Capsule Endoscopy and Enteroscopy in Celiac Disease

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KEYWORDS

- Celiac disease • Capsule endoscopy • VCE • Enteroscopy
- Device-assisted enteroscopy • Refractory celiac disease

KEY POINTS

- Capsule endoscopy is a well-tolerated, safe method to examine the small intestine, and is more sensitive than standard endoscopy to detect villus atrophy.
- Capsule endoscopy can assist in diagnosing Celiac disease for patients unable to have an endoscopy for duodenal biopsy and in cases of equivocal diagnosis.
- Capsule endoscopy and enteroscopy, in combination with radiographic enterography, are of proven benefit in the evaluation of complicated celiac disease especially refractory celiac disease type II.
- Limitations of video capsule endoscopy include the inability to obtain tissue diagnosis, subjective interpretation, possible capsule retention, and incomplete examinations.
- Computer-assisted programs to detect villus atrophy and capsule and enteroscopy design advances are in development.

INTRODUCTION

Video capsule endoscopy (VCE) is a minimally invasive examination that produces highly magnified views of the entire small bowel mucosa. It was introduced in 2001 and has revolutionized the diagnosis and management of small bowel diseases, including obscure gastrointestinal bleeding, small bowel Crohn's disease, other ulcerating diseases, polyposis syndromes, small bowel tumors, and complicated celiac disease.[1] The role of VCE in celiac disease is still evolving. The advantage over standard endoscopy is the highly magnified view of the mucosa for better detection of villus changes. There is also the ability to examine the entire small bowel mucosa that

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may be useful in cases of patchy villus atrophy. The main value is to detect complications in patients with celiac disease who have recurrent, persistent, or worrisome symptoms.

Duodenal biopsy is the gold standard for the diagnosis of celiac disease,[2] but it is not perfect. Villus atrophy can be patchy leading to false-negative results, or can be more distal than the duodenum and not reached by standard upper endoscopy, and therefore missed on biopsy.[3–6] Endoscopists may not obtain the recommended 4 to 6 biopsies during upper endoscopy, limiting diagnostic yield.[7] There is also variability in the interpretation of celiac histology such as in community hospitals or some commercial laboratories that may not consistently recognize the features of celiac disease.[8] Interpretation of the biopsies can also be affected by poor orientation. Endoscopy is invasive and may not be acceptable to patients owing to significant comorbidity or fear of the procedure. It involves anesthesia and days missed from school or work. In some cases, endoscopy with biopsies may be contraindicated owing to underlying medical conditions, such as significant cardiopulmonary disease and bleeding disorders.

The advantage of VCE is that it is minimally invasive, relatively safe,[9] and provides a high-resolution 8-fold magnification of the mucosa, similar to that of the dissection microscope.[10] In contrast with conventional endoscopy, the VCE examination is done without the use of air insufflation and the capsule is propelled distally by the normal peristalsis of the gastrointestinal tract. The capsule provides excellent visualization of the villus pattern (Fig. 1).

INDICATIONS FOR VIDEO CAPSULE ENDOSCOPY IN CELIAC DISEASE

There have been several guidelines proposed for the use of capsule endoscopy in celiac disease. An international consensus conference in 2005[11] advised that VCE can be considered in the evaluation of known or suspected celiac disease in certain circumstances, such as when a patient has positive serology and suspected celiac disease but is unable or unwilling to have a conventional endoscopy. It can be considered in cases of positive celiac serology (tissue transglutaminase or endomysial antibody (EMA)) and normal duodenal histology to examine more distal parts of the small bowel for villus atrophy. VCE is indicated in patients with celiac disease who develop warning signs such as anemia, weight loss, and gastrointestinal bleeding, and in those with
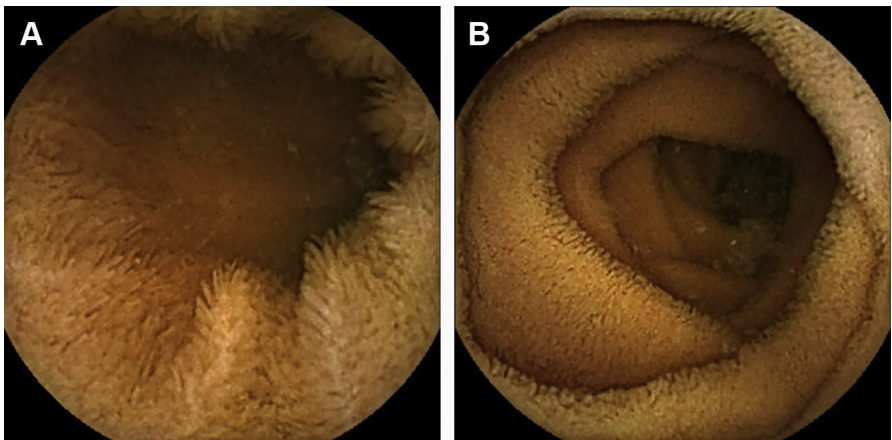

Fig. 1. (*A*) Normal villi example 1. (*B*) Normal villi example 2.

refractory celiac disease, especially type II, to evaluate for malignancy and other complications such as ulcerative jejunitis. In those with refractory celiac disease or suspected malignancy, VCE in combination with endoscopy, colonoscopy, and radiographic enterography followed by device-assisted enteroscopy may be required. The European Society of Gastrointestinal Endoscopy clinical guidelines, published in 2015,[12] concur with these recommendations. There is some disagreement as to the use of VCE for suspected celiac disease, particularly in the setting of a positive celiac disease serology and normal duodenal biopsy.[13]

Mucosal changes of celiac disease seen on upper endoscopy include scalloping of the mucosal folds, micronodularity, fissuring or mosaic pattern, and reduced duodenal folds,[14,15] changes readily identified on capsule endoscopy[16,17] (Fig. 2). VCE has excellent accuracy in identifying villus atrophy. Petroniene and colleagues[16] compared 10 patients with Marsh 3 histology with controls, and reported that VCE when compared with endoscopy was 100% specific, and tended toward a better sensitivity than endoscopy (70% vs 60%). There was a positive predictive value of 100% and a negative predictive value of 77%. Other studies have shown that VCE is more sensitive than optical endoscopy for detecting villus atrophy. In a study of 35 patients with villus atrophy, Murray and colleagues[3] found that VCE had a better
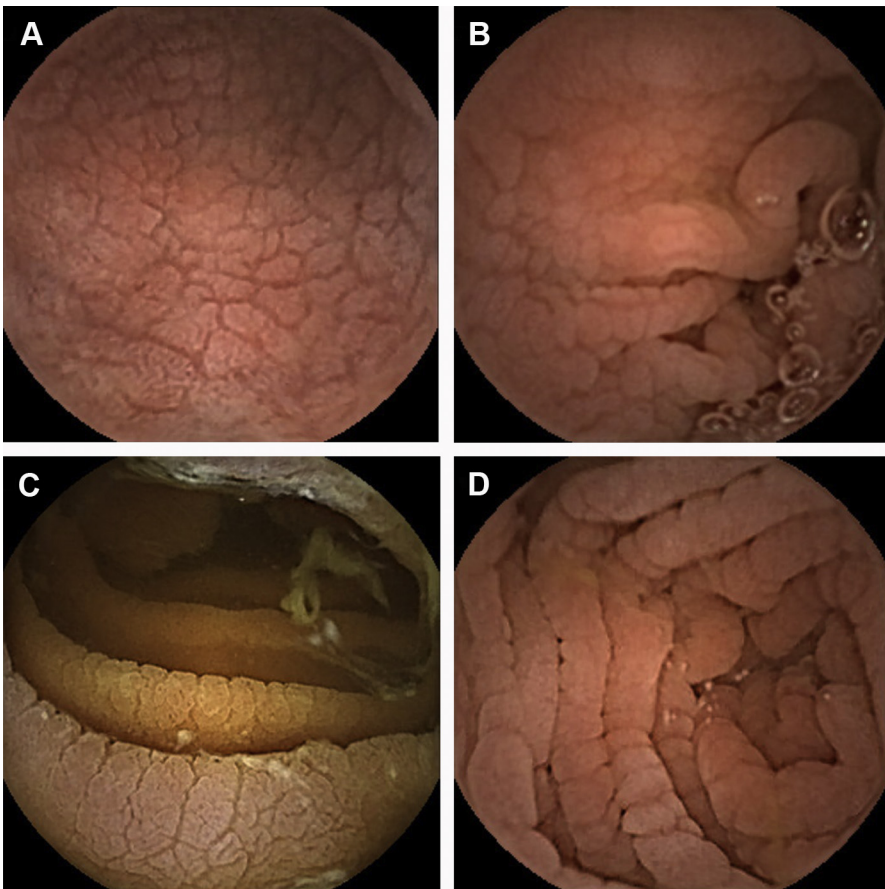

Fig. 2. (A) Mosaic pattern. (B) Nodularity. (C) Scalloped folds. (D) Scalloped layered folds.

sensitivity as compared with conventional endoscopy (92% vs 55%; P = .0005; specificity, 100%). In a study of 43 patients by Rondonotti and colleagues,[18] capsule endoscopy as compared with the gold standard of duodenal biopsy showed a sensitivity of 87.5%, specificity of 90.9%, positive predictive value of 96.5%, and negative predictive value of 71.4%. In a metaanalysis[19] of studies to determine the accuracy of VCE in celiac disease, a total of 166 patients from 6 studies were evaluated. The overall pooled VCE sensitivity was 89% (95% confidence interval, 82%–94%), and specificity 95% (95% confidence interval, 89%–98%).

When signs of villus atrophy are seen on VCE, there is a high probability that the patient has celiac disease; however, a normal capsule study does not exclude celiac disease. Biagi and colleagues[20] studied 32 patients to include Marsh scores 0 through 3 and reported a lower specificity of 63.6% comparing VCE findings and histology. They recommended that when VCE, done for any reason, detects villus atrophy, a biopsy should follow because the correlation with abnormal histology is high. However, a normal VCE does not exclude villus atrophy. This condition is also true for endoscopy; the absence of optical endoscopic features of celiac disease does not exclude celiac disease, and random biopsy of normal appearing mucosa is recommended.[21]

Interobserver agreement varies in studies based on the experience of the VCE reader. The interpretation of studies is subjective and agreement may be poor among capsule readers with limited exposure to celiac disease. Petroniene and colleagues[16] found the sensitivity and specificity of the test was 100% with experienced VCE readers, but agreement was poor among inexperienced readers. Rondonotti and colleagues[18] showed agreement ranging from 79.2% to 94.4% with kappa values indicating moderate to excellent agreement. Biagi and colleagues[20] proposed a 3-grade scale to standardize mucosal atrophy reading, but noted high interobserver variability, again suggesting that experience in VCE interpretation is important. With more experience in VCE reading and adoption of structured terminology of capsule findings, improvement in reader agreement is expected.[22,23]

In a recent multicenter, retrospective study,[24] 163 patients with suspicion of celiac disease who underwent VCE were analyzed for diagnostic yield, therapeutic impact, and safety. The diagnostic yield for all patients was 54% to include villus atrophy, complicated celiac disease, and other enteropathies. VCE results changed the therapeutic approach in 71.8% of cases. In patients with positive serology and negative atrophy on biopsy, VCE found intestinal atrophy in more than one-half of this group of 39 patients. These patients were treated with a gluten-free diet and 66.7% responded. They concluded that VCE was valuable in this group and that villus atrophy was missed owing to patchy distribution that may be more distal and not reached by endoscopic biopsies.

DOES VIDEO CAPSULE ENDOSCOPY HAVE A ROLE IN MONITORING?

One potential new application for VCE is noninvasive evaluation of the response to a gluten-free diet. Murray and colleagues[3] performed VCE on 35 patients at the time of celiac disease diagnosis, confirmed with duodenal biopsy and serology. VCE identified the distribution of villus atrophy; 59% showed extensive enteropathy from duodenum into the jejunum, 32% had villus changes confined to the duodenum, and 1 patient had villus changes seen only in the jejunum. Follow-up VCE showed that after a gluten-free diet for more than 6 months, healing occurred from distal to proximal in the small bowel.

Lidum and colleagues[25] evaluated the symptoms, serology, duodenal biopsy, and VCE in 12 patients after 1 year on a gluten-free diet. They also found healing from distal

to proximal. Importantly, in some patients duodenal follow-up biopsy remained abnormal, although their symptom scores, serology, and extent of villus atrophy on capsule examination improved. They concluded that small bowel mucosal healing as determined by VCE correlates with improvement in symptoms and that duodenal biopsy does not show the extent of improvement that has occurred more distally.

The European Society of Gastrointestinal Endoscopy guidelines[12] state that, at the present time, there is no role for the use of VCE to evaluate the extent of disease or response to a gluten free diet. More studies are needed to demonstrate a relationship between the quantitative extent of disease and severity of clinical presentation (**Boxes 1** and **2**).

CAPSULE ENDOSCOPY IN REFRACTORY CELIAC DISEASE

Capsule endoscopy has been evaluated in nonresponsive and refractory celiac disease. Patients with refractory celiac disease, particularly type II, are at risk for developing complications such as intestinal T-cell lymphoma and ulcerative jejunitis. These lesions are more commonly seen in the more distal small bowel[26–28] (**Fig. 3**).

Barret and colleagues[29] looked at the diagnostic yield of VCE in refractory celiac disease in 9 patients with symptomatic celiac disease, 11 patients with refractory celiac disease type I, and 18 patients with refractory celiac disease type II, and 45 patients without celiac disease. Villus atrophy and distal ulcers were more common in patients with celiac disease than controls. Low serum albumin correlated with more extensive mucosal disease and refractory celiac disease type II. Lymphoma was found in 3 patients.

In a study by Daum and colleagues,[27] 7 patients with refractory celiac disease type I and 7 patients with refractory celiac disease type II were examined by VCE, upper and lower endoscopy, and imaging with an abdominal computed tomography scan or MR tomography. Two patients had findings of intestinal T-cell lymphoma or jejunitis and 1 was found only by VCE. The other case was diagnosed by lymphadenopathy seen on computed tomography/MR tomography. This confirmed the value of VCE as well as other imaging modalities in patients with refractory celiac disease type II. They found no diagnostic benefit with advanced imaging in refractory celiac disease type I.

Other studies have frequently found positive celiac serologies in patients with nonresponsive celiac disease after adhering to a gluten-free diet for at least 6 months.[28] This finding supports eliminating other factors that can cause persistent symptoms before proceeding with further evaluation with VCE. Inadvertent gluten

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Box 1
Recommendations for VCE in celiac disease

1. Strong recommendation against VCE to make an initial diagnosis of celiac disease except for suspected celiac disease in a patient who is unable or unwilling to have a conventional endoscopy.

2. Equivocal diagnosis. Positive celiac serology but normal small bowel biopsy[11,12] (not all guidelines supportive[13]).

3. Celiac disease with unexplained or alarm symptoms, refractory celiac disease especially type II. Strong recommendation.

4. Currently no role for VCE in evaluating the extent of disease or response to a gluten free diet. Further studies needed.[12]

Abbreviation: VCE, video capsule endoscopy.

Box 2
Video capsule endoscopy in celiac disease: limitations to use

1. Unable to biopsy for tissue diagnosis.

2. Partial villus atrophy may be difficult to identify.

3. Interpretation is subjective and requires experience

4. There is interobserver variability.

5. Studies maybe incomplete

6. Possible additional cost factors.

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ingestion is common and can occur in up to 50% of patients. Others causes of continuing symptoms include lactose intolerance, fructose intolerance, small intestinal bacterial overgrowth, pancreatic insufficiency, irritable bowel syndrome, and microscopic colitis.[30]

The study by Atlas and colleagues[28] also found ulcerations and erosions of the small bowel in 18% of nonresponsive patients with celiac disease, 19% of controls, and 33% of uncomplicated celiac disease, and associated this with aspirin and nonsteroidal antiinflammatory drug use. They also identified 1 adenocarcinoma and 1 ulcerative jejunitis complication.

Efthymakis and colleagues[31] studied 26 patients with celiac disease and persistent iron deficiency anemia after at least 24 months on a gluten-free diet with documentation of normal celiac serologies. Iron deficiency anemia is a common finding at diagnosis and usually resolves after 12 months on a gluten-free diet.[32] Patients had an esophogastroduodenoscopy, colonoscopy, and VCE. VCE found significant disease in 3 patients including erosive jejunitis, and on subsequent enteroscopy and biopsy one was diagnosed as having refractory celiac disease type II and two were diagnosed as having Crohn's disease. They found a low albumin to be associated with the presence of more mucosal pathology, as was also seen in the study by Barret and colleagues[29]

VCE has identified complications of celiac disease such as lymphomas, adenocarcinomas, and ulcerative ileojejunitis, as well as other conditions such as Crohn's disease.[26–29] In a large, retrospective, multicenter European study,[33] 189 patients with
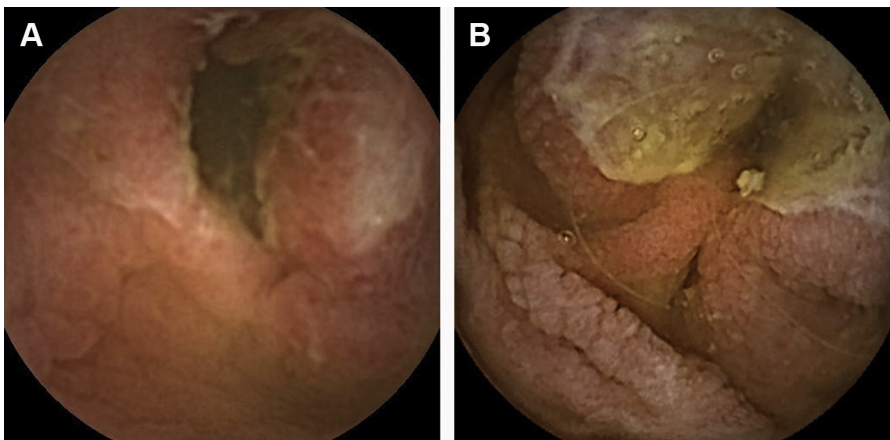
Fig. 3. (*A*) jejunal adenocarcinoma in celiac disease. (*B*) Ulcerative jejunitis.

celiac disease had VCE for nonresponsive celiac disease (n = 103), or celiac disease with alarm symptoms (n = 86). Findings included atrophic mucosa (48.7%), ulcerative jejunoileitis (11.1%), intestinal lymphoma (3.7%), and other enteropathies (3.7% including Crohn's disease and 1 neuroendocrine tumor). The overall diagnostic yield was 67.2% and this modified management in 59.3% of cases. They found the diagnostic yield was higher in the nonresponsive celiac disease group. They note that VCE had to be combined with other modalities such as balloon-assisted enteroscopy for histologic diagnosis. VCE was found to be valuable in the management of complicated celiac disease to identify or exclude significant pathology and guide deep enteroscopy.

Multiple guidelines recommend VCE in patients with celiac disease with unexplained persistent symptoms despite a gluten-free diet.

CAPSULE ENDOSCOPY AND CELIAC DISEASE: FUTURE DEVELOPMENTS

Limitations in the use of capsule endoscopy in celiac disease include subjective interpretation, its labor intensive nature, and an inability to detect mild villus atrophy. Virtual chromoendoscopy has been incorporated into capsule endoscopy. Flexible spectral imaging color enhancement, and blue mode filtering have been looked at to evaluate the usefulness of this technology primarily for increasing detection of vascular lesions and ulcerations.[34] The use of the 3 flexible spectral imaging color enhancement modes has not been shown to improve the detection rate for angioectasias and ulcers in a recent metaanalysis.[35] This visualization strategy has not been applied to capsule endoscopy and celiac disease.

There is much interest in the development of an observer-independent diagnostic method that could potentially bypass the difficulties in interpretation of both biopsy and capsule endoscopy for celiac disease. The development of an automated system for predicting celiac disease is being investigated.[36] Such technology could save costs, time, and manpower, and possibly increase safety if in some cases biopsies could ultimately be avoided.[37]

Ciaccio and colleagues[38] have reported on a computer-assisted method to detect and quantify villus atrophy by capsule endoscopy. Computer analysis of the 2-dimensional capsule image is used to generate a 3-dimensional mucosal structure, using shape-from-shading principles to measure the villus protrusions and detect and quantify villus atrophy. As compared with controls, patients with celiac disease and villus atrophy have more blunted protrusions. Image analysis is also done for texture differences between patients with celiac disease and controls. In VCE images of patients with celiac disease, there is significantly greater texture, which is a measure of the degree of variance in the images. Microscopic villus atrophy and macroscopic scalloping of folds, fissures, and mosaic pattern increase the heterogeneity of the pixel gray scale. The structural variation in patients with celiac disease with villus atrophy results in increased measure of texture. Quantitative image analysis has also been used to estimate motility by evaluating dynamic properties in a sequence of images and also by using the frequency spectrum generated by a series of capsule images. Using these methods and a polling protocol, villus atrophy was predicted with a sensitivity of 83.9% and specificity of 92.9%.[36] Further studies are now being done to validate this system in a larger study population.[38]

Summary

The role of capsule endoscopy in the diagnosis and monitoring of celiac disease is still being determined. Current consensus opinion limits VCE for diagnostic use under special circumstances, such as patients who are unwilling or medically unable to have an

upper endoscopy. There are strong recommendations against using VCE to make an initial diagnosis owing to its lower sensitivity to detect partial villus atrophy[13,39] and the need for duodenal biopsy for diagnosis in such patients. Positive celiac serology (tissue transglutaminase or EMA) and normal duodenal histology is a potential indication for VCE, although it is not supported by all studies.[18,25,40] In addition, a study by Kurien and colleagues[41] supports the use of VCE in equivocal cases of celiac disease with negative serology and villus atrophy or Marsh 1 and 2 lesions with a diagnostic yield of 18%. This and future study results may prompt change to the recommendations in those with equivocal celiac disease.

VCE is indicated in patients with celiac disease with alarm symptoms and particularly refractory celiac disease type II. VCE is only part of the evaluation, which includes upper endoscopy, colonoscopy, radiographic enterography, and device-assisted enteroscopy. The main limitation of VCE is the inability to obtain biopsies. Villus atrophy is not specific for celiac diagnosis. VCE interpretation is also subjective and dependent on the experience of the capsule reader. There is a risk of capsule retention in patients with refractory celiac disease type II and obstructive symptoms owing to stenosis related to ulcerative jejunitis, lymphoma, or in adenocarcinoma.

ENTEROSCOPY IN CELIAC DISEASE

Celiac disease involves predominantly the proximal small bowel, the first site of gluten exposure. In most patients, inflammation is found in the duodenum, which is easily reachable by standard endoscopy for diagnosis. Rarely, celiac disease spares the duodenum and involves the jejunum alone.[42] In such patients, enteroscopy is required for diagnosis. In a prospective study of push enteroscopy in responsive and refractory celiac disease, Cellier and colleagues[43] found similar endoscopic and histologic findings in the duodenum and jejunum of responsive celiac disease. Four patients had villus atrophy that was more severe in the duodenum than jejunum but this finding did not change management. Although there is little role for enteroscopy in the diagnosis of celiac disease, it is very useful to evaluate complications of the disease.

Celiac disease is associated with an increased risk for GI cancers that include adenocarcinoma of the small bowel (Fig. 4).

Fig. 4. Jejunal adenocarcinoma in celiac patient with persistent iron deficiency anemia.

Rarely (0.31%),[44] patients with celiac disease fail to respond to a gluten-free diet exhibit alarm symptoms and are diagnosed with refractory celiac disease. A subset of these patients, have aberrant intraepithelial T cells (refractory celiac disease type II) and develop ulcerative jejunitis and enteropathy-associated T-cell lymphoma (EATL) that is associated with a poor 5-year survival.[45] Patients with refractory celiac disease are usually older, male, and have severe diarrhea, weight loss, and hypopro-teinemia. Occasionally, obstructive symptoms are present owing to small bowel ulcer-ation and stenosis. Duodenal biopsies in refractory disease show severe villus atrophy, but ulcerating lesions and lymphoma are often deep in the small bowel, out of reach of standard endoscopy and require enteroscopy for diagnosis and man-agement (**Box 3**).

THE ROLE OF DEVICE-ASSIST ENTEROSCOPY IN CELIAC DISEASE

In 2001, Yamamoto[46] developed an enteroscope and overtube device with balloons at both ends to allow pleating of bowel on the back of the overtube and advancement of the enteroscope deep into the small bowel using a push and pull technique. Since then, other devices have become available for deep enteroscopy: single-balloon enteroscopy that uses a single balloon on the tip of the over tube, spiral enteroscopy that uses an overtube with spiral ridges and rotational energy to pleat bowel for advancement, and a through-the-scope balloon device using standard endoscopy.[47] These techniques are labor intensive, have steep learning curves and require dedi-cated staff. In small studies, the devices have similar diagnostic yields. Complications include bowel perforation, bleeding, and pancreatitis.[47] device-assist enteroscopy has revolutionized the diagnosis and therapy of small bowel disease, particularly small bowel bleeding and tumors.

The use of device-assist enteroscopy in celiac disease remains limited owing to the rare nature of the type of this complicated disease. Studies are few, small, and pre-dominately used double-balloon enteroscopy (DBE). In a study of patients with refrac-tory celiac disease by Hadithi and colleagues,[48] EATL was found in 5 of 21 patients (24%) and ulcerative jejunitis in 2 of 21 patients (9%). Endoscopic appearances of EATL included circumferential, discrete, or confluent ulcerations. In 4 patients with computed tomography findings suggestive of small bowel wall thickening, EATL was excluded. DBE was useful to both diagnose and exclude EATL. Tomba and col-leagues[49] reported on VCE and DBE in 53 patients with poor response or nonadher-ence to a gluten-free diet and alarm symptoms. DBE detected 3 malignancies (5.7%), 2 jejunal adenocarcinomas, and 1 ileal neuroendocrine tumor.

In a recent metaanalysis by Elli and colleagues[50] on the use of VCE and enteroscopy to detect malignant and premalignant small bowel lesions in 515 patients with compli-cated celiac disease, only 3 European studies (76 patients) met inclusion criteria using push enteroscopy or DBE. There were 8 small bowel malignancies (10%) detected—5 EATL, 2 adenocarcinoma, and 1 neuroendocrine tumor. Ulcerative jejunitis was found in 13 patients (17%). The overall diagnostic yield for enteroscopy was 27%. VCE and

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Box 3
Recommendations for enteroscopy in celiac disease

1. Strong clinical suspicion of celiac disease with negative duodenal biopsies[42] or equivocal diagnosis.

2. Celiac disease with unexplained or alarm symptoms, suspected malignancy, and refractory celiac disease especially type II.[48–50]

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enteroscopy were effective to detect small bowel malignancies and ulcerative jejunitis in complicated celiac disease.

SUMMARY

VCE is more sensitive than standard endoscopy to detect villus atrophy and define the extent of disease with good interobserver agreement with experienced capsule readers; however, it lacks the capacity to take a biopsy. VCE is currently used to assist in the diagnosis of celiac disease in special circumstances when duodenal biopsy is not possible. The role of VCE in the diagnosis and monitoring of celiac disease is evolving. Computer-assisted diagnosis by analysis of villus changes and motility using quantitative image analysis will be helpful in the future usefulness of VCE in celiac disease.

VCE and enteroscopy combined with radiographic enterography have proven benefit in patients with complicated celiac disease (alarm symptoms, iron deficiency anemia, refractory celiac disease type II, and suspected ulcerative jejunitis, T-cell lymphoma, or small bowel adenocarcinoma). Advances in VCE and device-assist enteroscopy design with developments enabling capsule biopsy and locomotion[51] and a motorized spiral device for enteroscopy are in development.

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