Review Article on Current Applications and Future Concepts of Capsule Endoscopy

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Key Words

Capsule endoscopy • Small bowel • Advanced imaging • Endomicroscopy • Inflammatory bowel disease

Abstract

Since the advent of capsule endoscopy (CE) more than one decade has passed. During this time, extensive efforts have been made to proof the relevance of CE for diagnosis of various disease entities within the esophagus, small bowel, and colon. To date, the most common indications for CE are obscure gastrointestinal bleeding, Crohn's disease, polyposis syndromes and evaluation of patients with complicated celiac disease. In this review we will focus on the current clinical applications of CE for imaging of the esophagus, small bowel and colon and will additionally give an outlook on future concepts and developments of CE.

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Introduction

Since the introduction of capsule endoscopy (CE) in 2000, various studies have shown the potential of this minimally invasive technique to improve diagnostic outcomes among a variety of gastrointestinal (GI) conditions [1–58].

To date, multiple CE systems from different companies are available. Nevertheless, currently only the Given M2A video capsule system (Given Imaging Ltd., Yoqneam, Israel) and the Olympus Endocapsule (Olympus, Tokyo, Japan) are FDA and CE approved. Capsule systems are available for examination of the esophagus, small bowel and colon. While suspected small bowel stenosis is a contraindication for performing CE a patency capsule (Agile capsule, Given Imaging) was developed for these patients. This capsule is a self-dissolving capsule with the same size as the conventional CE and contains a radiofrequency identification tag that allows it to be detected by a scanning device placed on the abdominal wall. In addition, it has a radiopaque coating that permits its location within the bowel using fluoroscopy. When its passage is blocked by a stenosis or tumor, the patency capsule dissolves within 40–80 h after ingestion.

Although the capsule is easily ingested and swallowed by most individuals, patients with severe dysphagia, large Zenker's diverticulum, pill phobia, significant gastropareses, and small children may have problems ingesting the device. For these situations, a capsule-loading device (AdvanCE, US Endoscopy, Mentor, Ohio, USA) is available to directly deliver the capsule into the stomach or duodenum. The disposable device is a 2.5-mm single-sheathed device which is first preloaded through the working channel of a standard endoscope. The activated

CE is than loaded into the specialized capsule cup and afterwards the endoscope and the loading device are carefully advanced through the esophagus. After reaching the stomach or duodenum the CE is released and the endoscope is withdrawn.

Based on a recent systematic review, the following were identified as the most common indications for CE: obscure GI bleeding, accounting for 66% of interventions, clinical symptoms only (10.6%), Crohn's disease (10.4%), others (7%), neoplastic lesions (3.5%), celiac disease (1.7%), and healthy subjects (0.8%) [2]. It is important to emphasize that CE has a low diagnostic yield in the evaluation of patients with abdominal pain or diarrhea in the absence of anemia or elevation of inflammatory markers [3].

Technical Specifications

At the time of writing this review, two FDA and CE-certified capsule devices are available consisting both of disposable plastic capsules. The Given small bowel capsule measures 11 × 26 mm and weighs less than 4 g. The field of view is 140 degrees and the system can detect objects less than 0.1 mm. The SB2/4 capsule is capable of capturing four images per second. The operating time is between 6 and 8 h. The Given capsule for esophageal diseases (PillCam Eso) has the same size like the SB capsule but is capable to take up to 18 images per second as it passes down the esophagus. The Endocapsule system from Olympus has a maximum field of view of 145°, a depth of field between 0 and 20 mm and a sampling rate of 2 frames per second. The dimensions of the capsule are 11 mm in diameter and 26 mm in length. The operating time of the device is about 8 h.

Relative and Absolute Contraindications

It is recommended to use the CE with caution in patients with known or suspected GI obstruction, fistulas, or motility disorders [4]. Nonexcretion of the CE was reported to occur in less than 1% of patients [5]. In this context, retention only occurred in cases with localized pathology while no retention has been reported in normal subjects or those with small bowel diverticulosis or appendiceal orifices [6]. In patients with suspected Crohn's disease and obscure GI bleeding capsule retention has been reported in between 1.5 and 5%. Although CE retention is usually clinically asymptomatic, it may require ei-

Fig. 1. Typical appearance of angiovascular malformations visualized using CE.

ther endoscopic or surgical removal to avoid further complications [7]. While there has been concern about the use of defibrillators and cardiac pacemakers, recent evidence suggests that CE can be safely performed in these patients with appropriate monitoring. Moreover, it was shown that capsule-induced electromagnetic interference remains a possibility but is unlikely to be clinically important. Cardiac pacemaker-induced interference of CE is also possible, but is infrequent and does not result in loss of images transmitted by the capsule [8]. In contrast, patients should not undergo magnetic resonance imaging after having excreted the CE. Plain radiographs can easily identify the CE in case of suspicion of any retention.

Patient Preparation

Patient preparation for CE of the esophagus is performed after the patient has fasted for at least 2 h. For small bowel CE there are several accepted preparation methods, which include fasting since the day before, clear liquid diet, the ingestion of 2–4 liters of polyethylene glycol solution or the use of mannitol. In addition, some experts recommend the use of simethicone before the ingestion of the capsule to reduce intraluminal foam and bubbles. Bowel cleansing for colon CE is of paramount importance and it is still under development and improvement.

Because CE is a minimally invasive technology patient compliance is good in most cases. Only a minority of patients have problems to swallow the capsule and some patients experienced problems drinking the amount of fluid necessary for optimal colon CE examination.

Fig. 2. Superficial ulcerous lesion in Crohn's disease.

Fig. 3. Engorged and flattened intestinal villi in patient with celiac disease.

Fig. 4. Small bowel polyp in a patient with Peutz-Jeghers syndrome visualized using CE.

Fig. 5. CE visualizes NSAID-induced small-bowel lesion.

Fig. 6. Appearance of enteropathy-associated T cell lymphoma on CE.

Fig. 7. Small-bowel carcinoid diagnosed with CE.

Clinical Applications

Esophagus

GERD and Barrett's Esophagus

Eliakim et al. [9] presented the results of a multicenter trial evaluating the diagnostic accuracy of PillCam ESO versus upper endoscopy in patients with chronic gastro-esophageal reflux disease. Overall, 106 patients were included and of those 66 patients had positive esophageal findings. CE identified esophageal abnormalities with a sensitivity and specificity of 92 and 95%, respectively. The per-protocol sensitivity, specificity, positive predictive value, and negative predictive value of CE for Barrett's esophagus were 97, 99, 97 and 99%, respectively, and for

esophagitis 89, 99, 97 and 94%, respectively. In this study, CE was preferred over standard upper endoscopy by all patients.

In 2008, Gralnek et al. [10] presented the results of the second-generation CE (PillCam ESO 2) for the detection of esophageal diseases. Compared with upper endoscopy for detecting suspected Barrett's esophagus and esophagitis, the PillCam ESO 2 had a sensitivity of 100% and a specificity of 74%, and a sensitivity of 80% and a specificity of 87%, respectively.

Another study compared the accuracy of upper endoscopy with esophageal CE in patients at risk of esophageal squamous cell cancer [11]. Overall, 68 patients were included. Sensitivity of CE for neoplasia diagnosis was 46%.

Fig. 8. Proposed algorithm for the diagnosis of obscure GI bleeding.

On a per-patient basis, the sensitivity, specificity and positive and negative predictive value of CE were 63, 86, 77 and 76%, respectively. Therefore, CE seemed not to be sensitive enough to diagnose neoplastic lesions in the esophagus.

In conclusion, CE of the esophagus seemed to be a convenient and sensitive method for visualization of Barrett's esophagus and esophagitis but is not sensitive enough to diagnose SCC.

Esophageal Varices

Various studies have evaluated the potential of CE for diagnosis of esophageal varices. One recent meta-analysis included 9 studies with 631 patients [12]. The pooled sensitivity and specificity of CE for detecting esophageal varices were 83 and 85%, respectively. Nevertheless, CE was not comparable to upper endoscopy. It was therefore concluded that esophageal CE could be an acceptable alternative to conventional endoscopy in certain situations but could not be recommended to replace standard upper endoscopy.

Small Bowel

Obscure Gastrointestinal Bleeding

Obscure GI bleeding is defined as either occult or overt bleeding of unknown origin that persists or recurs after an initial negative endoscopic evaluation including colonoscopy and EGD. Obscure GI bleeding accounts for

most (about 66%) of CE interventions and CE has been recommended as the 3rd diagnostic test for patients with obscure GI bleeding (after at least one normal upper and lower endoscopy) [2, 13]. It was shown that about 20–38% of patients with normal upper and lower endoscopy have significant intestinal lesions [14, 15] (fig. 1). Previous studies have demonstrated that CE is superior to radiographic studies, including barium follow-through and CT enterography [16, 17]. Moreover, a pooled analysis of 7 prospective studies showed a CE yield of 71% for identification of a bleeding source compared to push enteroscopy [18]. In case of ongoing bleeding, CE detected the bleeding source in 92%. In case of heme-positive stool and anemia, CE detected the bleeding source in 44% and in patients with a prior overt bleeding in about 13% of patients.

When comparing CE with intraoperative enteroscopy, the sensitivity, specificity positive, and negative predictive value of CE was 95, 75, 95 and 86%, respectively [19]. These findings are in line with other published data [20–22].

Balloon-assisted endoscopy (e.g. double-balloon or single-balloon endoscopy) has the potential to visualize the whole small intestine. One recent study compared double-balloon endoscopy with CE and identified nearly concordant findings in 12 out of 13 bleeding patients. In 1 patient, CE missed an ulcer [23]. Sheibani et al. [24] evaluated the long-term impact of CE in patients referred

Table 1. Indications for CE according to different locations (most common indications are underlined)

Esophagus
Gastroesophageal reflux disease
Barrett
Esophageal varices
Small bowel
<u>Obscure gastrointestinal bleeding</u>
<u>Intestinal tumors</u>
<u>Crohn's disease</u>
Celiac disease
Colon
Polyps
Cancer
General
Diarrhea
Abdominal pain

for iron deficiency anemia. CE had a diagnostic yield of 61% and the CE-based diagnosis led to a therapeutic intervention in about 26% of patients. Another study included 100 consecutive cases with recent negative upper and lower endoscopy [20]. In patients with ongoing overt GI bleeding CE yielded in positive findings in about 92%. In contrast, in patients with guaiac-positive stool tests, iron deficiency anemia and previous overt GI bleeding, CE yielded positive findings in about 44 and 13%, respectively. Sensitivity, specificity and positive and negative predictive values of CE were 89, 95, 97 and 83%, respectively. Figure 8 highlights our proposed algorithm for the diagnosis of obscure GI bleeding.

Intestinal Tumors

The frequency of intestinal tumors among patients investigated using CE for obscure bleeding ranges from 6 to 12% [25]. The most common tumors in the small bowel include adenocarcinomas, lymphomas, GI stromal tumors, neuroendocrine tumors and metastasis [26]. Nevertheless, there are several cases of missed tumors of the small bowel using CE, probably because these lesions grow predominantly in the submucosa and extraluminally rather than into the small bowel lumen [27, 28]. Moreover, small bowel tumors are sometimes relatively small and can therefore easily be missed with CE. In patients with polyposis syndromes, CE was shown to detect more polyps in comparison to small bowel follow through [29]. Moreover, CE seemed to be more effective than positron emission tomography in the detection of malignant melanomas and metastases [30]. Detection rates between

MRI and CE for identification of polyps larger than 15 mm were similar while CE was more sensitive to diagnose smaller intestinal polyps [31]. Nevertheless, one potential limitation of CE is the examination of the proximal duodenum and the perampullary region which could only be visualized in about 10% of examinations in one recent study [32]. In patients with familial adenomatous polyposis, CE was superior to conventional white-light endoscopy for the detection of small bowel polyps, but not for duodenal neoplasia [33]. Also for other hereditary polyposis syndromes, including Peutz-Jeghers syndrome and Lynch syndrome, recent data indicate that CE is a safe and effective method for small bowel surveillance and even yield in a better reproducibility than with CT enteroclysis [34–36] (fig. 4). Nevertheless, despite these promising results surveillance of the small bowel is currently mostly not recommended in Lynch syndrome [37].

Crohn's Disease

Various studies have shown the potential of CE for diagnosis of Crohn's disease [38–42] (fig. 2). Eliakim et al. [38] compared CE to barium follow through and computed tomography (CT) in patients with suspected Crohn's disease. CE yielded a diagnosis in 77% of patients, compared to 23 and 20% for barium follow through and CT, respectively. These results were also confirmed by other investigators [39, 40]. Notably, one recent small study including 39 patients reported on a sensitivity and specificity of 89 and 100%, respectively [41]. These results need to be critically discussed, because Crohn's disease-associated mucosal changes are nonspecific for the disease and can also be observed in up to 14% of healthy volunteers and in patients taking nonsteroidal anti-inflammatory drugs [42] (fig. 5). Therefore, it is important for the endoscopist to read the CE findings with extensive knowledge about the patient's history. One recent published meta-analysis evaluated the diagnostic yield of CE in patients with suspected and established small bowel Crohn's disease in comparison to push enteroscopy, ileocolonoscopy, small bowel radiography, CT enterography and magnetic resonance tomography [43]. The meta-analysis revealed that CE was superior to small bowel radiography, CT enterography and ileocolonoscopy in the evaluation of patients with suspected Crohn's disease. In patients with established Crohn's disease, CE was superior to small bowel radiography, CT enterography and push enteroscopy. Similar results were shown in another recent meta-analysis from Leighton et al. [44]. In contrast to these data, Solem et al. [45] found that the sensitivity of CE for diagnosis of active small bowel Crohn's disease was not sig-

Fig. 9. Proposed algorithm for the diagnosis of suspected small bowel Crohn's disease.

nificantly different from CT enterography, ileocolonoscopy, or small bowel follow through. The authors concluded that CE has only a limited value as the first-line test for small bowel Crohn's disease. Importantly, the risk of capsule retention in patients with known Crohn's disease must be considered and analyzed before the ingestion of CE. Although patients with suspected Crohn's disease have the same risk of retention as compared with the general population (1.6%), in patients with known or established Crohn's disease this risk of retention is up to 13%, with the consequent need of surgery in some cases [46]. Of note, balloon-assisted endoscopy is mostly successful to remove foreign bodies from the small bowel [47]. Figure 9 highlights our proposed algorithm for the diagnosis of Crohn's disease.

Celiac Disease

Advanced celiac disease is characterized by villous atrophy which can be visualized using CE Figure 3. One recent published meta-analysis described an overall pooled sensitivity of 89% (95% CI 82–94) and specificity of 95% (95% CI 89–98) for CE in celiac disease [48]. In a subgroup analysis of patients with complicated or refractory disease, CE documented unexpected findings such as strictures, ulcerations and neoplasms in up to 45% of cases [49]. Of note, CE can only diagnose advanced stages of celiac disease, as early stages are only based on histological findings. The most important use of CE in celiac disease is the evaluation of patients with refractory

celiac disease, investigating ulcerative changes or the development of T cell lymphomas. Besides, CE may also be sufficient to diagnose enteropathy-associated T cell lymphoma which is an intestinal tumor of intraepithelial lymphocytes [50] (fig. 6).

Colon

Polyps and Cancer

Colorectal cancer screening still remains a challenge because most patients decline to participate in screening programs due to anxiety directly related to the endoscopic procedure. In this context, the colon capsule has been proposed as an alternative minimally invasive tool for colorectal cancer screening (fig. 7).

In a prospective study, including 84 patients, CE was followed by standard white-light endoscopy on the same day [51]. 24% of patients had significant findings, defined as at least one polyp of 6 mm or more in size or three or more polyps of any size: 70% were identified with CE and 80% were identified by conventional colonoscopy. Polyps of any size were found in 45 patients, 76% found by CE and 80% by conventional colonoscopy. In comparison with conventional colonoscopy, false-positive findings on CE were recorded in 33%.

The second-generation colon capsule has several advantages when compared with the first colon capsule. It has an increased angle of view to 172° and an adaptive frame rate which alternates from 35 frames per second while in motion to 4 images when virtually stationary. This second-generation colon capsule was evaluated by the same group in a prospective, multicenter study [52]. Overall, data from 98 patients were analyzed. The capsule sensitivity for the detection of patients with polyps ≥ 6 mm was 89% (95% CI 70–97) and for those with polyps ≥ 10 mm 88% (95% CI 56–98). Specificity of CE for polyps ≥ 6 mm was 76% (95% CI 72–78) and for those with polyps ≥ 10 mm it was 89% (95% CI 86–90), respectively.

In addition, one recent study evaluated the feasibility, accuracy, and safety of the second-generation CE in a head-to-head comparison with colonoscopy [53]. Data from 109 patients were analyzed. The per-patient CE sensitivity for polyps ≥ 6 mm and ≥ 10 mm was 84 and 88%, with specificities of 64 and 95%, respectively. All 3 invasive carcinomas in the study population were detected by CE.

One large multicenter study included 328 patients and analyzed CE versus conventional colonoscopy for the detection of polyps and cancer [54]. The CE was excreted within 10 h after ingestion and before the end of the lifetime of the battery in about 93% of patients. CE yielded a

sensitivity and specificity for detecting polyps ≥ 6 mm of 64% (95% CI 59–72) and 84% (95% CI 81–87), respectively. For the detection of advanced adenoma, the sensitivity and specificity were 73% (95% CI 61–83) and 79% (95% CI 77–81), respectively. Of 19 cancers which were detected by colonoscopy, 14 were also detected by CE (sensitivity 74%; 95% CI 52–88). Mild-to-moderate adverse events were reported in about 8% of patients and were mostly related to the colon preparation.

It is still under debate if patients should undergo same-day colonoscopy in the setting of positive CE findings. In our opinion, it would be useful that the patient sign the informed consent for colonoscopy together with the informed consent for the capsule. The colonoscopy could then be performed on the same day, given the fact that the patient is good prepared for the colonoscopy, and does not have to undergo another preparation.

Future Concepts of Capsule Endoscopy

Small bowel imaging still remains the major indication for CE. Comparative studies between the Given Imaging and the Olympus CE have demonstrated similar efficacies of both systems [55]. Currently, new capsule devices are under development in order to enable targeted drug administration or even direct hemostatic therapy. The results of the respective pilot studies are highly anticipated as they will open new applications for CE.

In its current form, the colon capsule is no real alternative to conventional colonoscopy. CE procedure-related costs are extremely high and an exhaustive bowel preparation is needed to obtain reasonable polyp detection rates. Moreover, CE is not sensitive enough to predict histology of colorectal polyps so that every positive CE finding needs to be clarified by conventional endoscopy.

Nevertheless, new capsule devices may improve both, polyp detection and characterization rates. In this context, externally rechargeable batteries (using RF, microwave, ultrasound or electric induction) or even 'battery free' CE are developed. Moreover, integration of virtual chromoendoscopy techniques, like FICE or i-scan, will further improve image resolution and will help to better characterize colorectal lesions [56, 57]. Other devices such as capsules which will enable confocal imaging with near infrared light are also under development thereby allowing obtaining an optical biopsy during the CE procedure. The NEMO (nano-based CE with molecular imaging and optical biopsy) project tends to develop a new capsule that will combine optical and nano technologies, biosensing, and maneuvering technologies in order to further improve diagnostic and therapeutic possibilities

of the capsule system [56, 57]. Additionally, pilot studies have already demonstrated the feasibility of new capsule devices to obtain mucosal biopsies and to apply clips or coagulation for hemostasis. In order to actively control the CE, recently the prototype of a magnetically guided capsule endoscope (MGCE) system from Siemens and Olympus was introduced. The study demonstrated that the new technology appears to be feasible and sufficiently accurate for gastric examination and may permit endoscopic examinations that are more patient-friendly and without sedation [58].

Conclusion

CE has proven its efficacy in multiple trials since its introduction nearly 12 years ago. The main indications for CE interventions are still obscure GI bleeding, followed by clinical symptoms only and suspected Crohn's disease. Multiple studies have shown that CE for these interventions is superior to radiologic interventions and push enteroscopy. In case of positive CE findings balloon-assisted endoscopy (i.e. single- and double-balloon enteroscopy) offers the potential to apply targeted biopsies or therapy.

In the past, CE was only a diagnostic test and capsule movement was passive according to the gut movement. In the future, new capsule devices may offer a great potential for minimally invasive diagnosis and targeted therapy. Moreover, capsule movement will be actively controllable thereby opening new avenues for advanced specific diagnosis and targeted therapy.

Disclosure Statement

None.

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