Clinical Review of Small-Bowel Endoscopic Imaging

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Abstract: Endoscopic imaging of the small bowel, frequently used in gastroenterology practice, encompasses mainly video capsule endoscopy (VCE) and device-assisted enteroscopy (DAE). Both tests are essential diagnostic tools to evaluate obscure gastrointestinal bleeding and suspected small-bowel disorders, such as Crohn's disease. VCE solely identifies and localizes small-bowel pathology, whereas DAE offers both visualization and tissue sampling to diagnose diseased structures and perform therapeutic maneuvers, such as those needed to achieve hemostasis. In this context, VCE is frequently used as a screening test for small-bowel abnormalities that, when present, are then managed with DAE.

During the past decade, endoscopic imaging of the small bowel has become a story of success and progress. The small bowel consists of the duodenum, jejunum, and ileum and extends from the pylorus to the ileocecal valve. With the introduction of video capsule endoscopy (VCE) and device-assisted enteroscopy (DAE), small-bowel endoscopy has become an essential diagnostic tool for gastroenterologists treating patients with suspected small-bowel disorders.

Video Capsule Endoscopy

VCE became available for the US health care system in 2000. Currently, 3 small-bowel VCE systems approved by the US Food and Drug Administration are available: the PillCam SB (Given Imaging), the EndoCapsule (Olympus America), and the MiroCam Capsule Endoscope (Medivators). Each capsule system has its particular technical finesse; however, the few randomized tandem trials did not show significant differences among the capsules in terms of diagnostic yield.[1-3]

VCE is a noninvasive technique that can be performed as either an inpatient or outpatient procedure. The patient can swallow the video capsule actively, or it can be placed directly into the duodenum during upper gastrointestinal endoscopy, as is indicated in patients with gastroparesis or dysphagia. Approximately 2 dozen case reports describe aspiration of a video capsule.[4]

Before video capsule placement, all patients must fast for 8 to 12 hours and require bowel preparation with 2 L of polyethylene glycol. Immediately before video capsule placement, an antifoaming agent (simethicone) must be administered to reduce air bubble formation in the small bowel.[5] This protocol yielded the best results in a systematic review and meta-analysis focusing on the quality of visualization of the small bowel, VCE completion rate, diagnostic yield, and decrease in air bubbles.[6] A suboptimal bowel preparation limits the quality of images of the small bowel.

Following ingestion, the video capsule is propelled through the small bowel by peristalsis. Video capsules are usually passed with the stool and do not require retrieval because they are not recyclable. If passage of the video capsule through the ileocecal valve into the colon is not recorded, the patient needs to be made aware of the possibility of video capsule entrapment, which is overall a rare event. In this case, the patient is instructed to visually verify passage of the video capsule in a bowel movement. Unless the patient becomes symptomatic (eg, small-bowel occlusion or signs of perforation), video capsule passage can alternatively be confirmed with a plain radiograph study, which is usually performed within 5 to 7 days following video capsule placement. Before video capsule passage is confirmed, magnetic resonance imaging (MRI) should not be undertaken.

Following completion of the VCE study, the recorder is returned to the physician's office, and the images are downloaded and reviewed with specific software. In order to decrease the time required for reading captured VCE images, the suspected blood indicator (SBI) selects images with red pixels that might represent a bleed. However, the low rates of sensitivity (56.4%) and specificity (33.5%) limit the utility of the SBI, and a complete review of imaging is still necessary.[7]

At the present time, VCE is approved to assess for obscure gastrointestinal bleeding (OGIB), Crohn's disease, celiac sprue, and polyposis syndromes as well as to evaluate small-bowel abnormalities on imaging studies and otherwise unexplained small-bowel symptoms. Most studies, however, have focused on the diagnostic yield of VCE in OGIB and Crohn's disease. In this context, VCE provides images of the entire small bowel in approximately 83.5% of cases. In the remaining 16% of studies, the video capsule does not reach the ileocecal valve before recording is finished.[8,9]

Besides the high diagnostic yield, the main advantage of VCE is its noninvasive nature, which usually allows an outpatient workup. The main limitation is the inability to obtain biopsy specimens or conduct therapeutic procedures. Further limitations are incidental findings of unclear medical significance that can lead to false-positive test results. Incidental small-bowel mucosal breaks were found in 7.1% to 13.8% of healthy controls. In conjunction with nonsteroidal anti-inflammatory drug (NSAID) use for only 2 weeks, the rate of mucosal breaks can be as high as 55% to 68%.[10-12]

The most feared complication of VCE is entrapment of the video capsule in the small bowel. The largest systematic review reported pooled retention rates for all VCE examinations, workup for OGIB, workup for Crohn's disease, and workup for suspected neoplastic lesions of 1.4%, 1.2%, 2.6%, and 2.1%, respectively.[9] Other large case series not included in the systematic review reported rates of small-bowel entrapment as high as 17% in patients with small-bowel tumors.[13] In terms of complications, no significant differences were found between younger and elderly (octogenarian) patients.[14] Moreover, VCE was proven to be safe in 108 patients with implantable electromechanical cardiac devices, causing no detectable alterations in the function of pacemakers, implantable cardioverter defibrillators, and left ventricular assist devices.[15]

Device-Assisted Enteroscopy

DAE encompasses double-balloon enteroscopy (DBE), single-balloon enteroscopy (SBE), and spiral enteroscopy (SE). With few exceptions, DAE has made push enteroscopy and intraoperative enteroscopy obsolete.

Double-Balloon Enteroscopy

DBE was the first type of DAE and was introduced by Fujinon in 2004. The DBE system consists of an enteroscope with a working length of 200 cm, a polyurethane overtube with a length of 145 cm, and a latex balloon pump system that is fixed to the distal ends of both the enteroscope and the overtube. Advancement through the small bowel is based on a repetitive series of push-and-pull cycles, in which inflatable balloons are used to provide a grip on the intestine. The enteroscope can be inserted with either an antegrade (oral) or retrograde (anal) approach. Carbon dioxide is the preferred gas to insufflate and distend the lumen of the small bowel.[16]

The maximal small-bowel insertion of DBE ranges from 240 to 360 cm for the antegrade approach and 102 to 180 cm for the retrograde approach.[17-19] In the setting of OGIB, Crohn's disease, or unspecific abdominal symptoms, a total enteroscopy is often desired. This means that visualization of the entire small bowel is attempted, which can be achieved either with an antegrade-only or a combined antegrade-and-retrograde DBE approach. The success rate for total enteroscopy ranges from 45% to 86%.[17,20] Initial studies revealed a diagnostic yield in OGIB of almost 80%.[20,21]

As with all available DAE systems, besides visualization of the mucosa, DBE offers the option to obtain biopsy specimens from areas of suspected pathology. Additional options include therapeutic actions, such as polypectomy, stricture dilation, hemostasis with argon plasma coagulation, electrocoagulation, and endoscopic hemoclip placement, as well as the retrieval of foreign bodies. In light of the invasiveness of DBE, the need for general anesthesia or monitored anesthesia care is its main limitation.

The optimal approach (antegrade or retrograde) for a targeted enteroscopy, in which attempts are made to visualize and biopsy abnormalities seen previously on VCE, was addressed in 2 studies. Based on small-bowel video capsule transit time (from pylorus to ileocecal valve), lesions visualized in the proximal 60% to 75% can be reached with antegrade DBE, whereas lesions in the distal 40% to 25% of the small bowel can be reached with retrograde DBE.[22,23] In this context, the only standardized method to estimate the depth of enteroscopy insertion was presented by May and colleagues.[24] The endoscopist estimates the efficiency of each push-and-pull maneuver and records the estimated advancement of each cycle, ranging from 0 to 40 cm. The sum of the estimates equals the total estimated depth of insertion.[24]

Despite the invasiveness of DBE, complication rates range from 0.8% for diagnostic DBE to 4.3% for therapeutic DBE, with hemorrhage and perforation being the most common complications. Case reports have also revealed that acute pancreatitis can be a DBE-related complication.[25,26]

Single-Balloon Enteroscopy

The SBE system, introduced in 2007, consists of an enteroscope measuring 200 cm and an overtube of 140 cm. In contrast to DBE, SBE has only 1 balloon, which is at the distal end of the overtube. Both the overtube and balloon are made of silicone so that the system can be used in patients with latex allergy. Similar to DBE, the SBE system is advanced with push-and-pull cycles. The maximal depth of SBE system intubation was reported to be between 256 and 270 cm for the antegrade approach and between 163 and 199 cm for the retrograde approach. The success rate for total enteroscopy ranges from 0% to 25%, and the diagnostic yield ranges from 47% to 60%.[27-31] Similar to DBE, SBE offers therapeutic options, including biopsy, resection, hemostasis, and dilation.[27,30]

In direct comparison with DBE, SBE proved to be more favorable in terms of easier assembly of the device and a shorter learning curve; however, the rate of total enteroscopy was shown to be substantially lower.[29] Preliminary studies showed similar diagnostic yields in small-bowel pathology for DBE and SBE; however, these results are not consistent throughout the literature.[29,31]

Spiral Enteroscopy

SE is the latest enteroscopy system. It uses an overtube with a raised helix at its distal end. In contrast to the overtubes used with DBE and SBE, the SE overtube can also be placed over a regular enteroscope or a pediatric colonoscope. Following scope insertion beyond the ligament of Treitz, the overtube is inserted and fixed to the enteroscope. Spiral clockwise rotation is initiated, which pleats the small bowel on the enteroscope during the insertion.[32]

Most studies of interest have focused on the antegrade approach for SE, demonstrating a mean intubation depth ranging from 176 to 262 cm.[33-35] In direct comparisons with DBE, preliminary data suggest easier handling with SE, as well as faster and deeper small-bowel intubation. However, the data are conflicting with regard to the rate of total enteroscopy and the diagnostic yield, which currently favor DBE.[36,37] Complications of SE include mostly mucosal tears.[33-35]

Specific Indications for Small-Bowel Endoscopic Imaging

Occult and Overt Obscure Gastrointestinal Bleeding

Occult and overt OGIB are encountered in routine gastroenterology practice and are defined as gastrointestinal hemorrhage of unknown origin following unrevealing upper gastrointestinal endoscopy and colonoscopy. Overt bleeding is visible to the naked eye as hematemesis, hematochezia, or melena, whereas occult bleeding is detected only with fecal occult blood test kits. Expert guidelines, including the American Society of Gastrointestinal Endoscopy (ASGE) guidelines, distinguish further between active and inactive overt OGIB. Gastrointestinal hemorrhage originates between the ligament of Treitz and the ileocecal valve in up to 20% of cases.[38]

OGIB is related to angioectasia of the small bowel in 70% to 80% of cases.[39] Further pathologic findings are small-bowel tumors, including adenocarcinomas, carcinoids, lymphomas, and gastrointestinal stromal tumors (GISTs), and nontumorous lesions, such as Crohn's disease, Meckel diverticulum, NSAID ulcers, drug-induced enteropathy, and vasculitis, as well as hemobilia, hemosuccus pancreaticus, and aortoenteric fistulae (Figures 1-3).[40]

The age of the patient at the presentation of OGIB may suggest the cause; patients younger than 50 years are more likely to have a small-bowel tumor, Meckel diverticulum, or Crohn's disease, whereas elderly patients are more likely to have angioectasia.[41,42]

Video Capsule Endoscopy in Bleeding The most common indication for VCE is OGIB (66%), followed by a workup for abdominal symptoms (10.6%) and suspicion of Crohn's disease (10.4%).[9] A pooled analysis of 24 trials

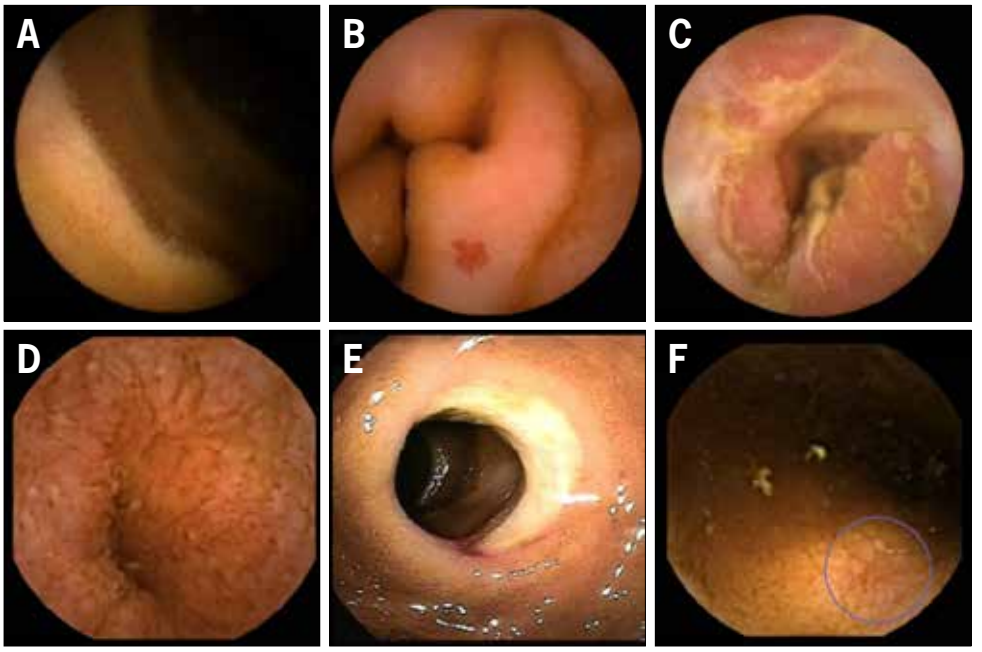

Figure 1. Video capsule endoscopy and enteroscopy images of normal studies and common benign conditions. Normal findings on video capsule endoscopy **(A)**. Arteriovenous malformations in the proximal jejunum on video capsule endoscopy **(B)**. Biopsy-proven Crohn's disease presenting with deep linear and stellate ulcers **(C)** as well as edema with strictures **(D)**. Biopsy-proven nonsteroidal anti-inflammatory drug enteropathy, which is characterized by an ulcerating stricture **(E)** and sharply demarcated ulcerations and erosions **(F)**.

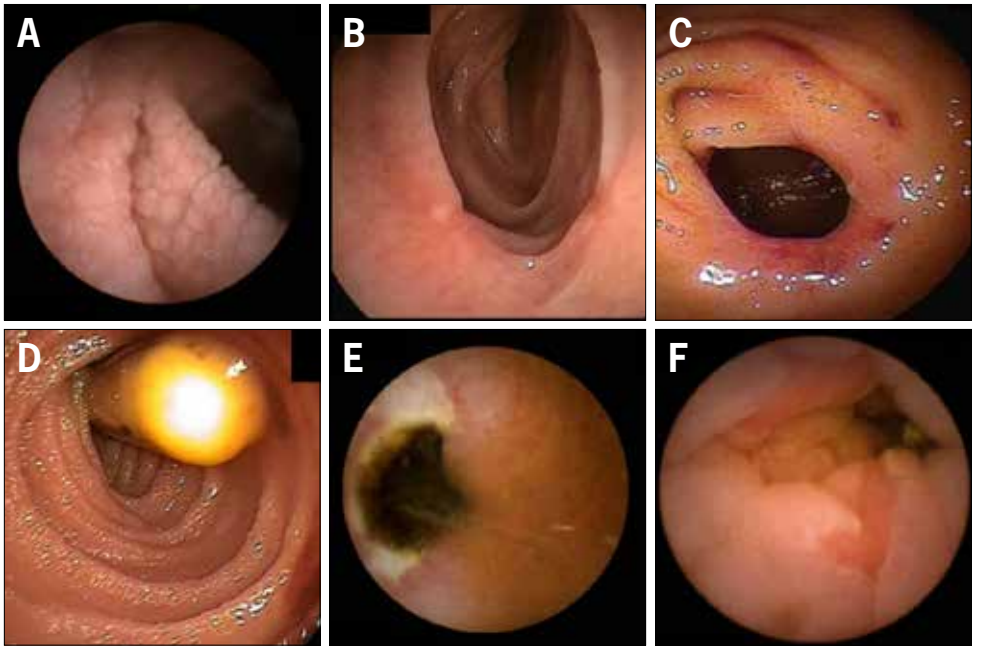

Figure 2. Video capsule endoscopy and enteroscopy images of less common benign conditions. Findings in celiac disease include absent or shortened villi, a mosaic mucosal pattern, and scalloped valvulae **(A)** as well as fissures and ulcers **(B)**. An enteroscopy image of a Meckel diverticulum with an ulcerated base **(C)**. An entrapped video capsule enteroscope visualized on enteroscopy **(D)**. Radiation enteropathy with pale mucosa, edematous folds, ulcers, and ectatic vessels **(E)**. Eosinophilic enteritis with smooth, erythematous patches and absent villi and without visible ulcers **(F)**.

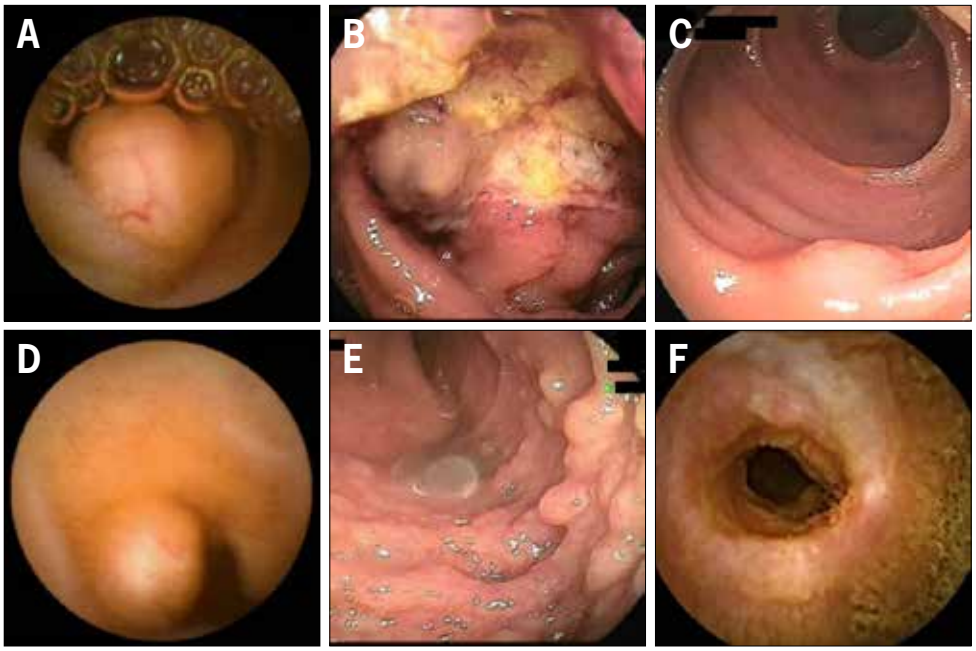

Figure 3. Video capsule endoscopy and enteroscopy images of small-bowel malignancies. A gastrointestinal stromal tumor presenting as a nodule with enlarged mucosal folds **(A)** or as a mass with abnormal surface vessels **(B)**. A carcinoid tumor presenting with a submucosal nodule or bulge, which can be associated with an ulcer **(C, D)**. A lymphoma with variable degrees of nodular mucosa **(E)** and occasional ulcerations and strictures **(F)**.

reported an overall diagnostic yield of 87% in OGIB.[43] Further studies reported a high positive predictive value (PPV), ranging from 94% to 97%, and a high negative predictive value (NPV), ranging from 83% to 100%.[44,45] The yield of VCE was highest in patients who had ongoing overt OGIB compared with those who had previous overt or occult OGIB (92.3% vs 12.9% vs 44.2%, respectively).[44] Similarly, Carey and colleagues described a decrease in the diagnostic yield from 87% to 46% when they compared patients with ongoing overt or occult OGIB.[46] In this context, the diagnostic yield rises when VCE is performed within 2 weeks of OGIB, when OGIB recurs, or when the hemoglobin level drops to below 10 g/dL.[47] A meta-analysis by Triester and colleagues compared different methods to identify the source of OGIB.[48] The yield of VCE was highest when compared with the yields of push enteroscopy (63% vs 28%), small-bowel radiography (67% vs 8%), and computed tomography (CT) enteroclysis (incremental yield of 38% for VCE).[48] A few studies have addressed the outcome of a negative VCE result in the setting of OGIB, showing a low rate of rebleeding, ranging from 5.6% to 11% at a follow-up of 1.5 years.[49,50] However, elderly patients with OGIB and a negative VCE evaluation were reported to have a higher risk for rebleeding (hazard ratio, 1.05).[51]

A second VCE following a negative VCE result for the evaluation of OGIB was shown to have a diagnostic yield of up to 75%.[52] Patients with initially negative VCE results particularly benefited from another VCE when the OGIB changed from occult to overt or when the hemoglobin level dropped by more than 4 g/dL.[53]

Device-Assisted Enteroscopy in Bleeding As with VCE, OGIB is the most common indication for DBE (62.5% of patients). DBE proved to be an effective diagnostic and therapeutic tool for OGIB.[54] Two systematic reviews and a meta-analysis calculated a diagnostic yield of 66% for DBE in OGIB.[55] However, the pooled diagnostic yields of VCE and DBE were not significantly different (60% vs 57% and 61.7% vs 55.5%, respectively) and included vascular malformations, inflammatory lesions, polyps, and tumors.[56,57] The concordance of VCE and DBE findings in OGIB ranges from 29% to 92%, with only a few lesions detected by DBE that were missed on VCE, and vice versa.[58]

As in VCE studies, a higher diagnostic yield for DBE was found in ongoing overt OGIB (100%) than in prior overt (48.4%) or occult (42%) OGIB.[59] The yield of DBE was greater after a positive VCE study than after a negative study (75% vs 27.5%, respectively).[57] Data on long-term outcomes following therapeutic DBE in OGIB are scant. Rebleeding rates of 42% to 46% at follow-up intervals of 30 to 55 months were reported. If rebleeding occurred following therapeutic DBE, a decreased requirement for transfusions was noticed.[60-62]

For SBE, a diagnostic yield of 47% to 60% in OGIB was reported. SBE led to new findings in 17.4% of patients in comparison with previous VCE.[27,30,63] Similarly, SE was reported to have a diagnostic yield of 65% in OGIB and 57% in all small-bowel pathology.[34,64]

A direct comparison between DBE and SBE had conflicting results. Overall, DBE was favored in light of a higher rate of total enteroscopy and diagnostic yield.[29,31,65] In terms of total enteroscopy rate and diagnostic yield, no significant differences were noticed between DBE and SE and between SBE and SE, although these studies included all small-bowel pathology.[37,66]

As of now, ASGE and other expert guidelines recommend DBE as a targeted follow-up procedure for both the diagnosis and treatment of OGIB following the identification of a target lesion by VCE unless massive hemorrhage occurs, which should prompt emergent angiography or even surgical evaluation.[67]

Crohn's Disease

The diagnosis of small-bowel Crohn's disease is challenging, as no single gold standard diagnostic test exists. The diagnosis of Crohn's disease is based on a constellation of symptoms, personal and family history, radiologic and laboratory findings, and findings on ileocolonoscopy, which is the primary diagnostic tool in conjunction with histopathology. In most cases, the diagnosis can be established with ileocolonoscopy. In this context, the endoscopic hallmarks of Crohn's disease include patchiness of the extent of disease, aphthous ulcers, erosions, granularity, nodules, and "cobblestone" appearance. The small bowel is affected in more than 50% of patients with Crohn's disease based on VCE.[68] Moreover, up to 30% of cases of Crohn's disease are limited to the small bowel, beyond the reach of ileocolonoscopy, creating a particular challenge in establishing the correct diagnosis.[69]

Video Capsule Endoscopy in Crohn's Disease The overall yield of VCE in the diagnosis of Crohn's disease ranges from 43% to 71%.[70-72] A recent trial demonstrated a diagnostic yield of 97.3% for small-bowel Crohn's disease when VCE was used in conjunction with ileocolonoscopy. Interestingly, no significant difference was found between the diagnostic yield of VCE and that of ileocolonoscopy.[73] In a meta-analysis of patients with suspected and established nonstricturing Crohn's disease, VCE had an incremental diagnostic yield of 38% over push enteroscopy, 40% over small-bowel radiography, 38% over CT enterography, and 15% over ileocolonoscopy for the diagnosis of Crohn's disease.[74] The data were confirmed in an updated meta-analysis.[75]

Current diagnostic algorithms for suspected small-bowel Crohn's disease focus on CT enterography and MRI enterography following ileocolonoscopy. Only a few pilot studies have compared the diagnostic yields of these 2 radiologic modalities and VCE. Available studies are mostly underpowered pilot projects, which may explain why no significant differences in diagnostic yield, sensitivity, or specificity were noticed, although VCE did show a trend toward higher sensitivity. This is based on the fact that VCE detects small-bowel erosions that are not seen on cross-sectional imaging.[76] A prospective study compared CT enterography, MRI enterography, and VCE for patients with suspected or newly diagnosed Crohn's disease. The sensitivity and specificity for Crohn's disease at the terminal ileum were 100% and 91% for VCE, 81% and 86% for MRI enterography, and 76% and 85% for CT enterography.[77] Another prospective study comparing VCE, CT enterography, and ileocolonoscopy for the evaluation of Crohn's disease showed a sensitivity of 83% for VCE and CT enterography, compared with 74% for ileocolonoscopy. This study also delineated the major limitation of VCE in Crohn's disease, which is a significantly lower specificity (53%) compared with other tests. VCE does not permit tissue sampling and cannot reliably differentiate Crohn's disease from other small-bowel inflammatory conditions and nonspecific findings, such as NSAID-induced pathology (Figure 1).[78]

According to expert opinion, VCE is offered to patients in whom small-bowel Crohn's disease is strongly suspected but whose ileocolonoscopy and cross-sectional imaging studies are negative. A normal VCE study in patients who meet these criteria has a high NPV for active small-bowel Crohn's disease.[79] This suggests that patient selection is key to optimize the pretest probability of VCE. Laboratory tests (eg, measurement of fecal calprotectin, fecal lactoferrin, and C-reactive protein levels and of the presence of thrombocytosis and anemia) and symptoms such as chronic abdominal pain, diarrhea, and weight loss were shown to play a role in patient selection.[80-82]

Most studies on the evaluation of Crohn's disease by VCE have 2 major limitations. First, a gold standard test is frequently missing. Consequently, the diagnostic yield is reported most of the time, as opposed to the sensitivity and specificity. Second, the labeling of small-bowel abnormalities on VCE as Crohn's disease is arbitrary. In this context, the spectrum of VCE findings described as Crohn's disease includes erythema, aphthous lesions, erosions, ulcers, and strictures. This partially explains the various reported rates of sensitivity, specificity, PPV, and NPV for the diagnosis of active small-bowel Crohn's disease.[83-85] The presence of more than 3 ulcerations in a patient not using NSAIDs is a common diagnostic criterion for small-bowel Crohn's disease.[86] Although studies that applied this criterion reported a PPV of only 50% for Crohn's disease, its strength lies in the high NPV of up to 96%.[86]

Device-Assisted Enteroscopy in Crohn's Disease DAE is recommended to diagnose Crohn's disease or to assess the response to medical therapy of Crohn's disease when patients are symptomatic but the results of ileocolonoscopy, VCE, and cross-sectional imaging are inconclusive.[87] It is not considered a first-line tool. DAE also offers the advantages of detailed mucosal inspection and the ability to obtain biopsy specimens. In addition, the extent and severity of Crohn's disease can be assessed.

The diagnostic yield of DBE to establish small-bowel Crohn's disease ranges from 30% to 69% and was shown to increase to 78% in patients with previously established Crohn's disease.[88-90] In 74% of cases, DBE findings resulted in a change of the medical management of small-bowel Crohn's disease.[91]

SBE was studied only in pediatric patients who had suspected or established Crohn's disease and showed a diagnostic yield for small-bowel Crohn's disease as high as 70%. In 60% of patients, changes consistent with small-bowel Crohn's disease beyond the reach of ileocolonoscopy and esophagogastroduodenoscopy were noted.[92] Data on the diagnostic yield of SE in Crohn's disease are lacking.

Small-bowel strictures are a known complication of long-standing Crohn's disease. Case series have demonstrated that DBE can successfully dilate Crohn's disease–related strictures of the small bowel. Additionally, retained objects, such as a video capsule, can be retrieved simultaneously.[93,94] Hirai and colleagues addressed the short- and long-term outcomes of endoscopic balloon dilation of Crohn's disease–related small-bowel strictures.[95] The short-term success rate was 80%. At the 3-year follow-up, 73% of patients did not require surgery.[95]

Complications of DBE and SBE in patients with Crohn's disease are rare (<1%).[90,92] However, in the setting of stricture dilation, the complication rate has been reported to be as high as 9.2%.[95]

Small-Bowel Tumors

Small-bowel tumors are rare and include benign pathology (eg, hemangiomas, hamartomas, and adenomatous polyps) and malignant pathology (eg, carcinoids, GISTs, lymphomas, primary adenocarcinomas, and metastasis). Presenting symptoms include occult and overt OGIB, abdominal pain, and recurrent small-bowel obstructions. VCE studies in patients with OGIB identified small-bowel tumors in 2.4% to 9%, with ulcers and nodules being the most common findings (Figure 3). The exact diagnosis can be established only by a biopsy during enteroscopy or surgical intervention. Up to 60% of small-bowel tumors are malignant.[96,97] However, despite the high sensitivity of VCE in OGIB, previous studies have reported that VCE misses small-bowel tumors in 10% to 66% of cases.[43,97-99] This is particularly true for proximal small-bowel tumors, including periampullary tumors, because of fast propulsive VCE transport in the proximal small bowel.[100] Therefore, a diagnostic DAE, such as DBE, is indicated in persisting OGIB when the results of cross-sectional imaging and VCE remain negative.[98]

Small-bowel entrapment of a video capsule occurs in up to 17% of patients with small-bowel tumors. The high retention rate limits the use of VCE in patients with an a priori higher likelihood of having a small-bowel tumor.[13] However, video capsule retention can also be considered as a "therapeutic complication," allowing both the detection and localization of a small-bowel tumor. In general, most small-bowel tumors require surgical resection, the main exceptions being asymptomatic benign pathology and lymphoma. The concept of a therapeutic complication needs to be discussed with the patient.

Summary

Endoscopic imaging of the small bowel is an important gastroenterologic tool for a variety of suspected or established medical conditions. VCE and DAE should be complementary to contrast-enhanced cross-sectional imaging, depending on the clinical scenario and local hospital availability and expertise.

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