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European Society of Gastrointestinal Endoscopy (ESGE) Video capsule endoscopy: Update to guidelines (May 2006)

Introduction

Video capsule endoscopy (VCE) has become a very important tool for diagnosing of many small-bowel disorders. Upcoming VCE techniques for the investigation of disorders of the esophagus, stomach, and colon may render it a promising technique for these organs as well.

The purpose of this review is to update the previous set of European Society of Gastrointestinal Endoscopy guidelines published in 2004. This update is based on our current knowledge of clinical practice and the published literature in this field.

Procedure

The procedure can be conducted on an ambulatory basis. Standard patient preparation includes a 12-hour fast prior to the procedure. Bowel preparation is a matter for debate. Some experts recommend partial or complete bowel preparation, with polyethylene glycol administered either the evening prior to the procedure, for example 16 hours [1] before the recording, or on the same day, at least 2–3 hours before the capsule examination. However, 80 mg of simethicone 20 minutes before the procedure can be recommended to all patients, the administration of 2 liters of a polyethylene glycol-based solution and 10 mg of metoclopramide can be considered optional. The rationale behind a prep solution is that, as the capsule advances through the small bowel, visualization of the mucosa may be impaired when there is dark luminal content and bubbles. The use of prokinetic agents is considered controversial. A recent study showed that erythromycin had no significant effect on capsule propulsion in the small bowel [2], in contrast to findings elsewhere that metoclopramide may increase the likelihood of successful small-bowel examination (metoclopramide decreases gastric transit time) [3]. At this stage, however, recommendations for use of prokinet-

ics are not fully justified. Patients are allowed to drink clear liquids 2 hours after ingestion of the capsule and to eat a light meal 4 hours after ingestion.

Currently, two types of video capsules are available for use. The Given Imaging capsule (PillCam SB) was used to pioneer the technique and employs complementary metal oxide silicon (COMS) technology. More than 300 000 PillCam capsules have been used worldwide since the development of this technique and up to now, all published evidence in peer reviewed journals is based on this form of capsule.

The Olympus capsule endoscope (EndoCapsule EC type 1), with technology based on a charge-coupled device (CCD) and with electronic enhancement of image quality, was launched recently (limited data have been presented at a few meetings [4]).

Both capsule systems also provide an external control system (real-time viewer) that allows real-time checking of the images from the capsule. This system can be used at the beginning of the examination to avoid the capsule's being trapped in the esophagus and/or to shorten transit time in the stomach. The medical benefit of this control system has yet to be proved in well-designed studies.

Reading the recorded images

Location

The Given Imaging workstation software that is used to process the capsule images incorporates a locating feature. This makes it technically possible to approximate the location of any pathological findings within an average range of 3.77 cm, but the relevance of this feature in clinical practice is unknown. Locating the position of the capsule in the abdomen is attempted by triangulation from the three closest sensors; these are identified ac-

ording to the strength of the signals received from the capsule by the eight sensors attached to the abdominal wall. The location is then calculated from the position of these sensors and displayed on the computer screen as a two-dimensional image.

The Olympus EndoCapsule software provides an antenna (eight antennas combined into one); the antenna receiving the strongest signal is highlighted, which gives an idea of the capsule's position. However in clinical practice, identification of the capsule's position is often considered imprecise, and its approximate location is usually guessed on the basis of sometimes different mucosal patterns in jejunum and ileum and is also assessed according to the time elapsed from the start of the examination. Furthermore, it is now possible to directly check the capsule images during the procedure using the Olympus external viewer.

Software

1. Multiview

Video capsule software has also recently had a "multiview" feature added for reading the VCE recordings. This allows for the simultaneous display in adjacent windows of two or even four consecutive images from the recording. The new software by Given allows for faster "quick view" browsing, has a "rapid atlas" tool for comparing pathological images, a "circumferential scale" to estimate the circumferential involvement of a finding such as a varix or an ulcer, and a new automatic viewing mode. Since software is constantly updated, guidelines can only report on the present status.

2. The "suspected blood indicator"

The newer versions of capsule endoscopy include software that detects the color red, which may help to identify bleeding in the small intestine. Both the PillCam and Olympus video capsules have this feature. Preliminary reports from a few studies regarding the accuracy of this feature are conflicting [5–7].

Indications

A Small-bowel diseases

1. Obscure gastrointestinal bleeding

The primary and most frequent indication for VCE of the small bowel has been for the diagnosis of obscure gastrointestinal bleeding. Obscure gastrointestinal bleeding accounts for up to 5% of gastrointestinal bleeding, and is defined as the absence of an identified source of recurrent or persistent gastrointestinal bleeding after standard evaluation by upper endoscopy and colonoscopy [8]. Patients with obscure gastrointestinal bleeding may also have obvious bleeding (overt obscure gastrointestinal bleeding), or positive guaiac stool test results and/or iron-deficiency anemia (occult obscure gastrointestinal bleeding). The yield of capsule endoscopy appears highest for patients with ongoing overt bleeding compared with obscure occult bleeding, as shown in a recent study [9] of 100 consecutive patients with obscure gastrointestinal bleeding. The diagnostic yield was 92% and 44% for overt active bleeding and obscure occult bleeding respectively. The most common lesions were angiodysplasia, in 29%, and inflammatory bowel disease, in 6%.

Compared with other diagnostic radiological tests, including barium radiography, push enteroscopy, and cross-sectional imaging, VCE has a significantly higher yield in patients with obscure gastrointestinal hemorrhage [9–16].

The overall yield for obscure gastrointestinal bleeding is in the range of 50%–81% as reported by various studies [9–16]. A recent meta-analysis indicated that the incremental yield of VCE over push enteroscopy and small-bowel barium radiography for clinically significant findings is $\geq 30\%$ with a number-needed-to-treat (NNT) of 3 [16]. VCE helps with management decisions with obscure gastrointestinal bleeding and can replace more complex and risky standard tests [17]

Based on findings from a recent study [10], the optimal timing (higher yield) for a video capsule investigation in obscure gastrointestinal bleeding is within the first few days post bleeding with the maximum wait being 2 weeks.

In conclusion, VCE with the Given Imaging PillCam technology has been widely studied, and is considered to be a very valuable tool for investigating obscure gastrointestinal bleeding. This can presumably translate to better management outcomes than obtained with other modalities for patients with obscure gastrointestinal bleeding, although additional trials are still needed to clarify this issue.

2. Crohn's disease

Capsule endoscopy has a high yield in findings small bowel lesions in Crohn's disease, as illustrated by several comparative studies, and may make the diagnosis in the subset of patients with clinical suspicion but negative upper and lower endoscopy including inspection of the terminal ileum [18–25]. VCE permitted confirmation of the diagnoses of small-bowel Crohn's disease in both patients with Crohn's and in those with suspected Crohn's disease in which the diagnosis was not possible by other conventional means of investigation. The diagnostic yield for this indication ranges from 43% to 71%, and according to recent studies VCE was superior to push enteroscopy [4] and enteroclysis [24,25]. VCE detected more proximal and middle small-bowel cases of Crohn's disease than computed tomography (CT) enterography and small-bowel follow-through (SBFT) [26]. These results have been used to indicate a role for VCE with regard to early disease management, but its impact on the management of patients with established CD is not fully clear. In the studies published, in some patients the medication dosage was either increased or decreased, with commencement of immunomodulator or anti-tumor necrosis factor (TNF) therapy, and in other patients surgery was said to be avoided [22]. Future studies will show which role VCE may have in assessing disease prognosis, activity, and tissue healing post therapy. It is also hoped that VCE may play a role in the management of Crohn's disease patients by defining the extent and severity of the disease in the small bowel [27]

There are still a few issues to be resolved. Firstly, the rate of false-positive and false-negative results with VCE has not yet been addressed. In other words, not all ulcers are Crohn's disease and not all biopsies are confirmatory. The differential diagnosis for Crohn-like pathologies on VCE should be elaborated, a full his-

tory provided, and relevant tests carried out to confirm the presence or absence of Crohn's disease. In addition, one should not overestimate mucosal abnormalities in patients with Crohn's disease, especially if the patient is taking nonsteroidal anti-inflammatory drugs (NSAIDs). The NSAIDs should be stopped 2 months prior to the test. Secondly, from a technical point of view, VCE does not offer the option of tissue sampling for these patients and they may ultimately need push enteroscopy or double-balloon endoscopy for tissue sampling. Thirdly, the gold standard test to compare with VCE is not yet ideal since, so far, VCE has been proved superior to these conventional tests in terms of diagnostic yield. Lastly, the interobserver reading variability may be a source of bias for some cases and confirmation by another gastroenterologist may be needed but not always possible in some small community hospitals. The risk for retention in patients with confirmed Crohn's disease is estimated to be 5%.

Further large, randomized prospective trials to specifically investigate each factor will obviously be necessary to define the ultimate role of CE in this setting.

3. Celiac disease

On the evidence of a few studies, capsule endoscopy may be useful in diagnosing celiac disease [28–32]. Since the test is done in the free air-insufflation environment of the small bowel, the visual images are taken very close to the mucosa and hence clear pictures of the mucosa are obtained. Furthermore, this technology, with its magnification capacity of 1:8, can provide good quality images of the small bowel, including the villi. The abnormalities detected include primary changes in small-bowel mucosa, namely villous atrophy [28] (scalloping, fissuring, mosaic pattern, flat mucosa, loss of the circular folds and nodularity), and complications related to celiac disease such as ulcerative jejunoileitis, enteropathy-associated T-cell lymphoma and adenocarcinoma of the small bowel [30].

The sensitivity and specificity of VCE in detection of villous abnormalities can be high when an experienced capsule endoscopist analyzes the data [28]. This finding shows that a gastroenterologist familiar with VCE may interpret the data better, making the test more accurate. There are no data comparing VCE with conventional endoscopy in diagnosing celiac disease in a low prevalence setting, but we know that, in general, magnification endoscopy is better than conventional endoscopy for such types of diagnosis [29]. Nevertheless, VCE is a relatively noninvasive test and may be as good as or better than magnification endoscopy. For this reason, the International Conference on Capsule Endoscopy (ICCE), sponsored by the company Given Imaging, has reached a consensus that VCE may be sufficient for establishing a primary diagnosis in patients with strongly suggestive serological markers for celiac disease who are unwilling or unable to undergo esophagogastroduodenoscopy (EGD) [33]. Management problems when histology is not performed have not been discussed in detail yet; further difficulties may arise in patients with positive serological markers and negative VCE, raising the possibility of partial villous atrophy.

Other potential indications for VCE in celiac disease include complications related to celiac disease. Patients with celiac disease and non-specific or alarm symptoms like persistent abdominal

pain, anemia, or bleeding will likely benefit from this investigation that explores all of the small bowel. The yield for detecting endoscopic findings due to complications related to celiac disease is higher [30] than with other modalities. However, one should ensure that it is determined whether these entities are related to celiac disease or are a separate phenomenon, although the management may not differ significantly unless these findings are secondary to an identifiable culprit such as NSAIDs.

In conclusion, and based on small studies, VCE provides detailed images of the small bowel in patients with celiac disease. This may facilitate the assessment of celiac disease and its related complications. Therefore, VCE may be of interest in the initial work-up of celiac disease (especially in high risk patients), in refractory celiac disease, and in case of alarm symptoms.

4. Hereditary polyposis syndromes

VCE can be used to detect small-bowel polyps related to hereditary polyposis syndromes. Recently, VCE has been found to have a higher yield for detecting such polyps than barium studies [34]. Another study that compared polyp detection by VCE and magnetic resonance imaging (MRI) in patients with hereditary polyposis found similar accuracy among patients with polyps larger than 15 mm. However, the detection rate for polyps between 5 and 15 mm was much higher with VCE, and polyps 5 mm and smaller were detected only by VCE [35]. In this study, MRI, however, was more accurate in determining the exact size and location of the polyps detected by both studies. Growing evidence from other studies confirms the usefulness of this technique for detecting polyps in selected patients with familial adenomatous polyposis (FAP) who have an increased risk of developing polyps in the distal part of the small bowel, and as a first-line procedure in patients with Peutz–Jeghers syndrome (PJS) [36,37]. The detection by VCE of these polyps in some patients with PJS has led to a change in management in a significant proportion of them. Capsule endoscopy therefore appears to be a promising alternative to the SBFT (enteroclysis) series for surveillance in patients with hereditary polyposis syndromes.

5. Small-bowel tumors

Diagnosis of small-bowel tumors is a new field for capsule endoscopy examination. Prior to the use of the video capsule, small-bowel tumors were considered rare (found in about 1% of patients according to radiological imaging studies) [38]. These tumors have often been diagnosed late in their stage of development or incidentally during a laparotomy or biopsy. With the advent of video capsule endoscopy, this could change. Some studies [38–40] have reported small-bowel tumors in 6%–9% of patients – many more than previously expected. The most common indication for video capsule endoscopy in patients with small-bowel tumors was obscure gastrointestinal bleeding/anemia (80%). Video capsule endoscopy detected small-bowel tumors after patients had undergone an average of 4.6 negative procedures. The majority of the detected small-bowel tumors were malignant (60%), consisting of adenocarcinomas, carcinomas, melanomas, lymphomas, and sarcomas. The benign small-bowel tumors (40%) were gastrointestinal stromal tumors (GISTs), hemangiomas, hamartomas, and adenomas. Therefore, in cases of unclear obscure gastrointestinal bleeding, the possibility of

small-bowel tumor should be considered and the patient assessed with video capsule endoscopy [38–45].

6. NSAID-related conditions

Considerable side effects and pathological lesions related to the gastrointestinal tract can be caused by NSAID use. VCE was useful in a recent study to detect lesions caused mainly by NSAIDs [46]. The most common lesions were mucosal breaks, seen in 40% of patients. Other lesions were reddened folds, petechiae, denuded mucosa, blood in the lumen, ulcers, and intestinal diaphragm.

In another similar study [47], VCE was able to detect small-bowel mucosal breaks in 55% of patients using naproxen, 16% of those using celecoxib, and in 7% of placebo patients with a normal baseline VCE prior to the study. VCE showed that NSAID damage is more frequent and extensive than suggested by studies of NSAID-associated small-bowel injury shown by ileoscopy performed at the time of colonoscopy or in autopsy examination [48]. Subsequent studies are needed to investigate whether there is a pattern of damage associated with outcomes such as unexplained iron-deficiency anemia or hypoalbuminemia among chronic NSAID users [48].

7. Miscellaneous

Different small-bowel lesions have been described using video capsule endoscopy. Case reports have demonstrated the possible usefulness of VCE in the diagnosis of Meckel's diverticulum, tuberculosis, *Ascaris* infection, and aortoduodenal fistulas [49–52]. Some centers have also evaluated capsule endoscopy for the study of gastrointestinal tract motility disorders, the assessment of bowels in post transplant patients, in unexplained abdominal pain and diarrhea. The usefulness of this technique for such indications has not yet been established.

8. Pediatrics

Capsule endoscopy has been used less frequently in pediatric populations for to some of the indications mentioned above (e.g. obscure bleeding and Crohn's disease); information has mainly been obtained from case reports and small series studies. The video capsule was superior to conventional studies (gastroscopy, colonoscopy with ileoscopy, and SBFT examinations) in finding lesions suggestive of Crohn's disease, in a small study involving patients between the ages of 12 and 16 [53]. In a recent small study, VCE was used in to examine children over the age of 10 with obscure small-bowel lesions; it was found that VCE is an accurate and noninvasive approach for diagnosing these lesions [54]. Safety issues may limit the use of VCE in the younger age group given that in this group there may be difficulties passing the capsule through the gastrointestinal tract, particularly through the pylorus and ileocecal valve.

B Esophageal capsule (PillCam ESO) investigation

The PillCam ESO, which was specifically designed to investigate esophageal diseases, has recently been evaluated and released [55–59]. Because there is only a short transit time in the esophagus, the video capsule is equipped with miniature sensors at both ends to improve image quality.

The patient is asked to fast for 2 hours prior to the procedure. The patient swallows the capsule while supine, maintains this position for 2 minutes, and is then asked to rise slowly to a 30-degree angle and then to increase the angle by 30 degrees every 2 minutes over a period of about 6 minutes until sitting upright (improvements in the ingestion procedure have recently been presented [60]). During this time, the capsule camera flashes 14 times per second to capture images from both ends of the capsule which are then transmitted to the three sensor arrays that are placed on the patient's chest.

The main potential indication for PillCam ESO investigation is for patients with gastroesophageal reflux disease (GERD) and Barrett's esophagus. It was approved by the US Food and Drug Administration (FDA), following a study by Eliakim et al. published in abstract form [55]. The sensitivity and specificity for both indications were very high (e.g. 100% and 80% respectively). This was subsequently confirmed by a larger multicenter study carried out by the same group which re-emphasized the previous findings [59]. Recently, a new device with an image production capability of 14 fps (frames per second) has been developed. This device has been compared with a 4-fps device in a recent study, and proved to be superior in terms of sensitivity and specificity for GERD, Barrett's esophagus, and for visibility of the upper esophageal sphincter [56].

Presumably, other esophageal diseases could also be detected by the PillCam ESO. Small pilot studies suggest that it is comparable to EGD in detecting esophageal varices and assessing portal hypertension in cirrhotic patients [57,58]. However, this comparison between VCE and EGD can be misleading in some cases for a few reasons. The EGD provides a more extensive area for examination including the stomach and small bowel, and has the advantage of allowing intervention, compared with the esophageal imaging only that is allowed by the capsule. On the other hand, in the studies comparing the two devices a regular EGD instrument was used (the XP in one study, type not mentioned in the other), as opposed to new-generation EGD devices with high magnification, which provide better imaging than regular EGD instruments. Additionally, the studies did not fully address issues such as detection and accuracy rate for short-segment compared with long-segment Barrett's esophagus, using the esophageal VCE technique. The problem of uncontrolled image production in VCE may play a significant role in the misdiagnosis of short-segment Barrett's esophagus in high-risk patients. On the other hand, esophageal VCE has been proved to be excellent for detection of erosive esophagitis. However, patients with nonerosive esophagitis who continue to have symptoms will likely require EGD for better evaluation.

In patients with pacemakers, there is a risk of interference with the pacemaker because of the proximity of the sensor arrays placed on the patient's chest when the esophageal capsule is used. This has not yet been confirmed by any trials.

In conclusion, use of the esophageal capsule should be determined on a case by case basis, depending on the patient's presentation. Those with suspected Barrett's esophagus should undergo EGD so that a biopsy can be obtained. The role of the esophageal capsule for other indications needs to be clarified further by lar-

ger prospective studies. The issue of the relative cost-effectiveness of esophageal capsule examination and EGD in such indications will also need to be clarified by further study.

B Colon capsule investigation

The first two pilot trials on colon capsule endoscopy have recently been published [61,62]. Using a specified preparation protocol and a specially designed biheaded capsule which switches itself on 2 hours after ingestion, the entire colon was visualized in the majority of cases and sensitivity and specificity rates for larger or multiple polyps between 60 and 80% could be achieved. Further trials will corroborate the clinical role of this new capsule in clinical practice especially in the screening setting.

Limitations and risks

Generally, VCE is very well tolerated by patients. However, there are a few limitations and risks which should be taken into consideration.

Capsule retention is defined as having an endoscopy capsule remain in the digestive tract for a minimum of 2 weeks [63]. This problem has been reported especially among patients with Crohn's disease and among those with a high risk for stricture formation, such as NSAID users and ischemic colitis (associated with small-bowel tumors, radiation enteritis, surgical anastomotic strictures). The occurrence of this problem is variable and largely dependent upon the nature and extent of the disease and the degree of stenosis. The rate has been reported as 1%–2% [64,65]. Recently, a "patency capsule," of similar size to the video capsule and able to dissolve spontaneously as it is mainly composed of lactose, has been developed to assess bowel patency and degree of stenosis. When passage of the patency capsule is blocked, the capsule dissolves in 40–100 hours. The safety and efficacy of this capsule has been questioned [66]. There is a risk that the capsule itself will exacerbate the stenosis and surgical intervention has been reported, especially among patients with Crohn's disease (mainly those with a high degree of stenosis) [66,67].

For this reason, if VCE is indicated, careful consideration must be given before performing VCE in high risk patients. VCE should be preceded by imaging tests to exclude stenosis in patients with suspected Crohn's disease. Patients with a history of abdominal obstruction, abdominal surgery, and abdominal or pelvic area radiation exposure should be excluded.

Medical treatment with corticosteroids or infliximab can release a trapped capsule but in some cases endoscopic or surgical removal is required.

The extent of false-negative results may be an issue, given the fact that VCE is largely dependent on peristalsis which affects its image angle accuracy. This is attributed to an "image skip" phenomenon since the visual field of the camera does not cover 360 degrees.

VCE should not be used in patients with swallowing disorders, due to the risk of aspiration. The safety of its use during pregnancy has not yet been studied. Electromagnetic interference with pacemakers can occur; however, this is without clinical significance and no potential dangerous inhibition of pacemakers was observed in a recent study [68]. The absence of reimbursement for the procedure in the majority of European countries is still a major drawback.

Future of capsule technology

The technology of capsule endoscopy is evolving very rapidly, and will certainly have an impact on many aspects of gastrointestinal disease. Ideas for therapeutic interventions using the capsule, such as delivery of medication to specific disease sites and the possible use of lasers, have already been discussed. Problems to overcome would be navigation of the capsule and real-time viewing of the study images, which may take several hours.

Conclusion

VCE is an important new diagnostic facility for the gastrointestinal tract, which has been adopted by gastroenterologists and has become part of regular clinical practice. Several new applications promise to expand its role in gastrointestinal disorders. It is a safe, noninvasive and very well-tolerated method if used in the right patient. VCE is a valuable tool in the diagnosis of small-bowel diseases, especially bleeding lesions and Crohn's disease. Larger studies will likely clarify its other possible roles in esophagus and colon in the future.

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