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Capsule Endoscopy: Strategies and Pitfalls of Interpretation

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1. Introduction

Video capsule endoscopy (VCE) introduced a new era in the study of small bowel disease (Iddan et al., 2000). Prior to VCE, visualization of the small intestine required radiographic or endoscopic methods that had significant disadvantages in terms of radiation hazard, patient discomfort as well as had low diagnostic sensitivity and specificity (Foutch et al., 1990; Rabe et al., 1981). In contrast, VCE allowed for evaluation of the entire small bowel mucosa without radiation, sedation or discomfort to the patient (Appleyard et al., 2000; Ell et al., 2002; Hahne et al., 2002; Lewis & Swain, 2002). The videocapsule is a 11×26 mm disposable device that weighs 3.7 g. and is covered with a biocompatible plastic containing a metal oxide silicon chip camera, lens, light source, battery, and radio-telemetry transmitter (Davis et al., 2005; Iddan et al., 2000). Images are transmitted to an antenna array worn on the abdomen and stored externally in a portable data recorder. VCE records stream images at rate of 2 per second over a 7 to 8 hours image acquisition period, yielding a total of approximately 50,000 image per examination. The image covers 140 degrees with 8-fold magnification and a depth of view of 1 to 30 mm (Swain, 2003). VCE has been available for clinical use since 2001 (Meron, 2000; Nakamura & Terano, 2008; Seidman, 2002). The primary indications for VCE include evaluation of patients with occult or overt obscure gastrointestinal bleeding, suspected Crohn's disease, non-steroidal anti-inflammatory drug-induced small bowel injury, celiac disease, and chronic diarrhea (Rondonotti et al., 2007; Scapa et al., 2002). VCE examination is now the accepted standard for examination of the small bowel worldwide. A variety of VCE devices are currently in development with the goal of extending the technology to different areas and capabilities (Aihara et al., 2011; Fireman, 2010; Moglia et al., 2009). VCE provides high resolution images that differ from those obtained by fiberoptic video endoscopy. VCE is passive and what is seen depends on small bowel motility. Current versions do not have an ability to insufflate air and distend bowel or to go back to an area of interest in order and review the site from different angles and degrees of illumination. As such, the visualization is not complete and important lesions may be missed (Selby & Prakoso, 2011). Interpretation of VCE small bowel images is both subjective and time consuming (Cave, 2004) with a significant potential for inter-

observer variation in the interpretation of the VCE results(Chen et al., 2006; Lai et al., 2006; Pezzoli et al., 2011). Industry has responded by continuing to develop software programs to assist in interpretation of the captured images (see below)(Gan et al., 2008; Spada et al., 2007). The relatively long time required to properly interpret a VCE examination has results in use of non-physicians being trained in interpretation of VCE examinations.(Levinthal et al., 2003; Sidhu et al., 2007).

This chapter discusses current issues regarding VCE reading and interpretation and highlights clinical aspects of inter-observer variation.

2. Reading a capsule endoscopy

2.1 General introduction

The technical issues regarding reliably obtaining a sufficient number of good images of the small intestine have a major focus of the software and hardware manufactures of VCE equipment. However, from the patient’s and clinician’s standpoint, the keys to a successful examination encompass the ability to capture the appropriate images and the ability to find and correctly interpret those images using the VCE reader software. VCE reading requires an extended period of focused concentration(Fleischer, 2002) and the first step to a successful result is to perform the reading in a comfortable environment with low background noise(Becker et al., 1995), ((Palinkas, 2001). The reader should be rested, physically comfortable, and alert(Lieberman et al., 2002) ((Lane & Phillips-Bute, 1998). Depending on the speed of the rapid scan, average time of interpretation may range from 30 to 90 minutes(Lewis, 2004; Melmed & Lo, 2005), It has been shown that for best results sustained concentration in reading a VED for 50 minutes should be followed by a rest period of approximately 10 minutes in order to sustain appropriate concentration(Cave, 2004; Lewis, 2004; Westerhof et al., 2009). The quality and accuracy of the reading can also be improved by providing the reader with clues regarding the condition or conditions that prompted the examination (e.g., obscure bleeding, or suspected small bowel tumor) (Table 1.)

Room is dark, but not dark
Comfortable seats
Comfortable clothing
Carbohydrate or caffeine
Appropriate air temperature
No background noise

Table 1. Items for an appropriate VCE reading room

2.2 Order of reading

The first step is to identify whether the examination was complete, (i.e., did the capsule pass into the colon during the time the images were being collected) or was the capsule still in the

stomach or small bowel when the battery died. To aid in reading one should mark the images (ie, time) when the capsule entered and left the stomach and when it reached the colon. This also provides a measure of the transit times through these organs. If the indication is evaluation of a patient with gastrointestinal bleeding, one can screen the examination using the Suspect Blood Indicator program (SBI). However, this useful software program has low sensitivity and does not obviate the need to do a proper full reading of the examination(D'Halluin et al., 2005). Experience has shown that many lesions responsible for the VCE examination are present in the proximal small intestine. The capsule also tends to move more quickly through the proximal than the distal small bowel such that the reader should keep a finger on the jog wheel so as to stop the image stream to take a closer look at suspected lesions. We recommend that one should also to take a short break in reading approximately every 30 minutes and that a thumbnail be captured at that time. Reading time can be reduced by using dual image playback rather than the original single-viewing mode. Importantly using the multi-image modality has not been shown to result in a lower detection rate of abnormal findings, at least among experienced readers(Melmed & Lo, 2005). Standard viewing speeds range from 15 to 21 frames/second. Faster viewing speeds do not necessarily shorten overall reading times because viewers are more likely to need to stop and review suspicious findings. In 2002 a consensus panel suggested that the optimal review rate was 15 images/second, which requires 64 minutes to read an 8-hour procedure(Lewis, 2004).The capsule records the mucosal images and thus one can generally identify whether the capsule is in the esophagus, stomach, or small bowel. Clearly, when one identifies an abnormality, one of the first questions is “where is it?” as this information is needed to plan what options are best to deal with the finding(Lewis & Goldfarb, 2003; Li et al., 2009). A computer program shows the approximate location of the capsule in terms of one of the 4 quadrants of the abdomen(Fig.1.).This information coupled with the time it elapsed after entering the small bowel before reaching the location of interest, and the time from the lesion to the ileocecal valve allows one to failly reliably identify where the lesion is likely located. The relation to thumbsnaill markings made of the esophagus, stomach, duodenum, small intestine, ileum, organs and anatomical landmarks such as the Z-line, pyloric, ampulla and ileocecal valve are especially helpful in this regard.

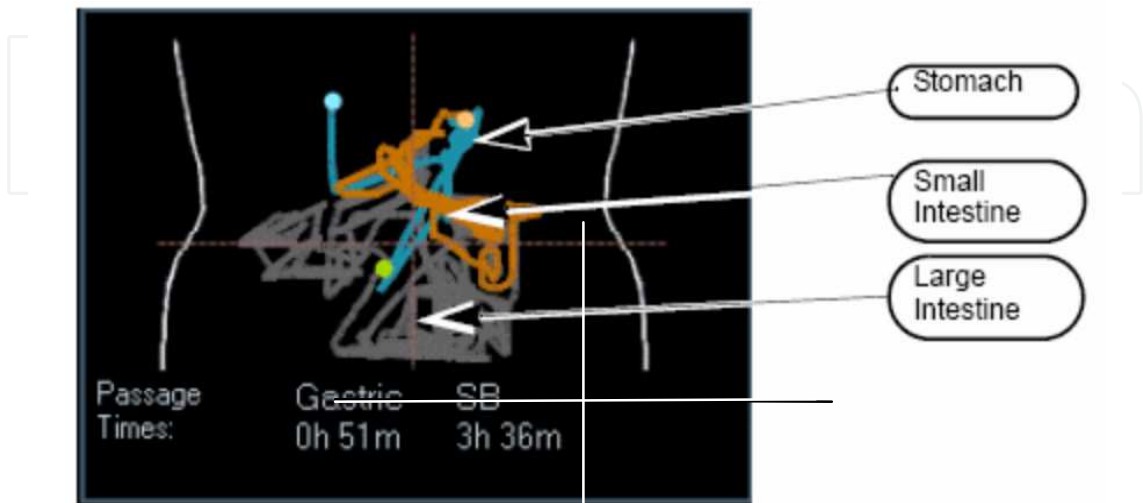


Fig. 1. Localization on capsule endoscope: A computer program shows the approximate location of the capsule in 4 quadrants of the abdomen.

Most divide the small bowel into 3 parts, proximal, middle and distal based on the time from the first image of the duodenum to first image of appendix according to elapsed time (Bocker et al., 2010; Goldstein et al., 2007). This method ignores the speed of the capsule and possible areas of delay in capsule transit. In general the small intestine transit time is 4 hours and 30 minutes. Proximal lesions (ie, those located in the left abdomen) can generally be reached by push enteroscopy (Fischer et al., 2004). If single or double balloon endoscopy is used to follow up lesions, those in the proximal half of the small bowel are often generally approached orally and those in the distal half trans rectally.

2.3 Video capsule reading software

The most widely available software for reading VCE is the software “RAPID” developed by Given Imaging. This chapter will describe capsule endoscopy reading using RAPID software. The software for reading VCE is proprietary to each company, however most are very similar. The current version of RAPID software is RAPID 6 however, new versions appear regularly each with slight to modest improvements (Glukhovsky & Jacob, 2004). The first step in reading is to determine which software and which version you have. In RAPID 1 and subsequent versions the small bowel images are down loaded from Data Recorder. The speed of the streaming images can be controlled using a speed control button. A localization function presents the position of capsule in gastrointestinal tract based on positioning of images on a sketch of the small intestine. RAPID 2 introduced a software program called Suspected Blood Indicator in which suspected bleeding points are expressed as red line on a tissue color bar. This software saves a video of 100 frames (for 20 seconds) which includes 50 frames before and after the thumbnail. RAPID 2 also introduced MultiView which enables one to see two continuous images at the same time. This is said to reduce reading time by 30-50%. RAPID 3 can also read images from the esophageal capsule and introduced QuadView which presents 4 images at the same time (Fig.2.). It also allows readers to store or delete term for the video capsule report using the My GI Dictionary program. Terms stored in the dictionary move automatically to the comment after a double-click or pressing the enter key. RAPID 4 introduced an Automatic Viewing Mode which automatically retarded the video playing times during rapid transit and quickens the viewing when there is slow transit. This stabilized rate the small bowel image changed and made for a smoother reading experience. The images can also be compared with those stored in an atlas (ie, the RAPID4 Atlas) allowing one to make direct side by side comparisons. The RAPID4-Circumference scale program allows one to assess the extent of esophageal varices or small bowel ulcerations: this is activated in reporter editor, click circumference scale button, can measure % of affected area. RAPID 5 supports the reading of PillCam SB2, PillCam ESO 2, PillCam colon, and includes a function called colon localization track. The Quick view function has been improved with improved image quality control. The addition of applications such as the (Lewis score, Rapid atlas, colon localization track, circumstance scale) also improved the efficiency of reading and reporting. This version enhance workflow can forward multiple exams simultaneously and RAPID 5 Access software has been shown to improve diagnostic yield while reducing reading time (Shiotani et al., 2011). RAPID 6 supports the PillCam Sensor Belt, a “patient-friendly” alternative to the sensorArray and its stick-on adhesive sleeves. The Image Adjustment program enables Flexible spectral Imaging Color Enhancement (FICE) which is a spectral image processing technology for high contrast display that may enhance viewing of subtle structural and color changes (Fig.3). The software includes Mosaic View which displays

multiple, consecutives images simultaneously for a convenient overview of 18 or 24 RAPID images at a time (Fig.4).



Fig. 2. View Mode of RAPID software. Single View(upper left), Double View(upper right) and QuadView(lower) in RAPID 4.

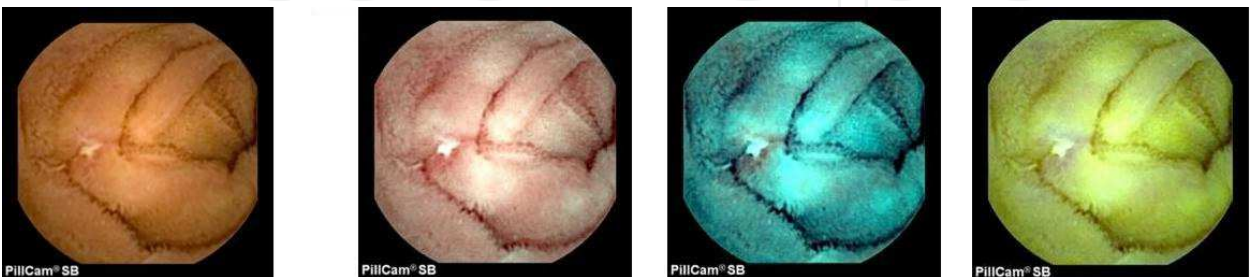


Fig. 3. FICE image display in RAPID 6. The FICE image is a spectral image processing technology for high contrast display that may enhance viewing of subtle structural and color changes.



Fig. 4. Mosaic view in RAPID 6 version. This View mode which displays multiple, consecutive images simultaneously for a convenient overview of 18 or 24 RAPID images at a time.

2.4 Normal finding

Because the VCE images are not real time continuous but are individual images taken at 2 per second, the appearance differs from that of conventional endoscopy (Appleyard et al., 2001) and those experienced in video endoscopy may misinterpret normal findings as an abnormal condition. However, the learning curve is short once one becomes familiar with the variability of normal findings. Here, we will discuss the normal small bowel structure observed by VCE. The capsule takes 2 pictures in a second starting from outside the body through the oral cavity, oropharynx, esophagus, stomach, small bowel, and colon. Oropharynx: The pharynx is located between posterior nasopalatine and 6th cervical spine and only 1 or 2 images are obtained as the capsule transits rapidly. The mean esophageal transit time is 6 second such that approximately 10 pictures can be taken. The Z-line is often visible because the lower esophageal sphincter delays the transit time at the level of esophago-gastric junction (Fig.5.). Capsule endoscopy designed for observing the esophagus has been developed and takes pictures at 14 frames/second from both ends of the capsule (Eliakim et al., 2004). The mean gastric transit time of the capsule through the stomach is about 1 hour but with a wide variation (Dai et al., 2005; Faigel & Fennerty, 2002). Because the antrum is not distended, the pylorus appears folded. The most common and characteristic findings in capsule endoscopy of the stomach is seeing the same image of large rugae as the capsule remains in one location. However, often a clear image of gastric mucosa along with peristalsis of antrum and pylorus

can be observed (Fig.6.). The length of small bowel is about 6 meters. The small bowel transit time is defined as the time elapsed from passing through the pyloric ring to the ileocecal valve. When the capsule enters the duodenum, one notices a color change as the image becomes brighter and bile can be seen. Bile flowing from the distal duodenum to the proximal part can sometimes be seen. The duodenal bulb is covered with villi and vessels are not seen. When the capsule passes the bulb, it enters to 2nd portion of the duodenum where the villi become more prominent. The ampulla of Vater can often be seen at the medial wall 3 to 6 cm from the edge of bulb. The minor papilla is located 2 to 4 cm from the ampulla, however, it is not often observed because it is hidden by a Kerckring fold. In the 2nd portion of the duodenum the Kerckring folds are often prominent and run perpendicular to the long axis of the duodenum (Fig.7.). There is often a moderated amount of fluid and because there is no luminal distension capability in capsule endoscopy, the villi appear more prominent than in conventional endoscopy. The capsule enters the jejunum after passing the ligament of Treitz. This can not be seen visually and entry into the jejunum is identified by the presence of the capsule being on the left side of the abdomen. The ileum is located at right lower quadrant in the pelvis and has a more narrow lumen than the jejunum. The small intestinal mucosa has many plicae circularis, Kerckring folds from the distal duodenum to the jejunum (Fig.8.). Lymphoid follicles may be seen at any site in the small bowel but are most frequently seen in the distal ileum. Small bowel villi are 0.5 to 1.5 mm “fingers” protruded into the lumen and appear longer in the distal duodenum and proximal jejunum than more distally. Vascular structures of the small intestine are often seen clearly after the capsule reaches distal jejunum and sometimes thick veins along with an artery can be seen (Fig.9.). Bile becomes increasingly concentrated as the capsule moves distally such that villi can often not be seen in the ileum (Fig.10). It is not possible to clearly discriminate the jejunum from the ileum so as noted above, it is traditional to divide the small bowel into proximal, mid and distal portions according to the small bowel transit time and the location of capsule in the tract image. The movement of the capsule from the terminal ileum to the cecum can generally be easily recognized seeing the more wide lumen and darker sometimes find fecal material. Passage of the capsule is often delayed in the distal ileum due to a closed ileocecal valve. After passing the ileocecal valve, the prominent vascular distribution of colon mucosa appears.



Fig. 5. Capsule endoscopy findings of normal esophagogastric junction. The Z-line is often visible because the lower esophageal sphincter delays the transit time at the level of esophago-gastric junction.



Fig. 6. Capsule endoscopy findings of normal antrum & pylorus. It shows gastric mucosa and normal rugal fold along with peristalsis of antrum and pylorus can be observed.



Fig. 7. Capsule endoscopy findings of duodenum: Kerckring folder and vili can be seen in 2nd portion of duodenum.



Fig. 8. Capsule endoscopy findings of normal jejunum: The small intestinal mucosa has many plicae circularis, Kerckring folds from the distal duodenum to the jejunum



Fig. 9. Capsule endoscopy findings of normal distal jejunum: Vascular structures of the small intestine are seen clearly after the capsule reaches distal jejunum and sometimes thick veins along with an artery can be seen.



Fig. 10. Capsule endoscopy findings of normal ileum: Bile is more concentrated and the height of villi is lower than jejunum in ileum.

3. Capsule endoscopy in disease

3.1 Obscure gastrointestinal bleeding

The most frequent indication for VCE is evaluation of obscure gastrointestinal bleeding (OGIB) defined as bleeding in which no diagnosis has been reached after upper endoscopy and colonoscopy have performed. OGIB represents approximately 5% of all gastrointestinal bleeding. The goal of VCE is to identify whether the site of bleeding is from the small bowel and if so what is the cause. Active bleeding will be associated with blood in the lumen which is often readily visible because of its red color with fresh red material on the villi. However, all that is red is not blood. For example, close contact of dome of VCE to the mucosa will cause normal mucosa to appear red and simulate a telangiectasia (Regula et al., 2008). As with any finding it is critical to be able to distinguish true from false positive lesions such as caused by food, feces, closeness to the mucosa, bile, etc.. The distinction between blood and bile may be difficult as the image may appear dark and it becomes

difficult to see the details of the surrounding mucosa. The greatest difficulty are when only one image of the lesion is seen, when the lesion appears to be submucosal, and when the lumen contains dark-colored blood or bile.

There are many potential causes of small bowel bleeding (Table 2.) (Concha et al., 2007) which can be broadly classified into vascular diseases (eg, arteriovenous diseases), inflammatory diseases (eg, Crohn's disease) (van Tuyl et al., 2007), systemic diseases (eg, amyloidosis), infectious diseases (eg, tuberculosis), tumors, and chemical/radiation injuries (Christodoulou et al., 2007; Maieron et al., 2004; Polese et al., 2008). Most of these conditions can be detected with VCE. The most common cause of bleeding from the small intestine are vascular ectasis (ie, angioectasia) which are especially likely in the elderly where they account for 30% to 40% of bleeding. In contrast tumors are a prominent cause in patients 30 to 50 years of age. Telangiectasia often clearly shows bright red border (Polese et al., 2008). Small bowel ulcer also cause bleeding. Both nonsteroidal anti-inflammatory drug use and Crohn's disease cause ulcers, erosions, and strictures, and should always be considered in the differential diagnosis of OGIB (Graham et al., 2005; Leighton et al., 2006; Shiotani et al., 2010; van Tuyl et al., 2003). Small bowel ulcers may also be simulated by material floating on normal mucosa. A Meckel's diverticulum with gastric metaplasia in the diverticulum can occasionally be seen but is a less common cause of OGIB (Sokol et al., 2009). Much more rarely bleeding may originate from a small bowel enteropathy or varices due to portal hypertension.

Occasionally the bleeding may originate from the stomach or colon which was missed during the pre-VCE endoscopic evaluation. If the initial VCE for OGIB is negative, there may be a role for repeating the VCE study in patients with recurrent gastrointestinal bleeding and those with limited visualization on their initial examination or with incomplete small-bowel visualization due to the capsule not reaching the colon. Repeat VCE in these settings can result in new findings that lead to changes in patient management (Min et al.). We believe that patients with recurrent obscure bleeding and prior negative VCE should have VCE done as soon as possible to the repeated episode as this likely increases the yield.

3.2 Small bowel tumors

Small intestinal bleeding might be the most frequently encountered presentation (Bailey et al., 2006). Small bowel tumors account for approximately 6% of obscure gastrointestinal bleeding. The second most common indication for VCE was unexplained abdominal pain, followed by unexplained weight loss, diarrhea (Liao et al., 2010). This is consistent with previously reported data suggesting that abdominal pain and weight loss are reliable factors for predicting small bowel tumors.

The terminology used for possible small intestinal tumors seen at VCE is primarily descriptive with findings described as "tumor", "tumor mass", "polypoid mass", "a bleeding polypoid mass", "ulcerated mass lesion", "thickened folds", and "irregular ulcer" (Trifan et al., 2010). Structured terminology for capsule endoscopy has been proposed (Korman, 2004; Korman et al., 2005) in which tumor-like lesions are divided into nodules, polyps, tumors and venous structure. A nodular lesion is defined as a 2 to 3 mm luminal protruding lesion without clear margins surrounded by normal mucosa. The differential diagnosis includes lymphoid follicle hyperplasia, lymphangiectasia and lymphoma. A polypoid lesion is defined as an intraluminal protrusion and can be sessile, pedunculated or unknown in terms of pedicle (Korman et al., 2005). The common differential diagnosis for such lesions includes lymphoid follicle hyperplasia, a pseudopolyp, inflammatory polyp, adenomatous polyp or hamartoma. Because the image by capsule endoscope is different from conventional image, it is important to

distinguish true lesion and normal image. The lymphoid follicle should not be interpreted as polyposis and the concentrated bile is sometimes confused with gastrointestinal bleeding. The mucus on the mucosa can be misdiagnosed as inflamed villi or lymphangiectasia. A tumor was defined as a either a subepithelial mass covered with normal mucosa, a fungating mass, or a frond-like/villous mass. VCE does not allow measurement of exact sizes and lesions are defined as being small, medium, or large with medium size being defined as occupying one-half of the bowel lumen upon close view. In general, benign tumors are not ulcerated and have regular and symmetric features. Malignant lesions tend to be large, ulcerated masses with an irregular and asymmetric appearance. We previously characterized(Cheung et al., 2010), small bowel tumors found at VCE as polyps, epithelial mases with fungation or ulceration, subepithelial tumor with/without bleeding, and vascular masses. Most of these tumors (59.6%) presented as subepithelial tumors. With VCE, it is not easy to distinguish between a subepithelial tumor and normal peristalsis. Subepithelial mucosal lesion are sometimes difficult to distinguish from intestinal loops and peristalsis. For suspected tumors it is important to examine the character of surface and whether there is an associated ulcer or bleeding which are suggestive of small bowel tumors. We found active bleeding in approximately 10.5% of suspected tumors. Approximately one third of the lesions in our series were either fungating or ulcerative masses. Such mucosa changes point to the mass being a true lesion. Four patients presented with polyps, and one patient presented with a vascular mass. When in doubt, single or double ballon endsscopy, CT enterography, or surgical resection may be needed to resolve the problem.

Lipomas appear as subepithelial masses with intact covering mucosa and yellowish hue generally be diagnosed with confidence. Subepithelial lesions with round or oval protruding contour are suggestive a leiomyomas or Gastrointestinal Stromal Tumor. The histologic findings of small bowel tumors found at VCE are described in Table 3 (Rondonotti et al., 2008).

Location	Cause of bleeding
Esophagus	Esophagitis
Stomach	Cameron erosion/ulcer, Dielafoy’s ulcer Angiodysplasia, Gastric antral vascular ectasia Portal hypertensive gastropathy
Duodenum	ampullary neoplasia, Distal duodenal neoplasia Aortoenteric fistular, Pancreatic aneurysm Hemobilia
Small bowel	angiodysplasia, Polyposis syndrome, Crohn’s disease Primary neoplasia (leiomyoma, leimyosarcoma, carcinoid) Metastasis (lung ca, breast ca, renal cell ca, melanoma) Meckel’s diverticulum, Medication induced bowel injury Portal hypertensive intestinal injury
Colon	Angiodysplasia Portal hypertensive colopathy
Others	Amyloidosis, hereditary telangiectasia, radiation

Table 2. Common cause of Occult Gastrointestinal bleed

Diagnosis of small bowel tumors (<i>n</i> = total)	No. patients with histological confirmation	Location of tumor
Non-neoplastic	-	-
Lymphoid hyperplasia (3)	3	D-I (1), J-I (1), I (1)
Hyperplastic polyp (1)	1	J (1)
Benign neoplastic	-	-
Adenoma (2)	2	D (1), J-I (1)
Leiomyoma (14)	1	J (7), I (7)
Lymphangioma (1)	1	J (1)
Hemangioma (1)	1	I (1)
Lipoma (2)	0	J (2)
Malignant neoplastic	-	-
Adenocarcinoma (3)	2	D (1), J (1), I (1)
Lymphoma (8)	8	J (2), I (5), D-I (1)
GIST (20)	20	J (15), I (5)
Metastatic cancer (2)	1	J (1), I (1)
Total (=57)	40	-

VCE, capsule endoscopy; GIST, gastrointestinal stromal tumor, D, duodenum, J, jejunum, I, ileum.

Table 3. Histological diagnoses of small bowel tumors found by VCE

3.3 Inflammatory bowel disease

There are no pathognomic findings of capsule findings in inflammatory bowel disease (IBD). Rather, the findings are those of an inflammatory condition and consist of mucosal redness, erosions, aphtous ulcers, linear and irregular shape ulcers, strictures and a cobblestone-like appearance(Arguelles-Arias et al., 2004; Fireman et al., 2003; Herrerias et al., 2003). VCE is considered useful to evaluate patients with suspected inflammatory bowel disease and possibly to examine those after surgical resection to identify early relapse(Fireman et al., 2003; Ge et al., 2004; Kornbluth et al., 2004; Leighton et al., 2007). The diagnosis of is IBD is a clinical one that integrates the history and physical examination with the radiological, endoscopic, and pathologic findings. VCE is superior to barium contrast small examinations which have a poor sensitivity for Crohn’s disease(Table 4.). The characteristic VCE finding in Crohn’s disease are mucosal ulcerations. Characteristics to be evaluated include whether the ulcer is longitudinal or transverse, the status of the surrounding mucosa, whether it is single or multiple, the size and the anatomical location. In small bowel Crohn’s disease one typically sees longitudinal ulcer with a cobblestone appearance of the mucosa(Legnani & Kornbluth, 2005) of the distal small bowel. Eliakim and Adler (Eliakim & Adler, 2004) studied 20 patients with Crohn’s disease suspected on the basis of abdominal pain, diarrhea, and weight loss. 16 of 20 patients had abnormalities including ulcers and erosions in 36%, erythema in 22%, aphthae in 17%, absent or blunted villi in 14%, and nodular lymphoid hyperplasia in 5.6%. Clearly, erythema, nodular lymphoid hyperplasia, absent or blunted villi, are not specific findings for IBD and small bowel ulcerations are seen in asymptomatic individuals, and especially those taking aspirins or non-aspirin nonsteroidal anti-inflammatory drugs. Thus, while capsule endoscopy clearly has a role to play in assisting in the diagnosis of Crohn’s disease, it is only one part of the evaluation and would should hesitate before a patients is labeled with this life-long disease based solely on VCE findings. VCE may provide helpful data in the evaluation of patients with indeterminate inflammatory bowel disease(Flamant et al., 2009). Mow et al(Mow et al., 2004) used VCE to examine 22 patients with either ulcerative colitis (UC) or indeterminate colitis (IC) and 9 (40%) were given a diagnosis of definite Crohn’s disease CD (40%) based on findings of linear erosions and multiple ulcerations. Five of the 9 patients had subsequent

histologic findings in agreement the clinical diagnosis of Crohn’s disease. There are several potential indications for performing VCE in patients with IBD: Suspected Crohn’s disease with negative findings on upper GI endoscopy and colonoscopy, evaluation of OGIB in patients with Crohn's disease, evaluation of disease extent in patients with Crohn's disease, if such information is likely to alter patient management, evaluation of postoperative recurrence, evaluation of patients with indeterminate colitis, evaluation of response to anti-inflammatory therapy, if clinically indicated(Di Nardo et al., 2011; Swaminath et al., 2010). However, contraindications for patients to have VCE include having a known or suspected gastrointestinal tract obstruction and/or known small bowel strictures , because of the increased risk of capsule retention in patients with Crohn’s disease. Retention rates specific to IBD populations are in the range of 1.4% to 6.7%, even among those in hwom the VCE was proceeded by a small bowel series that did not demonstrate the presence of a stricture(Buchman et al., 2004; Herrerias et al., 2003; Mow et al., 2004). The Agile Patency Capsule (Given Imaging Inc.) has been used in Europe and was recently FDA approved in the United States for use in patients with suspected small bowel obstruction or known stricture(Delvaux et al., 2005; Herrerias et al., 2003). The goal of this capsule is to avoid capsule retention and the resultant requirement for endoscopic or surgical intervention. The patency capsule is identical in size to the regular imaging capsule but is composed of lactose with barium, a radiofrequency identification (RFID) tag, and 2 side timer plugs with exposed windows. The capsule remains intact for a minimum of 30 hours and then begins to disintegrate. The system comes with an RFID patency scanner that can detect the RFID tag. If the patient witnesses excretion of the patency capsule intact or the scanner does not detect the RFID tag at or before 30 hours, it is considered safe to proceed with VCE . Although we await confirmation from other studies on the patency capsule data to date support its use in identifying patients who may be at risk of obstruction from VCE(Leighton et al., 2007).

Suspected small bowel crohn’s disease
Known crohn’s disease
evaluation of OGIB
evaluation of disease extent
evaluation of postoperative recurrence,
evaluation of response to treatment

Table 4. Indication of VCE in patients with Crohn’s disease

3.4 Finding of other diseases and indications

3.4.1 Small bowel intestinal tuberculosis

Small bowel intestinal tuberculosis on VCE shows multiple transverse and serpiginous ulcers, scattered small ulcers and multiple aphthous ulcer(Pulimood et al., 2011). Similar finding are also found in small bowel Crohn’s disease and NSAID enteropathy(Reddy et al., 2003). Although intestinal tuberculosis may involved the entire gastrointestinal tract, is most

often involves the terminal ileum and ascending colon and thus is frequently confused with Crohn's disease. Tuberculosis should especially be considered in areas where the disease is endemic and in patients from those areas. Tuberculosis is best confirmed by histology and staining for acid fast bacilli, along with culture or polymerase chain reaction identification of the organism.

3.4.2 Drug induced small bowel damage

Capsule findings of NSAID small bowel injury consists of ulcers, erosions, aphthous ulcers, small mucosal breaks, and mucosal redness. NSAID-induced small bowel injury is common and at least one half of patients on long term NSAIDs can be expected to have small bowel abnormalities seen at VCE (Goldstein et al., 2005; Graham et al., 2005).

3.4.3 Polyposis syndromes

VCE has been used for surveillance of polyposis syndromes (familial adenomatous polyposis and Peutz-Jegher's syndrome) (Schulmann et al., 2005). VCE is more accurate in detection of polyps than small bowel follow through and compared to MRI can detect smaller polyps. Whether there is a clinical benefit from the routine use of VCE in patients with polyposis syndromes is unknown and currently it is not advocated for surveillance.

4. Development of capsule endoscopy

VCE has changed the approach to diagnosis of small bowel disease making it a much less invasive, more complete, and more accurate examination. There are however competing technologies such as single and double-balloon endoscopy which offer the advantage of allowing biopsy and other endoscopic procedures. The more traditional endoscopic techniques are invasive, time consuming and uncomfortable procedures such that these technologies are best thought of as complementary with VCE being the initial diagnostic modality of choice in most instances. VCE is a mature but not yet ideal technology as problems remain in relation to image quality especially in the presence of bile or blood, the relatively short battery life which limits the examination, no ability to distend the bowel, and dependence on normal gut peristalsis for transit. VCE was initially made possible by miniaturization of digital chip camera technology, especially CMOS or CCD technology along with extensive software development. Both CMOS and CCD technology have their own advantages and disadvantages in terms of image quality and power consumption. Between the two, CCD technology produces a greater level of signal and the least amount of signal noise (ie, a higher signal to noise ratio). CMOS imagers require a more uniform illumination than CCD technology to get good images but require less power and are capable of having all of their electronic circuitry on a single microchip (Gerber et al., 2007). Newer ASIC imager chips, together with special power management algorithms, should enable CMOS-based capsules to produce higher frame rates, have a longer duration, and employ multiple head capsules (Swain, 2008). Clinically both technologies provide excellent images of the GI tract. Capsules designed for different locations employ different frame rates, 2 per second (fps) for the small bowel capsules, 14 fps for Given Imaging's esophagus capsule, and up to 4 fps for the colon capsule (Fireman & Kopelman, 2007). These frame rates are designed to optimize the data collection while maximizing the diagnostic yield (Fireman et al., 2004). Future VCE systems are expected to offer wireless power supplies, capsule guidance systems, drug

delivery systems, body fluid sampling technology, self-propelled capsules, and even an ultrasound capsule. Olympus using CCD technology has released their small bowel capsule system in Europe and the USA. One anticipates that continued development of both the hardware and software will provide more convenient and accurate capsule reading, interpretation of finding, with higher quality images.

5. Pitfalls in interpretation and inter-observer variation

Interpretation of VCE images is labor intensive and requires a different skill set than traditional endoscopy. The potential for inter-observer variation is high with regard to the interpretation of the VCE results. Inter-observer variation between gastroenterologists and endoscopy nurses with 12 years of experience was evaluated by Leviathan et al. (Levinthal et al., 2003). The nurses reviewed five training procedures provided by the capsule manufacturer prior to VCE evaluations. The sensitivity of the VCE readings was similar between the nurses and gastroenterologists (93% vs. 89%). The lesions most often missed by both groups were small angioectasias and subtle small bowel erosions. The difference in findings did not influence the management of the patients. Clearly, with training observers other than physicians can learn to read VCE examinations. A study of inter-observer variability between gastroenterologists and fourth year therapeutic endoscopy students (Adler et al., 2004), suggested that more than 15 cases of VCE reading were sufficient for competency in reading VCEs. Liv et al. (Niv & Niv, 2005) evaluated the ability of an experienced gastroenterology nurse in reading the VCEs of 50 patients. The nurse had 20 years of experience as a gastroenterology nurse and was trained to read the VCE videos on 15 procedures. The VCE findings of the physician were used as the gold standard. The lesions were classified as either significant (such as angiodysplasia, tumor, ulcer, flat mucosa, or capsule retention) or minor (such as redness or small isolated erosion). Complete agreement for normal findings between the gastroenterologist and nurse was achieved. For the other findings, there was agreement for 93 out of the 96 lesions defined as significant by the physician (96.9%). The three significant lesions missed by the nurse were a suspected short Barrett's esophagus in 1 case and flat mucosa in the duodenum in 2 cases. The four significant lesions missed by the physician were a clot in the gastric mucosa, a suspected short Barrett's esophagus, an ileal aphthous lesion, and an ileal polyp. The results suggested that training nurse practitioners for the first-pass interpretation of VCE results was cost effective and improved the accuracy of the evaluation. Petrofina et al. (Petroniene et al., 2005) studied agreement of VCE results in patients with celiac disease. The VCE reading by investigators with pre-study experience with VCE for celiac disease had greater agreement than novice readers. Therefore, experience with VCE reading appears to be important for reduction of the inter-observer variation. Lai et al. (Lai et al., 2006) reported on the inter-observer variation between two gastroenterology residents in their first year of specialty training in gastroenterology and gastroenterologists with seven years of experience in gastrointestinal endoscopy. Prior to interpreting the findings of 58 VCE examinations, they had training for VCE evaluation and had read at least 10 VCEs. The accuracy of the evaluations for gastric emptying time, small bowel transit time, and the small bowel diagnoses were significantly lower for the two residents than the experienced specialists. The characteristics of the lesions influenced the diagnostic accuracy. The diagnostic accuracy for Crohn's disease and active small bowel bleeding with no

identifiable source was high; however, the accuracy for angiodysplasia and small bowel tumors was only about 33%. The mean kappa value for the three reviewers was 0.56. The results of this study were consistent with prior studies showing that more prominent intraluminal lesions as well as prior experience with conventional endoscopy improved the diagnostic accuracy of reading VCEs and reduced variation in the interpretation of the findings. Therefore, increase in the level of training for VCEs would likely improve the accuracy of reading the findings of VCEs. Another report demonstrated that multiple novice readers are an alternative method to improve the accuracy of VCE reading (Chen et al., 2006). In addition, endoscopic nurse, gastroenterology students or medical residents abilities to detect abnormalities on VCE before physician begin to screen capsule endoscopy in clinical practice (Levinthal et al., 2003; Postgate et al., 2009; Sidhu et al., 2008).

Jang et al. (Jang et al., 2010) in a systematic study evaluated the inter-observer variation associated with capsule endoscopy interpretation by experts compared to trainees. The goal of this study was to evaluate the inter-observer agreement between these two groups and determine the factors associated with missing a lesion. The findings showed that the inter-observer differences were greatest for subtle lesions which were more often missed by trainees. The inter-observer variation in the expert group (the mean kappa value, 0.61, substantial agreement) was lower than in the trainee group (the mean kappa value, 0.46, moderate agreement). These findings underscore the importance of experience with conventional endoscopy in the review of VCE findings. We needed to better understand the learning curve for VCE and the education necessary to become proficient in reading VCEs. There are two aspects of reading: finding the lesions and interpretation of the findings. Training to find lesions and thumbnailing them is likely to be easier than learning how to interpret many findings. The use of improved software and the use of non-physician prereaders to focus the reading experience on interpretation should go a long way toward improving the usefulness of the technique in ordinary practice. The inclusion of an atlas as part of the reading software is also helpful.

6. Conclusions

The introduction of VCE resulted in a revolution in evaluation of the small bowel as it allows the mucosa of the entire small bowel to be visualized without pain. VCE is now available world wide and has greatly simplified the approach to evaluating and diagnosing small bowel diseases. Interpretation of the VCE small bowel images is both subjective and time consuming. Improved hardware and software with high speed reading techniques, multi-image viewing with dual image play back, and the computer-aided screening diagnosis should improve the experience and reduce interobserver variation. Continued software improvements coupled with higher quality images, dual head VCE, controlled high frame capture techniques, radio-control capsule movement, and lumen distending devices all should improve both the diagnostic accuracy and interpretation of VCE. Nonetheless, the best results will probably continue to rely on a good strategy in terms of the order of reading and interpretation strategy.

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8. References

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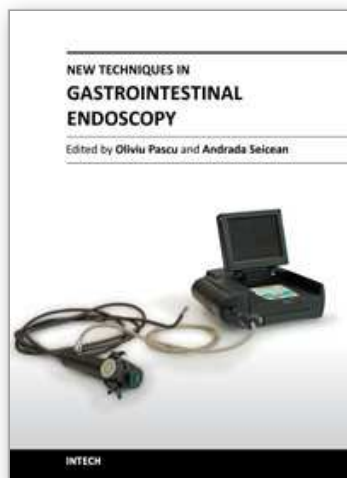
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As result of progress, endoscopy has became more complex, using more sophisticated devices and has claimed a special form. In this moment, the gastroenterologist performing endoscopy has to be an expert in macroscopic view of the lesions in the gut, with good skills for using standard endoscopes, with good experience in ultrasound (for performing endoscopic ultrasound), with pathology experience for confocal examination. It is compulsory to get experience and to have patience and attention for the follow-up of thousands of images transmitted during capsule endoscopy or to have knowledge in physics necessary for autofluorescence imaging endoscopy. Therefore, the idea of an endoscopist has changed. Examinations mentioned need a special formation, a superior level of instruction, accessible to those who have already gained enough experience in basic diagnostic endoscopy. This is the reason for what these new issues of endoscopy are presented in this book of New techniques in Gastrointestinal Endoscopy.

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