Current Status and Future of Capsule Endoscopy

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ABSTRACT

Endoscopic investigation has a critical role in the diagnosis and treatment of gastrointestinal (GI) disease. Since 2001, capsule endoscopy (CE) has been developed for small bowel exploration. Over the past decade, CE has achieved impressive improvements in areas such as miniaturization, resolution, and battery life. As a result, CE is a first-line tool for the investigation of the small bowel in obscure gastrointestinal bleeding (OGIB) and is a useful alternative of wired enteroscopy. Nevertheless, CE still has several limitations such as incomplete examination, diagnostic and therapeutic capability. To resolve this problem, many groups have suggested several models (controlled CO₂ insufflation system, magnetic navigation system, mobile robotic platform, tagging and biopsy equipment, targeted drug delivery system, etc.), which are in development. In the near future, new technological advances will improve the capabilities of CE and broaden its spectrum of applications not only for the small bowel but also for the colon, stomach and esophagus. The purpose of this review is to introduce the
current status of CE and promising solutions for limitations.

Key words: Capsule endoscopy; Small bowel; Esophagus; Colon; Stomach; Future

INTRODUCTION

CE has been available in clinical practice for the evaluation of small bowel disease since 2001. CE has most commonly been used in cases of OGIB.¹ There are now several small bowel capsules (PillCam®: Given Imaging, Yoqneam, Israel; EndoCapsule®: Olympus, Tokyo, Japan; MiroCam®: IntroMedic, Seoul, Korea; OMOM®: Jinhan Sience, Chongding, China; CapsoCam®: CapsoVision, Saratoga, USA) in the world.² CE has many advantages compared with conventional wired endoscopy such as acceptability and less invasiveness. However, CE still has several significant limitations to solve technically. First, the GI lumen is not inflated in CE, and only passive images can be attained while the capsule passes through the GI tract. Therefore, lesions may be missed in CE, and the Ampulla of
Vater or Ileocecal valve could be undetected in small bowel CE. Moreover, CE often produces vague images because of bile, mucus, etc. It takes too long to administer CE and interpret capsule images. Second, CE does not take a biopsy nor does it have therapeutic capabilities. To overcome this limitation, several groups have suggested alternatives, and these alternatives are currently in development. Here, we introduce research results about the future of CE.

**CURRENT STATUS OF CE**

**Small bowel CE**

With the progression of CE technology, CE has rapidly expanded the indication of investigation for GI tract. Given Imaging has installed more than 4,250 centers in about 60 countries and has sold more than 650,000 capsules. CE is a particularly useful tool for patients with suspected small-bowel disease, including OGIB, iron deficiency anemia, Crohn’s disease (CD), tumors, polyposis syndromes,
and celiac disease. A recent clinical guideline has recommended CE as a first-line investigation tool in patients with OGIB. The first available video capsule, brand name mouth to anus (M2A®; Given Imaging, Yoqneam, Israel), was approved by the Food and Drug Administration (FDA) in 2001 as an adjunctive tool for small intestinal imaging. At present, there are 5 small-bowel CE models in the market worldwide.⁴⁻⁵ CE models with U.S. FDA approval consist of PillCam®, Endocapsule®, and MiroCam®. Although the various capsules are similar in size and shape, they differ with regard to dimensions, frame rates, operating time, field of view, image sensor, and optical enhancements (Table 1). PillCam® and MiroCam® capture images using a complementary metal oxide silicon sensor (CMOS), while Endocapsule® and the OMOM® capsule use a charge-coupled device (CCD).⁶ In 2013, the third generation of PillCam® SB3 was launched and received FDA clearance. This capsule system has improved image detail and adaptive frame rate technology (2 to 6 frames per second) leading to increased visualization of the small bowel and improved efficiency.⁷ The CapsoCam® has four cameras that provide a 360° field of view, 12-20 frames per second (fps), and 15 hours of...
battery life. The CapsoCam® camera takes images at a rate of 5 fps for the first two hours and thereafter at a rate of 3 fps, resulting in 12 and 20 fps respectively. Smart Motion Sense Technology also enables the capsule to activate its cameras only during capsule motion.⁸

In order to improve the specificity of small-bowel CE findings, fecal calprotectin (FC) is considered a non-invasive, ‘gold standard’ marker of GI inflammation. An FC level greater than 100 μg/g is a good predictor of positive small bowel CE findings, and FC > 200 μg/g associated with higher small bowel CE yield (65%) and confirmed CD in 50% of patients.⁹

**Beyond small intestine, CE of colon, stomach and esophagus**

Colorectal cancer (CRC) screening programs in high-risk populations were reported to result in a 90% decrease in CRC incidence. However, no more than 25% compliance has been achieved in screening programs.¹⁰ Colon CE could be a good alternative in patients refusing conventional colonoscopy or when conventional colonoscopy is inappropriate or not possible. In a series of 328
consecutive cases, the rate of complete colon visualization before the end of the lifetime of the battery was 92.8%. European studies showed capsule sensitivity for polyps of any size of 69% and 76% with specificity of 81% and 64%. In two prospective studies with the newer colon CE (Pillcam® COLON 2; Given Imaging, Yoqneam, Israel), sensitivity reached 84% and 89% for detecting polyps greater than 6 mm. Although colon CE showed similar detection capabilities when compared with conventional colonoscopy in some studies, conventional colonoscopy remains more accurate than colon CE, and allows the simultaneous removal of polyps. The colon capsule has a potential future for CRC screening, but more data is needed in order to answer many pending uncertainties such as the best preparation method, the best scoring method (CECD activity index or Niv Score), the best booster, and mainly the best indications.

In the case of stomach, CE could also be used in patients unwilling or unable to have standard upper GI endoscopy. Limitations in conventional upper endoscopy, such as broad lumen, deep rugae, and sharp angle, also lead to incomplete CE
examination. Recently, some groups have shown that magnetic maneuverable capsules could improve the visualization of gastric mucosa.\textsuperscript{16} However, the system is not yet complete and should be developed further for clinical practice.

In 2004, The PillCam\textsuperscript{®} ESO (Given Imaging, Yoqneam, Israel), capable of studying esophageal diseases, was developed and approved by the FDA. It has two lenses at both ends and takes 18 images per second over approximately 30 min to maximize visualization. Although using conventional upper GI endoscopy is the gold standard, CE has been used to study patients with gastro esophageal reflux disease for the screening of Barrett's esophagus.\textsuperscript{17,18} In various studies, the sensitivity and specificity of CE for the diagnosis of Barrett's esophagus ranged between 67\% and 100\% and between 80\% and 95\%, respectively. In two studies, the concordance of the capsule findings with those of conventional upper GI endoscopy for assessing the presence of varices was 97\% and 84\%.\textsuperscript{19,20}

**Improvement of detectability during small bowel investigation**

1) \textit{In vitro} chromoendoscopy
The Fujinon intelligent chromo endoscopy (FICE) system is a new virtual chromoendoscopy technique that processes reflected photons to reconstruct virtual images with a choice of different wavelengths using computerized spectral estimation technology. The addition of FICE technology to small bowel CE may improve diagnostic yield. However, there is some controversy in regard to its effectiveness. In a study by Gupta et al., FICE assisted small bowel CE analysis was no better than white light for the diagnosis and characterization of significant lesions in the evaluation of OGIB. Matsumura et al. found that although there was no improvement in diagnostic yield, FICE detected a significantly higher number of small bowel lesions per examination than conventional imaging (2.5 ± 2.1 and 1.8 ± 1.7, respectively). Krystallis et al. compared FICE and white light in a total of 167 images. FICE was ineffective in improving endoscopic images except in blue mode. Blue filter provided image improvement in 83% of images when compared to white light. Imagawa et al. suggested the usefulness of FICE for visualizing small bowel lesions, such as angioectasis, erosions, ulcerations, and various tumors, in a retrospective study. However, in a prospective study, FICE
improved the detectability of only angioectasis.\textsuperscript{24}

Efficient microcancer detection in the small intestine can be realized by infrared fluorescence endoscopy (IRFE). IR fluorescence levels emitted by fluorophore indocyanine green (ICG) of different concentrations are able to discriminate low concentrations of ICG in early cancer in the small intestine.\textsuperscript{25}

2) Three-dimensional reconstruction

In recent years, research has been carried out to produce a three-dimensional (3D) reconstruction of the GI tract. 3D imaging in CE is not currently feasible due to hardware limitations (i.e., packaging and size constraints, power consumption). As an alternative method, a software-based approach (Shape-from-Shading) that enables 3D reconstruction from monocular two-dimensional (2D) images has become available.\textsuperscript{26} Koulaouzidis \textit{et al.} determined Enhanced visualization for 56% of vascular and <10% of protruding structures ($P = 0.007$ and 0.008, respectively).\textsuperscript{27} Rondonotti \textit{et al.} showed that the adjunction of 3D reconstructions to the standard 2D counterparts does not enhance the performance of expert
small bowel CE readers ($P = 0.245$), although it significantly improves the performance of novices in differentiating masses from bulging ($P = 0.045$). 28

**Limitations of Current CE**

CE has many advantages, but there are also several drawbacks (Table 2). Fortunately, many promising solutions have been proposed to resolve these problems (Table 3).

**Incomplete small-bowel examination**

1) *Air insufflation*

During transition along the GI tract, CE is limited by air inflation to expose all mucosa. Several groups have developed a novel device to achieve untethered controlled carbon dioxide (CO$_2$) insufflation suitable for CE. This device shows the feasibility of controlled inflation to facilitate visualization. 29,30

2) *Retention or delayed transition*
The most common causes of incomplete examinations are delayed gastric emptying and prolonged small bowel transit. These result in the exhaustion of the battery before the capsule reaches the cecum. Administration of water or intravenous metoclopramide could be used in an effort to overcome this problem, but it is necessary to use this method carefully for patients with dismotility since rapid transit time may diminish diagnostic yield. Use of the external real-time viewer to check the progress of the capsule significantly improved the completion rate (86% vs 66%, $P = 0.002$) and the rate of positive findings (80% vs 67%, $P = 0.04$) compared with the non-viewer group.31

3) Low battery life

CE battery life is usually 8 to 15 hours. Size reduction and battery life extension have become important challenges as novel CE and accessory tools have been developed in order to improve diagnostic yield and perform therapeutic work. Frame rate modulation decreases the frame rate outside of the targeted area and saves battery power, yielding a longer operating time. Consequently, completion
rate and diagnostic yield has increased significantly.\textsuperscript{32} Consumption also can be reduced by video compression and transmission technology such as compressed sensing theory and Impulse Radio-Ultra-Wideband.\textsuperscript{33} One group has proposed primary magnetic coils in a power-generating device outside of the body to send power to a capsule within the body in order to save space in the body.\textsuperscript{34}

**Localization**

Detection of the exact location of CE in the GI tract is very important because an observer could judge retention from the amount of time to the location, and knowledge of the location and orientation of the capsule also enables the physician to localize and assess the lesion, bleeding, or pathologies, and to recommend next steps for further treatment. Localization can be ascertained by using a capsule emitting a magnetic field or electromagnetic waves. Each method has a disadvantage. With the use of a magnetic field, interference may affect the estimation of an exact location. Electromagnetic waves could be attenuated by the human body, resulting in a loss of precision. Olympus Medical Systems
Corporation (Tokyo, Japan) has developed new software using 3D triangulation.\textsuperscript{35} In a study on this method, the average total spatial error by attenuation was 13.26 cm\textsuperscript{3}. Recently, one group proposed a conceptual CE design for localization, the Capsule-odometer, which in theory exhibits more accurate lesion localization. The capsule has two protruding wheels which can adapt to the diameter of the intestinal lumen and calculate the distance from the onset of the capsule investigation for the determination of an accurate location.\textsuperscript{36}

**Therapeutic or biopsy capability**

For reliable targeted tissue sampling or therapeutic function, CE must have delicate movement to the targeted lesion and for stabilization. However, continued peristalsis, liquid flow, and convoluted passage interrupt this performance in the GI tract.

1) **Controlled locomotion and positioning of CE**

Currently, the movement of the capsule is absolutely dependent on gravitational
and peristaltic force. So, many methods have been proposed for self or external ordinary positioning or propulsion (Fig. 1). Although there are differences among capsule models, they are classified into three types: magnetic force, motion of leg or paddle, and propeller. Magnetic enabled PillCam (Given, yoqneam, Israel) and Magnetic upper GI Olympus capsules (Olympus, Tokyo, Japan) have been devised for this purpose. Magnetic enabled PillCam was based on the Niobe® magnetic navigation system (Stereotaxis, St Louis, MO, USA). The core of this system consists of focused-field permanent magnets, made of a neodymium–iron–boron (Nd–Fe–B) compound. These large magnets are mounted on automatically operated arms in order to be easily arranged and oriented on either side. In an in vivo experiment, the capsules showed an accuracy of 1° and a localization error of 1 mm. In another study, the camera could be rotated in steps of 1.8°. Full 360° sight was possible in the stomach, but only 45° sight was possible in the colon. In 52 humans, a feasibility study of a magnetically-guided capsule from Olympus demonstrated that visualization of the antrum, body, fundus, and cardia were in 98%, 96%, 73% and 75%, respectively, and the feasibility of gastric
Endoscopic devices with flexible legs for ambulation have also been proposed. Legged locomotion mimicking inchworm motion has several advantages: better adaptability to different geometries of the GI tract, higher velocity, and simplified adhesion by friction between the device and the tissue. A new prototype with 8-legs has been devised. The two leg sets (each leg set consists of 4 legs) open independently in opposite directions, and rear legs are useful for propulsion, while frontal legs are useful for stopping. In *in vitro* tests, the 8-leg capsule showed a speed of 6 cm/min and capabilities of backward and vertical locomotion. A paddling-based locomotion mechanism enhanced CE using a paddling stroke. It provided fast locomotion speed and long travel distances. In one study, the mean velocity was 37.5 cm/min in the extracted porcine colon and 17cm/min in the colon of a living pig. Another study reported that CE with feedback controlled paddling had higher locomotion speed, showing an increase of 58% compared with the previous control method based on a given timer.
value. CE with an integrated propeller has been developed, and recently, novel CE with four propellers allows for a reliable 3D locomotion if the capsule has a neutral buoyancy. The number of blades per propeller usually varies from one to five, though three-blade propellers are commonly used. However, this type was useful only for situations in which a large amount of liquid was present. Therefore, liquid intake is required for filling the GI cavity.

For better locomotion and steering, some groups have suggested a hybrid of the magnetics system and self-propelled CE, as well as of the magnetics system and legged locomotion. However, these methods require further development with regard to the need for bulky and complex equipment for generating the magnetic field, and accuracy and stabilization levels that remain relatively low.

2) Further procedure beyond detecting abnormal lesion

One of the major limitations of CE is its inability to go beyond visualization. So, various types of CE that can exhibit mucosal tagging, biopsies or therapeutic interventions (clipping, hemostasis), or a drug delivery system are in development.
A tagging module can mark the precise location of a target lesion for future surgical or wired endoscopic therapy.\textsuperscript{47} One prototype microbiopsy module consists of a trigger with paraffin block, a rotating tissue-cutting razor with torsion spring, and a controller. It is constructed to operate sequentially so that the tissue sampling, sealing, and fixing are performed in one operation.\textsuperscript{48} Another form using a microactuator has been designed to perform microbiopsy. A microspike was incorporated into CE to obtain biopsy specimens. Experimental tests demonstrated that the developed microactuator with microspike successfully extracted tissue samples from a pig’s small intestines.\textsuperscript{49} One study reported that a magnetically-maneuvered capsule with a nitinol clip-releasing mechanism successfully clipped an iatrogenic bleeding lesion in a pig model.\textsuperscript{50} Two new capsules, Intellisite (Innovative devices; NC, United States) and Enterion (Phaeton Research; United Kingdom) have been developed for the collection of absorption data in the GI tract and can be used in the future for drug delivery.\textsuperscript{51} Non-video capsules that can deliver drugs with a pH-activated or temperature-activated release mechanism have also been evaluated. Wood \textit{et al.} have reported that a
CE prototype using pH, temperature and pressure sensing, and a pin for anchoring with a holding mechanism demonstrates a feasibility for targeted drug delivery.\textsuperscript{52}

The Nano-based CE with Molecular imaging and Optic biopsy (NEMO) project is developing a new capsule that combines optical and maneuvering technologies, biosensing, and nanotechnologies to enhance the diagnostic and therapeutic potential of CE. The Versatile Endoscopic Capsule for GI Tumor recognition and therapy (VECTOR) project is in the process of developing a mini robot for the screening and surveillance of GI cancer and magnetic and legged motion, drug delivery, and tissue sampling.\textsuperscript{4,53} A prototype coagulation capsule, which employs an exothermic chemical reaction to generate heat using the interaction of calcium oxide and water, has been tested.\textsuperscript{54} This may be potentially useful for hemostasis by thermal coagulation. However, improvement in capsule maneuvering capabilities is necessary before these capsules can be further developed.

**Delayed time of interpretation**
The interpretation of CE data is very time-consuming given that more than 50,000 images must be reviewed. For this reason, the Blood Indicator® (Given Imaging Inc, Duluth, Ga), multiviewing using simultaneous display images, and the QuickView® (Given Imaging, Yoqneam, Israel) program were added to CE for the reduction of interpretation time over the last few years. Quick View software selects the most significant images of entire frames by analyzing color and patterns and presents the selected images, and Olympus has a similar software function (express mode). In one study, Quick View reduced the interpretation time in CE by 75% compared with conventional viewing. While this saves time, these programs lead to lesion miss rates of 8% by physicians and nurses.\textsuperscript{55} Investigational image processing software reduces average image numbers generated by CE from 50,000 to 5,000 by selectively excluding mucosa with normal appearances, thereby decreasing the time needed for interpretation of images from 5 hours to 1 hour.\textsuperscript{56}

Epitomized summarization has been also proposed for efficient visualization. An
epitomized frame is generated for each short video segment, possibly reducing
the number of frames to be examined by the CE reader to less than one-tenth of
the original frames. Techniques that reduce the number of images examined in
CE save time, but are associated with considerable diagnostic miss rates.
Therefore, image processing software based on more highly accurate auto
detecting technology is needed in the future.

**Conclusion**

CE has evolved very rapidly to become an important tool for mucosal
visualization of the gut. Small-bowel CE is recommended as the first-line of
investigation in patients with OGIB and appears sufficiently accurate as an
alternative tool in other small bowel diseases such as CD, small tumor, celiac
disease, unexplained abdominal pain, and/or diarrhea. For complete and perfect
small bowel investigation, several limitations must be solved technically.
Fortunately, many methods have been proposed and are in development, such as enhanced image modality, controlled air insufflation, decreased battery consumption, and several therapeutic and biopsy tools (Fig. 2). With technological developments, advanced CE could become the standard endoscopy for many GI diseases in the future.

**Conflicts of Interest**

The authors have no financial conflicts of interest
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Figure legends

Fig. 1. New capsule endoscopy proposed for self or external ordinary positioning or propulsion. (A) A capsule using magnetic force. (B) A capsule with legs for mucosal ambulation. (C) A capsule using a paddling stroke. (D) A capsule with four propellers. Permissions for all pictures were obtained [(A) from open access, Lucarini et al. Int J Adv Robot Syst 2015;12:25; (B) and (C) from Elsevier Ltd. Quirini et al. Gastrointest Endosc 2008;67:1153-1158 and Kim et al. Gastrointest Endosc 2010;72:381-387, respectively, (D) from Taylor & Francis Online. Tortora et al. Minim Invasive Ther Allied Technol 2009;18:280-290.]

Fig. 2. Schematic illustration about future imaginary capsule endoscopy based upon current researches. This illustration was made by the present author, Won Gun Kwack.

Abbreviation: FICE, Fujinon Intelligent Color Enhancement; IRFE, infrared fluorescence endoscopy; 3D, three-dimensional; DSP, digital signal processing
<table>
<thead>
<tr>
<th></th>
<th>PillCam SB3</th>
<th>PillCam ESO2</th>
<th>PillCam Colon2</th>
<th>EndoCapsule</th>
<th>MiroCam</th>
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<th>Capsocam</th>
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<td>6-8 hr</td>
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Abbreviation: CMOS, Complementary metal oxide silicon; CCD, Charge-coupled device; RF, Radiofrequency; EFP, Electric field propagation; USB, Universal serial bus; NA, not applicable; FDA, Food and Drug Administration; LED, Light-emitting diode; FICE, Fujinon Intelligent Color Enhancement.
<table>
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