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Review

Capsule Endoscopy in Clinical Practice: Current Achievements

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Abstract

Since its introduction into clinical practice in 2001, capsule endoscopy (CE) has become the first-line investigation procedure in many small bowel pathologies. In addition, dedicated esophageal and colon CE allowed investigation of upper and lower gastrointestinal disorders. In a short time, CE has gained increased popularity in clinical practice, due to its non-invasive nature, safety, patient comfort, and ability to explore new segments of gastrointestinal tract, previously difficult to explore by traditional endoscopy. However, CE has several limitations, including the lack of therapeutic capabilities, inability to take biopsies and control its movement. Hopefully, most of these limitations will be overcome by modern technology. This review summarizes CE achievements through the entire gastrointestinal tract.

Keywords: Capsule endoscopy; Patency capsule; Crohn's disease; Obscure gastrointestinal bleeding; Small bowel tumors; Celiac disease

INTRODUCTION

The introduction of the capsule endoscopy (CE) in clinical practice revolutionized noninvasive, directly visualization of small bowel, considered until then the "black box" of the gastrointestinal (GI) tract. Launched in 2000 (Iddan et al., 2000), approved for clinical use in United States and Europe in 2001 (Nakamura and Terano, 2008) and recognized in 2003 by the US Food and Drug Administration (FDA) as first-line examination for the small bowel (Gay et al., 2004), CE has been extensively used during the past years, with more than 2 million capsules swallowed worldwide (Eliakim, 2013). As experience accumulated, CE has become increasingly popular among gastroenterologists, used in over 5,000 centers worldwide, and nearly 3,000 PubMed-listed studies pertaining to its different aspects have been published (Koulaouzidis et al., 2013). Technical progress led to the introduction of some updated versions (second- and third- generations) of CE for the small bowel and the manufacturing of the CE designed for esophagus and colon. Indications for CE have extended widely and are being continuously diversified, while solutions to avoid complications are being tested, some successfully. In only 17 years since its introduction in clinical practice, CE achievements have exceeded what was previously thought as possible, becoming the first-line diagnostic modality of obscure gastrointestinal bleeding and unexplained iron deficiency anemia, as well as contributing substantially to progress in noninvasive diagnosis and therapeutic decisions in Crohn's disease, celiac disease, small bowel polyps in hereditary polyposis syndromes. The rapid development of this technique, followed by definite results, comes to prove the unquestionable value of CE as a noninvasive diagnostic method for different GI pathologies. Still, CE is not an ideal tool, as it has several limitations, including the lack of therapeutic capabilities, inability to control its movement and thus, to revisualize critical areas and obtain biopsies, poor image resolution and subjective image interpretation by the examiner. Overcoming these limitations and developing a new generation of CE with

Table 1. Specifications of current available capsule endoscopic systems

Company	Model	Size (LxD) in mm	Weight (g)	Angle of view (degrees) (°)	Frame rate (per second)	Transmission mode	Image sensor	Image resolution (pixels)	Battery life (hours; minutes)
Given Imaging Ltd., Yoqneam, Israel	PillCam SB1	26x11	3.3	140°	2	RF	CMOS	256x256	6-8 h
	PillCam SB2	26x11	3.45	156°	2	RF	CMOS	256x256	9 h
	PillCam SB3	26x11	3	156°	2-6	RF	CMOS	256x256	11 h
	PillCam Eso 1	26x11	3.7	140°	2x7(14)	RF	2XCMOS	256x256	20 min
	PillCam Eso 2	26x11	2.9	169°	2x9(18)	RF	2xCMOS	256x256	20 min
	PillCam Eso3	31.5x11.6	2.9	172°	35	RF	2xCMOS	256x256	30 min
	PillCam Colon 1	31x11	2.9	156°	2x2(4)	RF	2xCMOS	256x256	10 h
	PillCam Colon 2	31x11	2.9	172°	4-35	RF	2xCMOS	256x256	10 h
Olympus Medical System Co., Tokyo, Japan	EndoCapsule	26x11	3.8	145°	2	RF	CCD	1920x1080	8-10 h
	EndoCapsule 10	26x11	3.3	160°	2	RF	CCD		8-12 h
Chongding Jinshan Science and Technology Co., Beijing, China	OMOM	27.9x13	6	140°	2	RF	CCD	640x480	7-9h
Intromedic, Seoul, South Korea	MiroCam	24x11	3.3	150°	3	EFP	CMOS	320x320	10-12h

L x D: Lenght x Diameter; RF: radiofrequency; EFP: electric field propagation; CMOS: complementary metal oxide silicon imaging; CCD: charge-coupled device

diagnostic and therapeutic capabilities is the objective of many research groups worldwide. Based on the tremendous running progresses of modern technology, it is expected that in the near future these limitations will be overcome and CE will be one of the major forms of digestive endoscopy, covering the entire GI tract from mouth to anus as its inventors have dreamed. This review summarizes the achievements obtained so far in the use of CE in clinical practice.

A Brief History

The first model of CE called M2A (meaning "mouth to anus") was manufactured by Given Imaging Ltd (Yoqneam, Israel) (Iddan and Swain, 2004) and was approved for clinical use in Europe by the European Medicines Agency and in USA by FDA in 2001 (Nakamura and Terano, 2008). Subsequently, M2A has been renamed M2A Plus and then PillCam SB (meaning "small bowel") after the advent of esophageal CE (PillCam ESO). Several other companies have also developed small bowel endoscopic capsules: EndoCapsule (Olympus Corp., Tokyo, Japan) (Rey et al., 2006), OMOM (Jinshan Science and Technology Company, Chongqing, China) (Li et al., 2008), MiroCam (IntroMedic Co., Seoul, South Korea) (Bang et al., 2009), and CapsoCam (CapsoVision, Saratoga, CA, USA) (Friedrich et al., 2013).

The other segments of GI tract (esophagus, stomach, and colon) have different anatomical and physiological characteristics than small bowel and require different capsule design for their examination. For the evaluation of esophageal and colonic diseases, Given Imaging has developed PillCam ESO and PillCam COLON, respectively (Eliakim et al., 2004; Eliakim et al., 2006).

Improvements in technology have led to the development of second- and third-generation of CE (PillCam SB2 and PillCam SB3, PillCam ESO2 and ESO3, and colon PillCam COLON2), all overcoming some limitations of the first-generation by increasing the view angle, extending the effective life of the battery, by

using an automatic light control, and by including several other systems such as an indicator of capsule's location during its passage in small bowell, as well as incorporation into the Given Imaging workstation of chromoendoscopy (Fuji Intelligent Color enhancement (FICE) software, a quick viewer, and an image atlas (Eliakim, 2012). Olympus also developed second-generation of its EndoCapsule (EndoCapsule 10) with increased resolution and 3D location software (Hosoe et al., 2016). Specifications of current available capsule endoscopic systems for clinical use are shown in Table 1.

Although the technical features may vary between the different manufacturers, all available capsule endoscopy systems have similar three components: 1) a swallowable capsule; 2) a sensing system including either a sensing belt or pad, a data recorder, and a battery pack, and 3) a personal computer workstation with proprietary software to download and analyse the capsule images (Spada et al., 2012).

Other capsule endoscopy systems

A "patency" radiopaque, non-video capsule was launched by Given Imaging with the aim to exclude the intestinal strictures that can determine capsule retention (Spada et al., 2005). It is a self-dissolving and biodegradable capsule with the same size as PillCam SB, and is made of lactose/5% barium sulphate. When its passage is blocked (stenosis, tumor), the patency capsule dissolves over a period of 40-100 hours after ingestion. The second-generation of patency capsule (Agile patency capsule), FDA approved, has two time-controlled plugs, so that dissolution starts at 30 hours or even less, and has proven to be as safe as computed tomography (CT)- or magnetic resonance (MR)- enterography, and superior to standard abdominal CT, in patients with Crohn's disease (CD) suspected with intestinal stricture (Yadav et al., 2011).

Wireless motility capsule (WMC) (SmartPill; Given Imaging) is a novel method that concurrently measures whole or regional transit time, intraluminal pH, pressure, and temperature. The US FDA has approved the WMC for the measurement of gastric emptying time in patients suspected with gastroparesis and the evaluation of colonic transit time in those with slow transit constipation. Farmer et al. (2013) in a recently review article provided full information about WMC test procedure, parameters it records, and comparison to other techniques currently available.

Delivery devices

Delivery devices have been used to deliver the capsule into the stomach and duodenum for patients with dysphagia or gastroparesis. The Advance (US Endoscopy, Mentor, Ohio), approved by FDA for use with the Given Imaging PillCam, is a disposable catheter with a diameter of 2.5 mm that is first preloaded through the working channel of a standard endoscope, while a capsule cap containing the activated videocapsule is screwed onto its distal end; the endoscope with the device is advanced to the stomach and duodenum, and the capsule is released via a deployment device at the proximal end of the catheter, and the endoscope is then withdrawn (Holden et al., 2007). PillCam Express is a capsule delivery device marked in 2010 by Given Imaging and specifically designed to work with PillCam SB2 for patients who have slow gastric emptying time or who are unable to swallow the capsule.

It is well established that delayed gastric transit of the capsule leads to incomplete small bowle examination, reducing the diagnostic yield. Recently, Jiang et al showed that magnetic steering of the capsule enhances gastric emptying of the capsule and may be useful in patients who have longer gastric transit time (Jiang et al., 2018).

Indications and Contraindications

The most common indications for small bowel CE are obscure GI bleeding (OGIB), suspected CD, suspected small intestine tumors, diagnosis as well as surveillance in patients with polyposis syndromes, and refractory malabsorptive syndromes (eg, celiac disease) (Fisher and Hasler, 2012; Neumann et al., 2014; Khan et al., 2013). CE has also been used in several clinical conditions such as irritable bowel syndrome, nonsteroidal anti-inflammatory drug (NSAID)-enteropathy, protein-loosing enteropathy, small bowel transplantation, and primitive intestinal lymphangiectasia (Liao et al., 2010).

The PillCam ESO2 is used in patients unable or unwilling to undergo conventional upper GI endoscopy for suspected Barrett's esophagus, esophagitis, or esophageal varices (Bhardwaj et al., 2009; Ishiguro et al., 2012), while PillCam COLON 2 is used for colon polyp screening, as well as an alternative for incomplete colonoscopy or patients unwilling to undergo colonoscopy (Eliakim et al., 2009).

CE contraindications include patients with dysphagia or swallowing disorder, known or suspected Zenker's diverticulum, gastrointestinal obstruction, strictures, fistulas, pregnancy, pill phobia, significant gastroparesis, prior major abdominal surgery of the gastrointestinal tract, and those with cardiac pacemakers or other implanted electromedical devices, although recent evidence suggests that CE can be safely used in such patients under appropriate monitoring (Harris et al., 2013).

Table 2. Indications and contraindications for capsule endoscopy

Indications	Contraindications
Small bowel capsule endoscopy	
Main clinical indications:	*Absolute*
Obscure gastrointestinal bleeding	Gastrointestinal obstruction, strictures, or fistulas
Unexplained iron deficiency anemia	Intestinal pseudo-obstruction
Suspected/known small bowel Crohn's disease	*Relative*
Indeterminate colitis	Dysphagia or swallowing disorder
Assessment of mucosal healing	Known or suspected Zenker's diverticulum
Determine post-operative recurrence	Pregnancy
Suspected small bowel tumors	Cardiac pacemakers or other implanted electromedical devices
Surveillance of polyposis syndromes	
Celiac disease	Prior major surgery of the gastrointestinal tract
Other indications:	Diverticulosis
Clinical symptoms (diarrhea, abdominal pain)	
Protein-loosing enteropathy	
NSAIDs-enteropathy	
Follow-up of small intestine transplantation	
Graft-versus-host disease	
Primitive intestinal lymphangiectasia	
Esophageal capsule endoscopy	
Surveillance of Barrett's esophagus	
Diagnosis of GERD (esophagitis) in patients unwilling to undergo standard endoscopy	
Diagnosis and surveillance of esophageal varices	
Colon capsule endoscopy	
Colon polyp screening	
Incomplete colonoscopy	
Patients unwilling to undergo colonoscopy	

GERD: gastroesophageal reflux disease

Complications

Generally, CE is a safe procedure, with very low complication rates. Capsule retention, defined as having a CE remain in GI tract for a minimum of 2 weeks, is the most frequent complication of the procedure, which can cause symptoms of intestinal obstruction that may require endoscopic or surgical removal of the capsule. In patients with high risk of retention (i.e., suspected or known CD, suspected bowel tumors, history of abdominal obstruction, abdominal surgery, radiation to the abdominal or pelvic areas), many authors recommend a prior imaging examination to exclude stenosis (Agile patency capsule, CT-enteroclysis).

Global incidence of capsule retention is 1%-2%, but there are large variations according to clinical indication for CE investigation and the selected population (Liao et al., 2010; Li et al., 2008; Singeap et al., 2011). In healthy volunteers, retention rate was null. Capsule retention was 1.6% in patients suspected with CD, compared with 13%, in those known with this disease (Cheifetz et al., 2006). Liao et al. (2010), in a systematic review of English-language published studies regarding indications of small bowel CE have reported retention rates of 1.2%, 2.1%, and 2.6% for OGIB, tumors, and CD, respectively. About six cases of intestinal perforation have been reported, most probable as a sequel to capsule retention (Palmer et al., 2011). Therefore, once retention is diagnosed, it is advisable that retained capsule should be removed by endoscopy or surgery (Cheifetz and Lewis, 2006).

Extending use of CE has led to new problems, with reported cases of capsule retention in other sites than small bowel such as umbilical hernia, Meckel's diverticulum, or Zenker's diverticulum. Aspiration of capsule into tracheobronchial tree has also been reported, up to now only in 37 cases (Yung et al., 2017), with increasing frequency, mostly in elderly patients with swallowing disorders (Despott et al., 2012). Usually, patients expectorate the capsule immediately after aspiration, although in some cases emergency bronchoscopy may be required.

Patient Preparation for Capsule Endoscopy

There are no clear recommendations regarding patient

preparation for small bowel CE. Thus, the manufacturers of CE systems recommend only a clear liquid diet the day before examination and an overnight fast. In order to obtain better visualization, diagnostic yield, and higher rates of examination completion, several studies have suggested different bowel preparation schedules to clean the small bowel from food residue, bile, and bubbles before CE. One meta-analysis showed that there was a significant benefit purgative preparation over clear liquid diet alone (Rokkas et al., 2009), while Hookey et al. (2017), in a randomized blinded controlled trial, found no benefit of active preparation compared with a clear liquid diet alone regarding both diagnostic yield and cleanliness.

Bowel cleansing for colon CE is of paramount importance and, similarly to colonoscopy, bowel preparation includes the administration of liquid diet the day before examination and 4L of PEG in a split-dose fashion prior to colon capsule ingestion. Also, 1 or 2 doses of sodium phosphate are added to accelerate capsule transit through both small and large bowel within operating time of capsule battery (Spada et al., 2012).

For CE of the esophagus, the patient preparation is very simple, and requires only 4 hours fasting before examination.

CLINICAL APPLICATIONS

Small Bowel Capsule Endoscopy

Obscure gastrointestinal bleeding and unexplained iron deficiency anemia

Obscure gastrointestinal bleeding (OGIB) is defined as bleeding of unknown origin that persists or recurs after an initial negative endoscopic evaluation including upper endoscopy and ileocolonoscopy and represents approximately 5% of all GI tract bleeding (Lewis, 2007). OGIB is classified as either overt (melena or hematochezia) or occult (positive fecal occult blood test or persistent iron deficiency anemia). Iron deficiency anemia (IDA) occurs in 3-5% of adult subjects, and esogastroduodenoscopy (EGD) or ileocolonoscopy identifies the cause of bleeding in about approximately 75% (Fireman and Kopelman, 2004). CE revolutionized the evaluation of OGIB and IDA (Lewis, 2007; Appleyard et al., 2001; Kopylov and Seidman, 2013), becoming, in recent years, the first-line diagnostic modality for both situations.

CE diagnostic yield (ratio of the number of positive result examinations to the number of all procedures) in OGIB ranges from 32% to 91% depending on various factors such as type of bleeding investigated, timing of examination, and definition of positive findings. Current guidelines of all international gastroenterology – endoscopy societies recommend CE as the first test in patients with OGIB, after negative EGD and ileocolonoscopy results. In a systematic review including 227 studies and 22,840 CE procedures, the diagnostic yield for OGIB was 61% (Koulaouzidis et al., 2013).

Compared with radiographic barium studies, CE has an increased diagnostic yield of 25%-50% for detection of OGIB sources in the small bowel (Laine et al., Triester et al., Saperas et al., 2007; Koulaouzidis et al., 2012; Hartmann et al., 2005). A meta-analysis found a CE diagnostic yield of 42%, compared to only 6% for small bowel barium radiography in patients with OGIB (Triester et al., 2005). Moreover, CE achieves superior results in patients with OGIB/IDA when compared with more advanced radiographic technologies such as CT-enterography, CT-angiography and MR-enterography (Saperas et al., 2007; Wang et al., 2013). He et al. (2014) found a significantly higher diagnostic yield for CE than for a 64-slice multiphase CT enterography (68.7% and 47.6%, respectively; P=0.01). In a systematic review of 24 studies comprising 1960 patients, global diagnostic yield for CE in IDA was 47%; however, when only those patients with confirmed IDA by established levels for hemoglobin and ferritin were included, the diagnostic yield of CE was 67% (Koulaouzidis et al., 2012). The diagnostic yield of CE was significantly higher than that of angiography (53.3% and 20%, respectively) (Leung et al., 2012).

CE has repeatedly proven superior in detecting small bowel sources of bleeding to the old classical gold standard for OGIB, the intraoperative enteroscopy (Hartmann et al., 2005), or to push enteroscopy (de Leusse et al., 2007).

When CE was compared to double-balloon enteroscopy (DBE), a similar diagnostic accuracy for OGIB was reported (Pasha et al., 2008). In a meta-analysis, CE had a higher yield than DBE using a single approach, but lower yield than DBE using a combined antegrade-retrograde approach (Chen et al., 2007). However, due to its excellent tolerability and safety profile, and being more likely to achieve total small bowel enteroscopy, CE should be the diagnostic procedure of first choice, while DBE should be reserved for therapeutic purpose only (Arakawa et al., 2009). CE may also help to select DBE insertion routes.

Timing of CE examination is associated to diagnostic yield, patients with on-going bleeding having the highest yield. In one study, CE diagnostic yield was 92% in patients with on-going obscure overt bleeding, compared to 44.2 % in patients with obscure occult bleeding, and 13% in those with previous obscure occult bleeding which stopped (Pennazio et al., 2004).

Several studies showed that CE had a significant clinical impact on patient management and outcomes for OGIB. For these patients, the objectives are to stop the bleeding or resolve anemia, diminish the necessity for transfusions, as well as reduce costs related to hospitalizations and supplementary diagnoses, and

improve quality of life. CE leads to therapeutic endoscopic or surgical interventions and, consequently, to bleeding being stopped and improved outcomes. CE helps direct further therapeutic interventions or change medical therapy in 37-87% of patients (Arakawa et al., 2009; van Tuyl et al., 2007). CE also helped in localizing bleeding sites prior to intraoperative enteroscopy or surgical resection. One study reported that 51% of their patients which had a definite diagnosis on CE had a change in management, as well as in medication, undergoing an endoscopic procedure and surgery (van Tuyl et al., 2007). More recently, other studies have reported a positive impact of CE on OGIB patients' outcome (Cañas-Ventura et al., 2013).

Several studies have shown that CE repeated in the setting of one negative CE for OGIB gave positive findings ranging from 40% to 75% upon a second CE; a second such examination is indicated in patients with a previous nondiagnostic CE where bleeding presentation changed from occult to overt (Viazis et al., 2009).

Since its clinical application, CE has led to a major paradigm shift in the diagnosis and treatment of OGIB/IDA, overcoming most limitations of the previously used diagnostic methods. All the same, despite its incontestable advantages, CE also has several limitations regarding diagnosis and management in patients with OGIB as follows: 1) lack of small bowel insufflation hinders lesions, thus leading to false-negative results; 2) quality of image inferior to that obtained under conventional endoscopy; debris and bubbles obscure visualization, while the capsule has no possibilities of aspiration and washing of mucosa; 3) absence of control over capsule movement and thus, inability to repeat visualization of the suspected bleeding source; 4) difficulties in localizing the lesion; visual anatomical reference points are imprecise (the only certain point of reference on the small bowel itinerary is the papilla of Vater); 5) not all CE investigations visualize the entire small bowel; 6) biopsy is impossible; in the light of the last two limitations, CE and enteroscopy may complement each other, but with higher costs and more investigations for the patient to undergo; 7) CE being only a diagnostic technique, endoscopy is still required for biopsy and therapeutics. There are hopes that many of these limitations will be overcome with a next generation CE.

Inflammatory bowel diseases

Crohn's disease

In the absence of a single diagnostic test, Crohn's disease (CD) diagnosis is still based on a combination of clinical, biological, radiological, endoscopic and histologic findings. Generally, CD diagnosis is difficult to establish due to variability of clinical presentations, with manifestations that differ according to age of disease onset, localization, as well as to difficulties in exploring the small bowel (lack of constant intubation of the terminal ileum during colonoscopy, low sensitivity of small bowel radiography, limitations in CT-enterography and MR-enterography for incipient lesions). Traditional ileocolonoscopy has been the most important method for diagnosis and surveillance of CD, with the disadvantage that it does not make the diagnosis if the disease is localized to more proximal segments of small bowel. Thanks to its capacity to directly visualize mucosa of the entire small bowel, CE has undoubtedly contributed to substantial progress in diagnosis, therapeutic decision, and outcome of CD patient. CE diagnostic advantage in patients with CD, apart of exploring the whole small bowel, is also based on the characteristic discontinuity of mucosal lesions (severely affected bowel segments are separated by "skip areas" of apparently normal bowel), as well as in visualization of incipient lesions.

Findings associated with CD on CE include erythema, ulcerations, mucosal edema, loss of villi, mucosal fissures, and strictures. It should be underlined that none of them are pathognomonic for CD diagnosis, minor mucosal breaks occurring in 10%-15% of normal individuals, while mucosal erosions are present in two thirds of patients taking NSAIDs (Sidhu et al., 2010) and also in many others pathologies (radiation enteritis, lymphoma, intestinal tuberculosis). Ulcerative lesions are considered "major" lesions, with high rate of diagnostic correlation. "Minor" lesions present a much lower rate of diagnostic correlation, but do not rule out completely CD diagnosis, some authors considering them as incipient lesions, based on the argument that patients show clinical amelioration under specific treatment for CD (Bar-Meir, 2006).

Diagnostic criteria for CD on the basis of lesions described only by CE are still subject to a validation. An accepted set of diagnostic criteria for CD, proposed in 2004 by Mow et al. (2004), consists in the presence of more than three small bowel ulcerations detected by CE in the absence of NSAIDs use. An alternative suggestion came from Voderholzer et al. (2005) who claimed that a minimum of ten aphtoid lesions are suggestive for CD diagnosis. In order to objectively evaluate and quantify the severity and extent of small bowel lesions seen on CE in CD, several diagnostic scores have been proposed. The first and most frequently used is the Lewis score (Gralnek et al., 2008) which divides the small bowel into three tertiles or equal parts (proximal, middle, and distal thirds), and disease activity is based on three endoscopic variables: villous edema, ulcers, and stenosis. The small bowel tertile with the most points determines the final score. A score below 135 is considered normal, while one between 135 and 790 indicates mild inflammation, and one higher than 790 indicates moderate to severe inflammation. This score is incorporated into the RAPID® software (Given® Imaging

Ltd., Yoqneam, Israel), and has never been prospectively validated. More recently, a new scoring system called the Niv or CECDAI (Capsule Endoscopy Crohn's Disease Activity Index) score which again uses three CD parameters to grade severity: inflammation, disease extension and the presence of strictures in the two parts of the small bowel (proximal and distal) has been validated by a multicentric study, although it doesn't correlate with clinical indices of disease activity such as CDAI (CD activity index) or with that assessing quality of life (Niv et al., 2012).

Suspected CD. CE usefulness has been proved especially in patients suspected of CD, with negative ileocolonoscopy and/or radiological investigations. An international OMED (*Organisation Mondiale d'Endoscopie Digestive*) - ECCO (*European Crohn's and Colitis Organisation*) consensus stated that CE is able to identify lesions compatible with CD in patients where other diagnostic modalities have been non-diagnostic (Bourreille et al., 2009). Reviews of existent literature on CE diagnostic yield for both suspected and known small bowel CD show it to be superior to other diagnostic techniques such as small bowel follow-through (SBFT), enteroclysis, push-enteroscopy, ileo-colonoscopy, and CT-enterography (Leighton et al., 2014; Triester et al., 2006; Dionisio et al., 2010). CE is superior to MR-enterography at identifying small bowel mucosal lesions, while MR-enterography is superior to CE at diagnosing mural and extra-enteric lesions (Crook et al., 2009). In an early meta-analysis evaluating patients with both suspected and known small bowel CD, CE had a higher diagnostic yield when compared to SBFT (64% vs 24%), ileocolonoscopy (61% vs 46%), or CT-enterography (69% vs 30%) (Triester et al., 2006). A second meta-analysis including 12 studies with 428 patients showed higher yields for CE compared to SBFT (52% vs 16%), CT-enterography (68% vs 21%), and ileocolonoscopy (47% vs 25%) in patients with suspected CD, and to SBFT (71% vs 36%), CT-enterography (71% vs 39%), and push enteroscopy (66% vs 9%) in those with known CD (Dionisio et al., 2010). Jensen et al. (2011) evaluated prospectively the diagnostic accuracy of CE, CT-enterography and MR-enterography in comparation to ileocolonoscopy in 95 patients with suspected CD and found that sensitivity and specificity were 100% and 91% by CE, 81% and 86% by MR-enterography, and 76% and 85% by CT-enterography, respectively. Proximal small bowel CD was detected by CE in a significant greater number of patients compared to MR-enterography and CT-enterography (18 vs 2 and 6, respectively; $P<0.05$). A prospective, international, multicenter, blinded study reported that CE performed before ilecolonoscopy has a diagnostic yield higher that SBFT and equivalent to ileocolonoscopy in patients with suspected small bowel CD (Leighton et al., 2014). Despite the high diagnostic yield of CE in suspected CD, proved in several studies, it should be underlined that according to current guidelines, ileocolonoscopy with biopsy is still the gold standard for diagnosis of CD in suspected patients.

Known CD. In patients with established CD, the main concern in using CE is capsule retention due to the strictures and adhesions often seen in such patients. Therefore, bowel stenosis should be ruled out by the use of the patency capsule before CE is performed. CE may alter disease management of patients with known CD by assessing mucosal healing after medical therapy. Mucosal healing, understood as the absence of inflammation at endoscopy, is considered to be a predictive factor for favourable long-term outcome, associated with low risk of complications and surgical interventions. Efthymiou et al. (2008) have evaluated mucosal healing with CE in patients with small bowel CD in a study without a validated scoring system for mucosal inflammation. More recently, in two prospective studies CE has proved useful for evaluating mucosal healing after immunomodulator or biologic therapy (Hall et al., 2014; Niv et al., 2014). Thus, Hall et al. (2014) performed the first prospective study to assess mucosal healing and deep remission rates following 52 weeks of therapy with adalimumab (n=36) or thiopurine (n=7) in a cohort of 43 symptomatic small bowel CD patients, and found CE as safe and effective means of assessing treatment response. Niv et al. (2014) in a prospective randomized trial including patients with known active CD, performed sequential CE examinations at baseline and after 4, 12, and 24 weeks during different treatments, and found that such method provides reliable information on mucosal changes and might serve as independent and objective follow-up tool in such patients. In a retrospective single center study including patients with known CD, small bowel CE diagnosed proximal intestinal lesions previously missed by other imaging modalities, and it contributed to therapeutic management of CD towards an earlier introduction of immunomodulators and/or biological therapy (Cotter et al., 2014).

There are conflicting results regarding the value of CE in detecting postoperative CD recurrence compared with ileocolonoscopy. Using the Rutgeerts endoscopic score, in one study CE had 62%-76% sensitivity and 90%-100% specificity in detecting postoperative recurrence compared with 90% and 100% with ileocolonoscopy (Bourreille et al., 2006), while according to another study, CE detected neo-terminal ileum recurrence in 62% of cases compared with 25% by ileocolonoscopy (Pons Beltrán et al., 2007). By consensus, in evaluating post-operative CD recurrence, CE is recommended as first choice investigation for patients with small bowel proximal resection in which surgical anastomosis is not accessible to colonoscopy and for those with ileal or ileo-cecal resection only when ileocolonoscopy is contraindicated, refused by the patient or impossible, while ileocolonoscopy should remain the procedure of choice in cases in which anastomosis is readily accessible at endoscopy (Swaminath et al., 2010).

As mentioned in case of OGIB, CE has also several limitations in diagnosis of CD. Thus, there are no standardized validated capsules criteria for the diagnosis of small bowel CD, and its inability to obtain biopsy makes the diagnosis difficult as lesions seen on CE are also seen in patients using NSAIDs and even in healthy subjects.

Ulcerative colitis

Diagnosis of ulcerative colitis (UC) does not require CE. However, consensus statements recommend small bowel investigation in cases of UC refractory to medical treatment, prior to colectomy, as well as in cases of UC with unexplained anemia or abdominal pain. To date, only a handful of studies have evaluated colonic capsule for diagnosis and monitoring of UC, two of them reporting a significant correlation of findings (i.e., disease severity and extent) between colon capsule and colonoscopy (Ye et al., 2013; Hosoe et al., 2013). However, to date, colon capsule cannot replace conventional endoscopy in diagnostic and surveillance of patients with colonic IBD.

Unclassified IBD

At least 10% of colonic IBD patients remain unclassified as UC or CD based on colonoscopic and biopsy findings. CE seems to be a useful investigation in such patients, providing a more definitive diagnosis for reclassification of unclassified IBD (Kopylov et al., 2014).

Celiac disease

The diagnosis of celiac disease is based on a combination of serologic, endoscopic and histological changes of the small bowel biopsy in clinically suspected patients. Characteristic endoscopic changes suggestive of celiac disease include absence or reduced villi, mosaic mucosal pattern, scalloping or loss of the duodenal folds, and nodularity of the mucosa. The images provided by CE may contain part or all these changes. CE has an 8-fold magnification capacity and a minimum size of lesion detection of 0.1-0.2 mm, so that villi can be easily observed during a procedure that does not imply distension, thus offering a much better analysis of the macroscopic aspect.

Several studies have reported good CE sensitivity (85%-92%), specificity (91%-100%), high predictive positive value (PPV) and negative predictive value (NPV) (96.5%-100% and 71.4%-88.9%, respectively) for celiac disease diagnosis using duodenal histology as the gold standard (Rondonotti et al., 2007; Rokkas and Niv, 2012). Rondonotti et al. (2007) in a multicentre European study evaluated patients with positive serologic markers and symptoms of celiac disease who underwent both endoscopy and CE found changes representative of celiac disease in 32 patients, the diagnostic sensitivity of CE being 87,5% with a specificity of 91%. One meta-analysis including 166 patients from 6 studies reported CE sensitivity and specificity for celiac disease diagnosis at 89% and 95%, respectively (Rokkas et al., 2012). CE was found to be useful in equivocal celiac disease cases, particularly in patients with antibody negative-villous atrophy, and also in monitoring complications of refractory celiac disease such as ulcerative jejunoileitis and small bowel tumors (Culliford et al., 2005).

It should be underlined that CE has several limitations in the diagnosis of celiac disease, including inability to obtain mucosal biopsies and inter-observer variability in the evaluation of villous atrophy. CE is actually an alternative to endoscopy with biopsy only in clinically suspected patients unable or unwilling to undergo conventional endoscopy.

Small bowel tumors and hereditary polyposis syndromes

Small bowel tumors (SBTs) are rare, accounting for 1%-3% of primary GI tumors. Once CE became routine practice, they turned to be more frequent than previously estimated, amounting to 9%-12% (Rondonotti et al., 2008). Most SBTs were detected by CE when the procedure was carried out in patients with OGIB.

SBTs frequency on CE varies, according to selection criteria. In the largest multicentric European study of 5129 patients undergoing CE, Rondonotti et al. (2008) found SBTs in 2.4% (one third being gastrointestinal stromal tumors) of the cohort, while in another study including 1,000 CE investigations, the frequency of SBTs was 1.6% (Pasha et al., 2008). From Korea, a multicentre study including 1332 CE examinations demonstrated tumors in 4%, of which half were dignosed by CE and missed by radiographic investigations (Cheung et al., 2010). Other studies, including less than 200 patients, reported SBTs in 5%-10% of cases (Trifan et al., 2010). CE and DBE are comparable for the diagnosis of SBTs, but DBE has the advantage of biopsy and therapeutic potential. Generally, SBT appearance on CE resembles mass lesions (polypoid in 70-80%) or, less frequently, ulcers or stenosis (20-30%), with no capacity of distinguishing between the types of tumor. Moreover, making the difference between a true mass lesion and a false positive lesion (as in extrinsic compression, mucosal bulge, and intussusception) is often difficult. Images provided by CE cannot be manipulated in terms of angle, recording durations or revisualization of the same lesion in a different moment of peristaltis. These impediments increase difficulty in assessing the nature of a “mass” type of lesion pointed out by CE.

CE is also useful as a screening and surveillance tool

for inherited gastrointestinal polyposis syndromes such as Peutz-Jeghers syndrome or familial adenomatous polyposis (FAP). Several studies have shown that CE is superior to other imaging modalities for the diagnosis of small bowel polyps. In one study CE was more accurate than MR-enterography to diagnose intestinal polyps smaller than 15 mm, while identification of large polyps (>15 mm) was similar between CE and MR-enterography (Gupta et al., 2010). CE has proven to be accurate for the detection of polyps especially in the medium and distal small bowel, but cannot determine with precision their size or localisation. CE does not have the same reliability in detecting polyps in the periampullary region, its sensitivity for this location being inferior to that of push enteroscopy or DBE. Koulaouzidis and Plevris (2012) evaluated the detection rate of the ampulla of Vater during CE examinations and found a low detection rate regardless of SBCE systems used (10.7% with PillCam SB 1, 8.8% with PillCam SB 2; 8.6% with MiroCam). The authors concluded that if ampulla of Vater is taken as a surrogate marker of small polyp detection, SBCE cannot replace side-viewing standard endoscope in the evaluation of periampulary polyps in FAP and that it is an infallible technique in other small bowel polyposis states. However, CapsoCam SV1 with a 360° panoramic view, pointed out the papilla in 71% of cases, in comparison with 10-44% of cases investigated with conventional CE (Friedrich et al., 2013).

In addition to its inability to obtain biopsies, other CE limitations consist in interpretation difficulties (transient bulges into the small bowel lumen may appear to be submucosal tumors), and missed lesions in the duodenum and proximal jejunum (potential blind points of CE because of its rapid transit through these areas).

Other Clinical Applications

NSAIDs-enteropathy

The use of enteroscopy and CE revealed that incidence of NSAIDs-pathology at the level of the small bowel is much higher than it was previously thought (Leighton et al., 2014). NSAIDs-induced lesions may be erosions, ulcers, villous atrophy, diaphragms, stenosis, or perforations. However, interpreting lesions seen at CE is difficult, as some may occur in healthy subjects, in the absence of NSAIDs use or any symptomatology, while others raise the problem of differential diagnose with other small bowel pathologies (NSAID-induced enteropathy is the most common mimicker of CD).

Acute upper gastrointestinal bleeding (UGIB)

Esophageal CE was proposed for risk stratification in acute UGIB, aiming to identify patients which do not require hospitalization and can be investigated in outpatient clinics (Chandran et al., 2013). Schlag et al. (2015) evaluated for the first time in a prospective study the impact of emergency small bowel CE in patients with acute severe GI bleeding immediately after an initial negative upper endoscopy result and showed that CE had a diagnostic yield of 75% (95% CI=51%-91%) and correctly guided further diagnostic and therapeutic procedures in 85% of cases (95% CI=62%-97%).

Recently, esophageal CE was has been used in few emergency department (ED) for the diagnosis of upper GI bleeding. Meltzer et al. (2013) assessed the diagnostic in patients with acute GI bleeding and reported an 88% sensitivity (95% CI: 65%-100%) and 64% specificity (95% CI: 35%-92%) for the detection of fresh blood compared with traditional EGD (upper GI endoscopy) performed within next 24 hours. Gralnek et al. (2013) reported that CE detected blood in 83% of patients with suspected GI bleeding compared with 33.3% detected by nasogastric aspiration.

Chronic abdominal pain

It may require CE, but clinical benefit of such examination is unconfirmed. Xue et al. (2015) evaluated the diagnostic yield of CE in patients with unexplained chronic abdominal pain in a systematic review including 1520 patients from 21 studies and found a low CE diagnostic yield (20.9%).

Esophageal Capsule Endoscopy

Several studies have evaluated PillCam ESO 1 and ESO 2 for the diagnosis of gastroesophageal reflux disease (GERD), esophagitis, and Barrett's esophagus, as well as for the screening of esophageal varices in cirrhotic patients. Overall, PillCam ESO 1/ESO 2 have shown low sensitivity for the diagnosis of esophagitis and Barrett's esophagus, and consequently, standard upper endoscopy remains the gold standard method in such patients. An initial meta-analysis including 7 studies with 446 patients showed PillCam ESO sensitivity and specificity for detecting esophageal varices of 85.2% and 80.5%, respectively, compared with standard endoscopy (Lu et al., 2009), and more recently, a study from Japan confirmed the high diagnostic yield and the usefulness for the esophageal variceal screening of PillCam ESO (Ishiguro et al., 2011). However, most data suggest that PillCam ESO 2 is inferior to upper endoscopy for the diagnosis and grading of esophageal varices in patients with portal hypertension (ASGE Technology Committee, Wang et al., 2013).

Colon Capsule Endoscopy

Colon capsule endoscopy (CCE) has been developed with the aim of colorectal cancer (CRC) screening. Low compliance of the general population worldwide in CRC screening programs is due to fear of pain, need for sedation, concerns about possible complications, and the unease about the invasion of one's privacy. Certainly, CCE offers an alternative as a painless procedure, and no need for sedation, air insufflation, radiation, or invasion of one's privacy. However, the results for first generation CCE-1 (PillCam COLON 1) have been disappointing. Comparative trials that used colonoscopy as the gold standard reported CCE2 sensitivity between 72% and 95% for patients with polyps ≥ 6 mm and between 75% and 92% for polyps ≥ 10 mm, while specificity between 64% and 91% for patients with polyps ≥ 6 mm, and between 89% and 100% for patients with polyps ≥ 10 mm (Eliakim et al., 2009; Spada et al., 2011a). A prospective, multicenter study including 328 patients with known or suspected colonic diseases, reported a CCE-1 sensitivity and specificity to detect polyps ≥ 6 mm in size of 64% and 84%, respectively, compared with colonoscopy (Van Gossum et al., 2009). A meta-analysis including 8 studies with 837 patients, reported a low sensitivity of CCE-1 (71%) for polyps of any size and for "significant findings" (68%) as compared with conventional colonoscopy (Spada et al., 2010), while another meta-analysis found CCE-1 sensitivity of 69% and specificity of 89% for significant polyps (Rokkas et al., 2010). Several other studies using CCE-1 for significant findings (polyps ≥ 6 mm in size or ≥ 3 polyps) have reported variable sensitivity (39%-100%) and specificity (70%-95%) (Sacher-Huvelin et al., 2010; Spada et al., 2011b). Since its introduction in 2006, CCE underwent major technological improvements mentioned in the history section of this review. Using the second-generation CCE (CCE-2), one study reported the sensitivity and specificity for detecting polyps ≥6 mm of 89% and 76%, respectively, while for polyps ≥10 mm the corresponding figures were 88% and 89%, respectively (Eliakim et al., 2009). In a recent prospective, blinded trial to determine the accuracy of PillCam CCE-2 and CT-colonography, Spada et al. (2015) found that both methods had comparable efficacy in completing colon evaluation after incomplete colonoscopy, although overall diagnostic yield of CCE-2 was superior to CT-colonography. Subsequently, CCE-2 is now recommended in patients with incomplete colonoscopy (FDA approved), in addition to those who are unwilling or unable to undergo colonoscopy. Negreanu et al. (2013) found CCE-2 an effective procedure in detecting significant lesions and an adequate alternative diagnostic tool in patients unwilling or unable to undergo colonoscopy. A prospective, multicenter international (10 centers in the United States and 6 in Israel) study in an average-risk screening population reported that CCE-2 identified subjects with 1 or more polyps 6 mm or larger with 88% sensitivity and 82% specificity; the authors concluded that CCE is an appropriate method for detecting such polyps for patients who cannot undergo optical colonoscopy or had incomplete colonoscopy, although colonoscopy remains the gold standard for the diagnosis of colorectal polyps (Rex et al., 2015). Adrián-de-Ganzo et al. (2015) in a prospective study of 329 asymptomatic first-degree relatives of patients with colorectal cancer found that CCE-2 was as effective as colonoscopy in detecting significant lesions, and thus, CCE could be a valid strategy for individuals unwilling undergo screening colonoscopy. However, despite a good sensitivity and specificity of CCE for detecting polyps and cancers, the rigurous data of CCE on colorectal cancer screening are lacking. In one study (Holleran et al., 2014), CCE was effective in detecting polyps and cancer in a positive fecal immunochemical test (FIT) cohort. However, in the absence of specific studies in colorectal cancer screening, CCE cannot be included in any screening programs.

CCE may be useful for evaluating IBD, particularly in UC patients. Thus, Hosoe et al. (2013) reported that CCE-2 might be feasible for assessing the severity of mucosal inflammation in patients with UC. The same team performed a second CCE-2 study (Usui et al., 2014) in UC patients with a low-volume (2L) PEG and prokinetics regimen and found that 85% of the patients achieved total examination. In pediatric UC, one study compared the diagnostic accuracy of CCE-2 with colonoscopy and found a 96% sensitivity and 100% specificity for CCE-2 (Oliva et al., 2014). Sung et al. (2012) in a multicenter study involving 100 suspected or known patients with UC reported the sensitivity of CCE to detect active colonic inflammation of 89% and specificity was 75%. More recently, D'Haens et al. (2015) in a multicenter pilot study assessed the safety and feasibility of the CCE-2 in evaluating the severity of CD; the study included 40 patients with active colonic CD who underwent CCE-2 and optical colonoscopy procedures. The authors found substantial agreement between CCE-2 and optical colonoscopy in the measurement of the Crohn's Disease Endoscopic Index of Severity (CDEIS). CCE-2 had 86% sensitivity and 40% specificity in detecting colonic ulcerations, it had no adverse effects, and was better tolerated than colonoscopy; the majority of patients would favor CCE-2 for a future endoscopic examination, a finding which supports previous assessments of patient preference (Oliva et al., 2014).

The clinical indications for CCE and detected findings have been published as a ESGE (European Society of Gastrointestinal Endoscopy) guidelines (Spada et al., 2012). Despite encouraging results, CCE cannot replace conventional colonoscopy as every positive CCE finding needs colonoscopy for a definitive diagnosis. According to the European Society of Gastrointestinal Endoscopy (ESGE) guidelines, CCE is indicated in patients with

incomplete colonoscopy, in those patients unwilling or unable to undergo colonoscopy (Spada et al., 2012).

Limitations of Capsule Endoscopy

Besides the recognized advantages, CE has also several limitations. CE is a purely visual technique with no ability to control its movement, take biopsy or perform therapeutic manoeuvres. All of the available capsules for clinical use are powered by limited-life batteries which may be depleted before the examination is completed in patients with delayed gastric emptying or previous small bowel surgery. In addition, a poor bowel cleansing and hospitalization also contribute to an incomplete examination. Missed lesions by CE usually were large lesions and most often located in the duodenum and proximal jejunum where the transit is more rapid than in distal segment of the small bowel. Locating small bowel lesions remains an important unsolved clinical problem as well as sizing of the lesions, CE being unreliable to detect large polyps. Reading time for interpretation is another limitation of CE, taking over 1 h to read a full 8-h examination. CE procedure is not operator-dependent, and an accurate diagnostic in CE is a combination of lesion detection and ability of the reviewer to read and interpret the lesion. Some studies reported that a reliable interpretation of the CE findings requires experienced readers, preferably gastroenterologists. However, several other studies have compared CE reading between gastroenterologists, endoscopy fellows, nurses, and medical students, and found no significant differences regarding missing pathology in CE reading (Drew et al., 2011). Finally, costs are still high.

Several research groups are currently working to overcome these limitations, while novel devices able to control capsule movement, obtain high quality images, insufflate the gut lumen, perform chromoendoscopy, biopsy of suspect lesions, or even direct targeted drugs to specific sites are under development. Overlooking current limitations, especially as some of them have already been successfully overcome, the last chapter on CE has not yet been written. Tremendous progresses made in modern technology enable us to look forward to a next generation CE which is on the horizon. We believe that, by the end of next decade, CE will remain the major form of digestive endoscopy.

CONCLUSION

Undoubtedly, CE has opened a new era in endoscopic diagnosis for gastroenterologists and has set a milestone in the evolution of endoscopic examination of the GI tract without discomfort or need for sedation, or the risks that conventional endoscopy implied for the patient. During a relatively short period of time (17 years), CE has proven its high diagnostic yield in multiple pathologies of the small bowel such as obscure GI bleeding, Crohn's disease, celiac disease, and small bowel tumors. More recently, dedicated esophageal and colon CE have expanded the field of applications to include the evaluation of upper and lower GI disorders. However, the endoscopic capsules currently available are only diagnostic tools, and still have several limitations (passive locomotion, inability to perform biopsy or deliver therapy etc). Modern technology continues to achieve tremendous progresses in CE which have no epilogue, surpassing the above-mentioned limitations in current CE.

Author Contributions

Singeap AM, Stanciu C, Cojocariu C and Trifan A contributed equally to the conception and design of the review; Singeap AM and Cojocariu C performed acquisition of data; Stanciu C analysed the data, coordinated the manuscript drafting and revised it critically; Trifan A participated in the analysis and interpretation of data, and critically revised the manuscript for important intellectual content; all authors read and approved the final version of the manuscript.

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