rectal varices

identifying external anal sphincter atrophy [73]. Internal anal sphincter defects likely represent more severe anorectal injury and are typically related to childbirth [74]. MRI or barium defecography is used for evaluation of defecatory disorders; EUS does not have a role [72•]. At our center and others, urogynecologists or colorectal surgeons have more experience than gastroenterologists in performing endoanal ultrasound to evaluate for sphincter defects in preoperative evaluation. EUS combined with anorectal manometry can provide an assessment of anorectal anatomy and function in children following surgical repair of congenital anorectal malformations [75].

Therapeutic EUS in the Lower Gastrointestinal Tract

Initially, EUS was a purely diagnostic procedure. With the goal of providing less invasive alternatives to surgical intervention, many therapies have been developed for use through EUS. Most EUS-guided therapies have been aimed at use in the upper GI tract, including EUS-guided drainage of pancreatic fluid collections, celiac plexus block, and fiducial placement, among others. In the lower GI tract, the most experience and success with EUS-guided therapy has been with drainage of fluid collections; the principles and techniques are the same as used in the upper GI tract. Other therapies include treatment of rectal varices with banding, sclerosant, and/or coils, fiducial placement to guide radiotherapy for rectal cancer, and EUS-guided drug delivery.

Drainage of Fluid Collections

EUS-guided drainage of fluid collections is a common procedure and well described for peri-pancreatic fluid collections, but less well described and reported for perirectal, abdominal, or pelvic collections. Over the last few years, however, interventional endoscopists have become more comfortable applying similar techniques and principles used in the upper GI tract to abscesses and fluid collections in the rectum and sigmoid. Typically, fluid collections or abscesses in the pelvis are related to previous colorectal or gynecologic surgery, but they also occur in IBD, diverticular disease, and sexually transmitted diseases, among other medical conditions. The evidence regarding success and safety of EUS-guided drainage is largely based on case series data, but a large retrospective review found that transrectal and transcolonic drainage of fluid collections with EUS guidance is safe and effective, with 100% technical success [76•]. Initially, plastic stents and catheters were used, but fully covered metal stents and lumen apposing stents have also been used with success [77–79]. Long-term success (median of 64 months) of EUS-guided pelvic abscess drainage was 86.5% [80•].

Fiducial Markers

In pancreatic cancer, EUS has been used to guide the insertion of fiducials to guide precise radiotherapy with good technical success and safety [81]. In lower GI malignancy, fiducial placement has not been extensively studied, but case series and retrospective studies show almost 100% technical success for fiducial placement in rectal cancer [82–84]. Outcomes data are limited, but one retrospective study that followed 11 patients over a median of 8.1 months after fiducial placement showed 100% survival and 100% successful surgical resection after radiation, with no resection margin involvement [83•]. EUS has also been used for placement of fiducials into the prostate to guide radiotherapy before initial treatment (16 patients, 100% success) or into prostate fossa after surgery with recurrence (6 patients, 100% success) [85, 86]. There were no complications of fiducial placement in the study of untreated prostate cancer patients, but 33.3% of the patients having fiducial placement before being treated for cancer recurrence developed urinary tract infections related to fiducial placement [85, 86].

Angiotherapy

There are no guidelines or recommendations for treatment of rectal varices as compared to esophageal varices [87]. Understanding the optimal management of bleeding from rectal varices is complicated by the relative infrequency of significant bleeding from rectal varices, difficulty identifying the site of bleeding, and no head-to-head comparison of treatment options. Typically, the management of bleeding from rectal varices utilizes a multidisciplinary approach with endoscopic management, interventional radiologic approaches, such as transjugular portosystemic shunts or balloon, plug, or coil, assisted retrograde transvenous obliteration, and surgery if needed. Endoscopic management includes band ligation, injection sclerotherapy, and coiling. Band ligation is performed in the same manner as in esophageal variceal banding but can be met with high recurrence rates [88•]. EUS can improve banding success by using hemodynamic assessment of endoscopically inevident varices with color Doppler to identify the optimal site of banding at the highest point of inflow [69]. Sclerotherapy may be more effective than banding with lower rates of recurrent varices (33.0% vs 55.6%, p: NS) and recurrent bleeding (0.0% vs 44.4%, $p < 0.05$), especially if EUS was used to identify appropriate target varices and guide injection [88•]. Initially, the use of sclerosant agents required large volumes with an increased risk of systemic embolization, but with newer introduction of glue therapy, the volume needed for effective hemostasis and risk of embolization decreased [66]. Further, EUS-guided coil deployment can be used for variceal obliteration and provides a scaffold for subsequent glue injection as a part of dual therapy [89]. EUS allows visualization of regional collaterals with targeted

management based on Doppler assessment of inflow and observed treatment with coil and/or sclerosant or glue. Finally, EUS with Doppler can confirm absence of flow after therapy [66].

Drug Delivery

Drug delivery through EUS provides the potential to deliver various treatments directly to a tumor or lesion in high concentrations while minimizing systemic side effects. This use has been evaluated in upper GI EUS, with fewer reports of EUS-guided therapy through lower EUS.

In a pilot study, EUS-guided delivery of a mutated adenovirus (TNFerade) in combination with chemoradiotherapy for locally advanced rectal cancer was feasible with pathologic response similar to chemoradiation alone [90]. Delivery of chemotherapy or immunotherapy by EUS has been evaluated for esophageal cancer and pancreatic cancer but not specifically for lower GI cancers [91]. Brachytherapy delivery by EUS has been tested for unresectable pancreatic cancer but not lower GI malignancy [91]. EUS-guided tumor ablation with alcohol, radiofrequency, photodynamic therapy, and laser therapy has been reported for various pancreaticobiliary or liver tumors but not lower GI neoplasm [91]. In general, studies evaluating targeted delivery of anticancer therapy have not shown survival benefit compared to conventional therapies, but these studies are limited by small sample sizes.

Finally, microbubble ultrasound contrast agents have been developed with the potential for various designs and incorporation of various substances attached to the surface or incorporated into the structure of the microbubbles. These substances would be injected with EUS guidance and then interact with ultrasound waves to trigger enhanced cellular uptake by destabilizing the microbubble and increasing target tissue permeability [92]. In a mouse model, colon tumors treated with endostatin microbubbles resulted in size reduction and decreased tumor vascularization [93].

Quality and Safety

The American Society for Gastrointestinal Endoscopy published a set of quality indicators for EUS, with some specific indicators for lower EUS [22••]. Outcomes tend to be difficult to measure and require a large amount of data that is typically unavailable for rectal EUS. It is important to perform lower EUS for an appropriate indication and make sure the indication is documented. There is no consensus on specific training length, intensity, curriculum, or minimum number of procedures required to ensure competency in EUS in general, with even less consensus for the less commonly performed lower EUS [22••]. Accurate documentation of relevant structures specific to the indication for EUS should occur in a target of 98% of procedures [22••]. For example, in EUS for rectal cancer staging, the location of the tumor, visualization of surrounding structures, such as iliac vessels, genitourinary structures, and sphincter apparatus, and evaluation of lymphadenopathy should be documented. The staging system appropriate for the malignancy being assessed should be documented in 98% of cases [22••]. The EUS wall layers involved by a subepithelial mass should be documented in 98% of cases [22••]. If lesions outside the primary field are seen and accessible, they should be sampled by FNA when the diagnosis outside the primary field would alter management. The target diagnostic rate of EUS-FNA in solid tumors is 85% [22••].

There is less information on safety and adverse event rates of lower EUS, but diagnostic EUS is typically safe, with similar event rates compared to upper EUS. Risk of perforation increases with a stricture, but miniprobes are an alternative in patients with a luminal stricture [94]. With FNA or FNB, bleeding, infection, and perforation are possible complications, with an overall complication rate of 0–2.5% [94]. The incidence of bacteremia following FNA of rectal and perirectal lesions is low and typically subclinical if it occurs. Therefore, antibiotic prophylaxis is not recommended before EUS-FNA of solid lesions or lymph nodes of the lower GI tract. On the other hand, antibiotic prophylaxis is recommended after FNA of cystic lesions and can be made on a case-by-case basis of other lesions [22••, 94]. Other experts recommend prophylactic antibiotics as well as 48 h of antibiotics following FNA of the perirectal space [33]. Bleeding is typically mild and self-limited, with clinically significant bleeding occurring in 0–0.5%. Extraluminal bleeding has been reported in 1.3–2.6% [94]. Tumor seeding is a potential complication of FNA but has not been studied systematically in lower GI EUS. False positive rates of EUS-FNA is low (1.1–5.3%) but is better studied in pancreatic cancer. The number of needle passes, needle size, and use of FNB vs. FNA, do not appear to alter risk of adverse events, but most data are underpowered [22••].

Summary

To conclude, in this review we have described the current status of rectal EUS in clinical practice and summarized recent developments in diagnostic and therapeutic rectal EUS. In the past, the primary indication for rectal EUS was for rectal cancer staging, but updated guidelines recommend rectal EUS as a second-line modality in cases where MRI is contraindicated. Rectal EUS is useful for T1/T2 staging and may be useful in differentiating post-treatment recurrence from treatment-induced changes. EUS performs worse than MRI in T3/T4 and N staging.

EUS also has role in evaluating lesions proximal to the rectum with forward viewing echoendoscopes and EUS miniprobes. For all lesions in the colon, EUS provides the

ability for guided tissue acquisition with FNA and FNB. EUS has a clear role in differentiating and diagnosing subepithelial lesions. In evaluating subepithelial lesions, the image features on EUS, including the layer of origin, size, echogenicity, and vascularity, can confirm a specific diagnosis or help narrow the differential diagnosis. These findings are then used to determine the method of tissue acquisition and appropriate method of resection, if needed. Image characteristics on EUS and hemodynamic assessment with Doppler flow can be used to confirm the diagnosis of rectal varices, but experience for this use varies across centers. Treatment of rectal varices guided by EUS with hemodynamic assessment can be successful, but widespread clinical experience is limited. EUS has potential diagnostic and therapeutic uses in IBD as well, including the assessment of perianal disease and drainage of pelvic abscesses, along with newer applications currently under investigation. EUS with elastography has potential diagnostic utility in a few settings but needs larger studies and wider clinical adoption. Therapeutic rectal EUS is emerging as a promising modality for pelvic fluid collection drainage and fiducial placement for rectal or prostate cancer. Drug delivery mechanisms and substances are in varying stages of development or have been trialed in a small number of patients. These emerging therapies may increase the scope of therapy, need for expertise, and clinical volume of rectal and lower GI EUS.

Compliance with Ethical Standards

Conflict of Interest Stephen Hasak is funded through NIH/NIDDK (T32 DK 052574).

Stephen Hasak and Vladimir Kushnir declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
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