



Capsule endoscopy: The road ahead

Ana-Maria Singeap, Carol Stanciu, Anca Trifan

Ana-Maria Singeap, Anca Trifan, Gastroenterology and Hepatology Institute, “Gr. T. Popa” University of Medicine and Pharmacy, “St. Spiridon” Emergency Hospital, 700111 Iasi, Romania

Carol Stanciu, Gastroenterology and Hepatology Institute, “St. Spiridon” Emergency Hospital, 700111 Iasi, Romania

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Correspondence to: Carol Stanciu, MD, FRCP, Professor, Gastroenterology and Hepatology Institute, “St. Spiridon” Emergency Hospital, Independentei 1, 700111 Iasi, Romania. stanciucarol@yahoo.com
Telephone: +40-732-402860
Fax: +40-232-246611

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Abstract

Since its introduction into clinical practice 15 years ago, capsule endoscopy (CE) has become the first-line investigation procedure in some small bowel pathologies, and more recently, dedicated esophageal and colon CE have expanded the fields of application to include the upper and lower gastrointestinal disorders. During this time, CE has become increasingly popular among gastroenterologists, with more than 2 million capsule examinations performed worldwide, and nearly 3000 PubMed-listed studies on its different aspects published. This huge interest in CE may be explained by its non-invasive nature, patient comfort, safety, and access to anatomical regions unattainable *via* conventional endoscopy. However, CE has several limitations which impede its wider clinical applications, including the lack of therapeutic capabilities, inability to obtain biopsies and control its locomotion. 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 deliver targeted drugs directly to specific sites are under development. Overlooking current limitations, especially as some of them have already been successfully surmounted, and based on the tremendous progress in technology, it is expected that, by the end of next 15 years, CE able to perform both diagnostic and therapeutic procedures will remain the major form of digestive endoscopy. This review summarizes the literature that prognosticates about the future developments of CE.

Key words: Capsule endoscopy; Biopsy; Drug delivery systems; Capsule endoscope locomotion; Capsule localization

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Core tip: Since its introduction into clinical practice 15 years ago, small bowel capsule endoscopy (CE) has

revolutionized direct endoscopic imaging of the gut. During this time, CE has gained tremendous popularity among gastroenterologists, and a vast research pertaining to its different aspects has been published. Dedicated esophageal and colon CE have expanded the field of application to upper and lower gastrointestinal disorders. However, besides its recognized advantages, CE also has several limitations such as the lack of therapeutic capabilities, the inability to obtain biopsies and control its locomotion. Active research is in progress to overcome the current limitations, while the latest advances in CE technology enable us to look forward to a next generation CE capable of performing both diagnostic and therapeutic procedures. This review summarizes the literature that prognosticates about the future of CE.

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INTRODUCTION

Fifteen years have passed since small bowel capsule endoscopy (CE) was launched^[1], revolutionizing noninvasive direct visualization of the small bowel, considered until then the “black box” of the gastrointestinal (GI) tract. During this time, CE has been used extensively, with more than 2 million capsules swallowed worldwide^[2] and nearly 3000 PubMed-listed studies pertaining to its different aspects published^[3]. Technical progress led to the introduction of some updated versions (2nd and 3rd generations) of CE for the small bowel and the manufacturing of the CE designed for esophagus and colon. In just a few years, CE has evolved very rapidly, becoming an invaluable tool for examination of almost the entire GI tract, and its diagnostic achievements have by far exceeded early expectations. Still, CE is not an ideal tool, as it has several limitations, including the lack of therapeutic capabilities, inability to control its locomotion and thus, to revisualize critical areas and obtain biopsies. The objective of many research groups worldwide is to overcome these limitations and develop a new generation of CE with higher diagnostic yield and therapeutic capabilities. Of course, it is very difficult to predict the future in medicine, and would be for CE. However, based on the extraordinary developments seen in just 15 years since its emergence, and the tremendous progresses of modern technology, it can be anticipated that, by the end of next 15 years, the new generation of CE able to perform both diagnostic and therapeutic procedures in a noninvasive, painless, and elegant manner will remain the major form of digestive

endoscopy, covering the entire GI tract from mouth to anus, as its inventors have dreamed. This review summarizes available literature that prognosticates about the future developments in CE.

BRIEF LOOK BACK AND THE CURRENT STATUS

The first model of CE called M2A (meaning “mouth to anus”) was launched in 2000 by Given Diagnostic Imaging, Yoqneam, Israel^[4], and the merits for its design belonged, in a similar degree, to the Israeli engineer Gavriel Iddan and the British gastroenterologist Paul Swain^[1,4]. A year later, M2A was approved for clinical use in Europe and the United States, and after the advent of esophageal CE, M2A changed its name into PillCam SB (meaning “small bowel”). Several other companies have also developed small bowel endoscopic capsules: EndoCapsule (Olympus Corp., Tokyo, Japan)^[5], OMOM capsule (Jinshan Science and Technology Company, Chongqing, China)^[6], Mirocam (IntroMedic Co., Seoul, South Korea)^[7], and CapsoCam SV1 (CapsoVision, Saratoga, CA, United States)^[8], all having many similar characteristics and diagnostic performances to PillCam SB, but differing with regard to image acquisition rate, field of view, battery life, dimensions, and technology for transmission of images. Given Imaging has also developed PillCam ESO and PillCam COLON for the evaluation of esophageal and colonic diseases, respectively^[9,10]. Improvements in technology have led to the development of 2nd and 3rd generation CEs which overcome some limitations of the 1st generation CE by increasing the view angle, extending the effective battery life, and including several others systems which offer superior image quality, tissue coverage, and interpretation efficiency^[11-13].

In only 15 years since the introduction of CE into clinical practice, its achievements have exceeded what was previously thought as possible. Thus, CE has revolutionized the evaluation of obscure gastrointestinal bleeding (OGIB) and unexplained iron deficiency anemia (IDA)^[13-15], becoming the first-line modality in the diagnosis of both. The role of CE in OGIB/IDA is supported mainly by its diagnostic performance, which is superior to other diagnostic modalities (push enteroscopy, intraoperative enteroscopy, small bowel barium radiography, CT-enterography, CT-angiography, MR-enterography), as well as by its positive impact on patient management and outcome^[14,16-21]. When CE was compared to double-balloon enteroscopy, a similar diagnostic accuracy for OGIB was reported^[22]. CE examination leads to therapeutic endoscopic or surgical interventions and, consequently, to bleeding being stopped and outcomes improved^[23,24].

Thanks to its capacity to directly visualize mucosa of the entire small bowel, CE has undoubtedly contributed substantially to progress in diagnosis, therapeutic

decision, and outcome in Crohn's disease (CD). 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, enteroclysis, push-enteroscopy, ileo-colonoscopy, and CT-enterography^[25-27]. CE is superior to MR-enterography in identifying small bowel mucosal lesions, while MR-enterography is superior to CE in diagnosing mural and extra-enteric lesions^[28]. In patients with known CD, an important treatment goal is mucosal healing which can be reliably assessed by CE^[29-31].

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; therefore, it may be a useful noninvasive diagnostic tool in patients with suspected or established celiac disease^[32,33]. However, CE is actually an alternative to endoscopy with biopsy only in patients clinically suspected of celiac disease unable or unwilling to undergo conventional endoscopy.

CE has become the procedure of choice for detecting small bowel polyps in hereditary polyposis syndromes like Peutz-Jegher syndrome and familial adenomatous polyposis^[34,35]. In addition, widespread use of CE has more than doubled the diagnosis rate in small bowel tumors^[36-41].

Esophageal capsule endoscopy, although at 3rd generation, has limited role in clinical practice and it is still under evaluation^[42]. Colon capsule is also under evaluation, and is currently recommended in case of incomplete colonoscopy and in patients unwilling or unable to perform colonoscopy^[43,44].

Limitations of current capsule endoscopy

Although CE has seen tremendous advances in a short period of time since its introduction in clinical practice, it has several limitations. Thus, CE remains a purely visual technique with no ability to obtain biopsy specimens or perform therapeutic maneuvers. The most obvious drawback is the operator's inability to control its locomotion through GI tract. The capsules presently on the market are unable to localize or mark the location of detected lesions. Visualization may be impaired by the presence of food materials or bubbles and, in contrast with conventional endoscopy, CE cannot perform flushing, suctioning, or air insufflation to obtain better images. All capsules for clinical use are powered by limited-life batteries which may be depleted before the examination is complete. The rate of missed lesions is still high for those located in the duodenum and proximal jejunum, where the transit is more rapid than in the distal segment of the small bowel. Reading time for interpretation is another shortcoming of CE, as it takes more than 1 h to read a full 8-h examination. Finally, the costs are still high.

FUTURE EXPECTATIONS IN CAPSULE ENDOSCOPY

The future of CE is difficult to predict ("Prediction is very difficult, especially about the future" - Niels Bohr, Nobel Prize winner, 1885-1962), although novel technologies may lead to developments which today seem almost unimaginable. Improvements achieved in just 15 years since the introduction of CE in clinical practice go beyond what was previously thought as possible. GI endoscopy has had a similar history: initially limited only to viewing the esophagus/gastric lumen, it has improved progressively over a few decades, developing into an accurate diagnostic and therapeutic technique. CE also started as a tool for visualizing only the "black box" (small bowel) which has long been the final frontier of the GI endoscopy, and it evolved very rapidly to become a non-invasive endoscopic tool in the examination of almost the entire GI tract.

Most likely, over the next 15 years, CE will slowly replace diagnostic standard endoscopy and take over most therapeutic procedures with no pain and no need for sedation. We know that several research groups throughout the world are working to develop new multifunctional capsules with diagnostic and therapeutic capabilities extending far beyond our imagination. What we do not yet know is whether the future CE will be "universal", containing both diagnostic and therapeutic modules (an "ideal" CE)^[45] or "specific", for diagnosis or therapy^[11].

Maneuverable capsules

In contrast to standard endoscopy, the movement of the current capsule endoscopes through the GI tract is passive, ensured by peristaltic motion, the operator being unable to control the endoscopic navigation (right and left, back and forth) in a given area. It is of the utmost importance to solving the CE's maneuvering limitation so as to increase its diagnostic yield and allow targeted biopsy and even drug delivery. Besides enhancing diagnostic yield, a capsule whose locomotion can be controlled will reduce the amount of energy consumed, examination time, as well as the rate of capsule retention. Even more, an active control of the endoscopic capsule would allow us to examine the stomach, and finally, the entire GI tract^[46].

Systems that can be used to propel or steer the capsule are under development. There are two locomotion systems: an internal one, integrated on-board the capsule, and an external one (outside the capsule), most frequently based on magnetic fields. Some proposed internal systems consist of legged-like mechanisms (propellers/paddles) that can be deployed by the capsule to resist peristaltic movements, while the external locomotion systems usually use a capsule

covered with a magnetic shield which can interact with external magnetic fields created by an electromagnet or permanent magnet. Electromagnets require bulkier equipment by comparison to permanent magnets^[47-50].

The legged-like device approach consists of providing the capsule with propellers/paddles which will start functioning on demand during capsule navigation through various segments of the GI tract. A four-legged capsule, two in the front and two in the rear, has been proposed, an eight-legged capsule was also suggested to be feasible, and even a twelve-legged locomotion capsule was designed to improve propulsion and reduce tissue injury^[47,51-53]. However, several technical drawbacks such as insufficient space available within the capsule and high power consumption should be overcome. In addition, a failure in the synchronization of the legs may cause damage to the GI tissue.

Magnetic control appears to be the most attractive and promising approach. It is based on the principle that a large external magnetic field created by a permanent magnet or electromagnet near the patient interacts with a small internal magnet component integrated into the capsule to provide an active control of the endoscopic capsule^[48]. Given Imaging has incorporated a magnet inside one of the domes of a standard PillCam colon capsule, which can be manipulated with an external handheld magnet moved on the patient's abdomen^[54,55]. Using such magnetically maneuverable capsule, one study reported > 75% of gastric mucosa visualized and no adverse events^[55]. Siemens (Siemens Medical, Erlangen, Germany) and Olympus (Olympus America, Center Valley, PA, United States) have recently tested the prototype of a magnetically guided capsule endoscope that uses a three-dimensional, external magnetic field which interacts with the magnet inside the capsule, allowing the capsule to be moved forward or backward^[56,57]. Rey *et al.*^[58,59] made the first blinded comparative clinical trial on gastric examination in humans, comparing a magnetically guided capsule endoscope with a conventional high-definition gastroscope, and found a similar diagnostic yield for both methods. Rahman *et al.*^[60], using the Intromedic MiroCam-Navi system, reported a high degree of visualization, control, and maneuverability with this system. A robotic magnetic navigation system used in cardiology (Niobe, Stereotaxis Inc., St. Louis, MO, United States) has been suggested for CE but has been tested only in plastic phantoms^[61]. Several other versions of endoscopic capsules magnetically propelled by a robotic arm have been proposed^[62].

Two research projects funded by the European Union aim to develop a self-propelling minirobot pill. One is *VECTOR* (Versatile Endoscopic Capsule for gastrointestinal Tumor Recognition and Therapy) for early diagnosis and treatment of GI cancer^[63], and the other is *NEMO* (Nano-based capsule Endoscopy

with Molecular imaging and Optical biopsy) which designed to combine optical, nano, and maneuvering technologies in a new capsule with different diagnostic and therapeutic capabilities^[64].

A videocapsule endoscope called Compact Photonic Explorer (CPE), measuring 5 mm in size, has been developed at the City University and City College of New York. It can be manipulated externally by remote controlled radio signal and may be used in the future for diagnostic and therapeutic means^[65]. Recently, a mathematical model of an electrically propelled capsule endoscopy has been proposed, using double pairs of electrodes, and which is able to move the capsule forward and backward at a speed of 2.91 mm/s and 2.23 mm/s, respectively^[66].

To summarize, the development of propelled/steerable capsules will represent a major advance of capsule technology, which will open a myriad of possibilities, including a more detailed evaluation of affected areas and prelevation of biopsy specimens, endoscopic targeted therapy, examination of the stomach, thus the entire GI tract becoming virtually as accessible as the skin^[67]!

Biopsy

Once a maneuverable capsule is developed, the next step is to obtain a tissue sample. Several biopsy devices have been developed and used on animal models. A spring-loaded device similar to the Crosby capsule, guided by real-time imaging and RF-controlled remote manipulation, and a capsule using Micro-Electro-Mechanical-Systems (MEMS) technology have been successfully tested^[68]. Both *NEMO* and *VECTOR* projects develop capsules designed for virtual biopsies and drug delivery^[63,64]. The rotational Micro Biopsy Capsule Device (Seoul, South Korea) which contains a triggering part with paraffin block and a rotational tissue-cutting razor (biopsy part) has been tested^[69]. A tethered capsule endomicroscopy of the esophagus, which uses optical frequency domain imaging technology and enables 3D imaging of esophagus in microscopic detail, has also been developed^[70]. This capsule endomicroscope is able to differentiate Barrett's esophagus from normal esophageal mucosa. Other magnetic capsules using untethered microgrippers to grab tissue samples or magnetic torsion spring mechanism have been designed^[71,72].

Optical enhancing techniques could lead to optical "biopsy", which refers to a method of obtaining a morphological diagnosis without biopsy specimens, and prototype endoscopic capsules with such technology have been developed, including the wireless spectroscopic compact photonic explorer for diagnostic optical imaging to detect microscopic malignancy^[65]. One research group integrated near-infrared fluorescent probe in CE to enhance optical diagnosis of neoplasia, which proved able to distinguish adenomatous tissue in

experimental colitis in mice^[73].

Power source

At present, available endoscopic capsules use two coin-shaped, silver-oxide batteries that can generate 20 mW of energy, far too little to accomplish the multiple diagnostic and therapeutic tasks of the future capsule, most of them requiring power consumption. In addition, batteries occupy most of the space in an endoscopic capsule. Therefore, increased power supply and reduced size of batteries, to leave enough space to incorporate diagnostic/therapeutic components into the capsule, are essential for further developments in CE technology. A solution may be lithium ion microbattery technology which could provide a power density up to 2000-times higher than other microbatteries^[74]. Recently, Rathore *et al.*^[75] using Ultrascale FinFET 16 nm technology for manufacturing endoscopic capsules (instead of 18 μm used for conventional endoscopic capsules) have reported an increased battery life, reduced power consumption with up to 50%, and a reduced size of the capsule by 12% compared to traditional capsules. An alternative method to reduce battery consumption is to use low complexity video compression technology that saves radiofrequency (RF) transmitting power^[76].

External rechargeable batteries (from an extracorporeal power supply) using RF, microwave or electric induction, and even "battery free" CE using wireless power transmission (WPT) technology are created. An excellent overview of the development of emergency WPT technique for application in CE has been recently published by Basar *et al.*^[77]. WPT system employs a transmitting coil positioned outside the human body and a receiving coil installed within the CE, thereby eliminating the need for an internal battery^[78]. Thus, the RF System Lab (Nagano, Japan) was the first to use WPT technology in their Sayaka and Norika capsules^[79], and several publications centered on WPT technology for the endoscopic capsule^[77,80]. Jia *et al.*^[80], using WPT technology, have reported on its ability to transmit 500 mW of electricity, which is significantly higher than the amount generated by current batteries used for the endoscopic capsules available on the market.

An alternative solution will be the development of three-dimensional microbattery technology for geometrical energy and power density of battery^[81,82], and many research groups are working in the field, still progressing in several laboratories.

Targeted drug delivery

Unfortunately, none of the current capsules is able to perform therapy. New capsule devices are under development in order to enable drug delivery in specific diseased areas of the GI tract. A number of clinical situations can benefit from targeted drug delivery such as the use of hemostatic spray to an

active bleeding lesion or localized application of steroid/immunomodulation for CD. One capsule prototype is able to deliver an injection of 1 mL of targeted medication while using a holding mechanism^[83]. To achieve this, an accurate control mechanism of capsule positioning and a drug release mechanism should be incorporated into a capsule endoscope. As future capsules will most likely be smaller, space limitation within the capsule is an important impediment when incorporating such mechanisms^[84].

Philips company (Philips Research, Eindhoven, The Netherlands) has launched an "intelligent" pill (iPill) measuring 11 mm \times 26 mm and incorporating a microprocessor, battery, pH sensor, temperature sensor, radiofrequency transceiver, fluid pump, and a drug reservoir^[85]. Tracking of the iPill in the GI tract is based on information regarding pH change and gut transit time. Once tracked in the aimed area, the iPill will open and deliver the drug under the control of the microprocessor. The iPill is under trial in CD and colorectal cancer^[68,85,86].

Several other wireless capsules, such as the Gastro-target telemetric capsule (Gastrotarget, Tonawanda, NY, United States), High-frequency capsule (Battelle-Institute V, Frankfurt, Germany), Telemetric capsule (INSERM UG1, Strasbourg, Cedex, France), Enterion capsule (Pheaton Research, Nottingham, United Kingdom), and the IntelliSite capsule (Innovative Devices, Raleigh, NC, United States), have been developed for targeted drug delivery in specific areas of the GI tract^[68]. However, capsule tracking is inaccurate due to lack of an anchoring mechanism and thus, drug release cannot be fully controlled. Two therapeutic capsule endoscopes have recently been proposed for bioadhesive patch release and targeted drug delivery, respectively, both capsules being controlled by an external permanent magnetic source^[83,87]. A soft magnetically actuated capsule, capable of multimodal gradual or sudden drug release, has also been developed^[88].

Even with a new CE designed for targeted drug delivery, several other problems should be taken into consideration. Thus, in some diseases of GI tract such as CD, drug delivery is required on a daily basis, for several days or even weeks. To overcome this problem, a pre-programmed non-viewing capsule for targeted drug delivery has been proposed^[89].

Luminal insufflation

CE visualization, especially of the colonic mucosa, is limited as the capsule is unable to provide insufflation in order to distend the intestine and expose all mucosal surfaces for examination. This shortcoming is a potential cause for CE's high false-negative diagnostic rate in the colon. Experiments and insufflation capsule prototypes show the feasibility of generating large volumes of gas from a small volume of liquid hydrogen peroxide, weak acids and bases in a capsule to provide wireless insufflation for enhancing visualization^[90,91].

Recently, a method of controlled colonic insufflation (CO₂) via an untethered capsule *in vivo* has been reported^[67].

Shorter reading time

Future CE should allow shorter reading time for interpretation of images acquired by capsule, and this may be achieved by development of more efficient software^[92]. A computer-aided lesion detection will significantly reduce reading time.

Home procedure

In the near future, CE (small bowel capsule endoscopy and especially colon capsule endoscopy) will become a home procedure that could be done on weekends, thus avoiding work absence^[93,94].

Accurate location of detected lesion

A tagging module consisting of a micro tag, compressed spring and thermal ignitor can be integrated within future CEs; when activated by an external signal, the micro tag is impaled into the mucosa to mark the precise location of a lesion for the following endoscopic therapy^[95]. Location of lesion and estimation of its size is possible by using Rapid 6 system of software developed by Given Imaging^[96].

Automated capsule localization

Automated capsule localization with a software using color image analysis to discriminate between different segments of GI tract (esophagus, stomach, small bowel, colon) identified CE passage across the pylorus in 93% of cases^[97-99]. The next step will be development of the software program to increase the frame rate while CE is traversing the duodenum, in order to improve identification of the ampulla of Vater and detect more lesions in the periampullary region^[100,101] which is poorly visualized by CE, CT- and MR-enterography^[102,103].

Entire GI tract visualization

An ideal CE would be able to visualize the entire GI tract, from mouth to anus, during a single procedure. Currently available capsules cannot be used for this purpose because of the significant physiological differences of the various segments of the GI tract, and therefore, only specific esophageal, small bowel, and colon capsules are available. However, the colon capsule (PillCam COLON 2, Given Imaging) developed for evaluation of the colon, can also be used to visualize almost the entire GI tract. This capsule is provided with two cameras able to record video images from both ends, with an adaptive frame acquisition rate (between 4 and 35 frames per second). Thus, it may visualize the esophagus, examine the stomach and duodenum with an external maneuvering system to control capsule locomotion, then the small intestine and, finally, the colon. Preliminary studies have already

concluded that GI tract evaluation with PillCam COLON 2 is feasible, especially for small bowel, although other segments (esophagus, stomach) need technical improvements to obtain a good visualization^[46]. In the near future, a pan-endoscopy with CE may be a reality^[29,104,105].

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 implied by conventional endoscopy. During a relatively short period of time (15 years), CE has proven its high diagnostic yield in multiple pathologies of the GI tract such as obscure GI bleeding, CD, celiac disease, as well as in small and large bowel tumors. Nevertheless, the endoscopic capsules currently available are diagnostic tools only, and still have several limitations (passive locomotion, inability to perform biopsy or deliver therapy, etc). Modern technology continues to make tremendous progress in CE, helping it overcome the above mentioned limitations. Although it is difficult to make predictions about the future, we believe that in the next 15 years, our dreams of an efficient diagnostic and therapeutic CE for the diverse pathologies of the entire GI tract will become a reality.

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