Advances in Capsule Endoscopy

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Abstract: Wireless video capsule endoscopy (VCE) is a minimally invasive technology that has revolutionized the approach to small intestinal disease investigation and management. Designed primarily to provide diagnostic imaging of the small intestine, VCE is used predominantly for obscure gastrointestinal bleeding and suspected Crohn's disease; however, numerous other indications have been established, including the assessment of celiac disease, investigation of small bowel tumors, and surveillance of hereditary polyposis syndromes. Since the introduction of small bowel VCE in 2000, more than 1600 articles have been published describing the evolution of this technology. The main adverse outcome is capsule retention, which can potentially be avoided by careful patient selection or by using a patency capsule. Despite the numerous advances in the past 15 years, limitations such as incomplete VCE studies, missed lesions, and time-consuming reporting remain. The inability to control capsule movement for the application of targeted therapy or the acquisition of tissue for histologic analysis remains among the greatest challenges in the further development of capsule technology. This article outlines the recent technological and clinical advances in VCE and the future directions of research in this field.

Keywords
Video capsule endoscopy, small bowel imaging, obscure gastrointestinal bleeding

The introduction of video capsule endoscopy (VCE) into clinical practice in 2000 provided a novel, minimally invasive method to evaluate the small bowel.[1] Since then, a large number of studies have been published describing the use of VCE in a variety of gastrointestinal (GI) conditions (eg, celiac disease, small bowel tumors, hereditary polyposis syndromes). The number of indications has increased as the technology has evolved over the past 15 years. VCE was initially developed for the examination of the small bowel; subsequently, multiple small bowel capsule devices have emerged from different companies, including PillCam SB (Given Imaging; Figure), EndoCapsule (Olympus), MiroCam (IntroMedic), CapsoCam SV1 (CapsoVision), and OMOM pill (Jinshan Science & Technology). There are now capsule systems

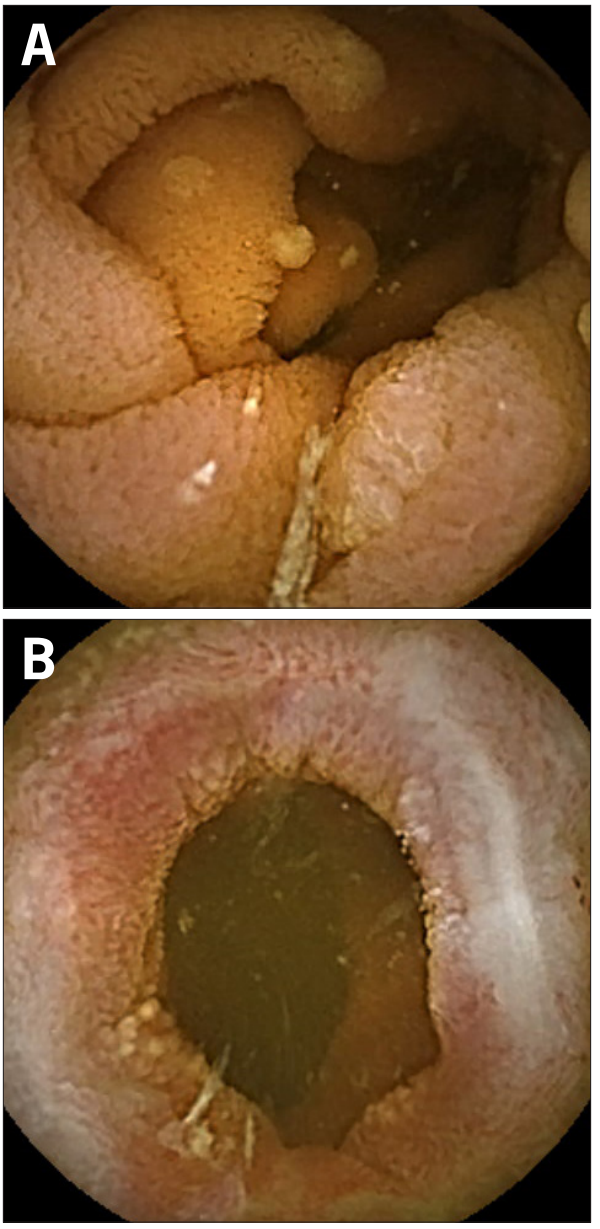

Figure. A diminutive polyp (**A**) and circumferential ulceration (**B**) seen on capsule endoscopy.

adapted for the evaluation of the esophagus (PillCam ESO, Given Imaging) and the colon (PillCam COLON, Given Imaging), with some penetration into clinical practice. A second-generation patency capsule (Agile Patency Capsule, Given Imaging) has also been developed for patients with potentially stenotic lesions; if passage is obstructed, the capsule will dissolve within 40 to 80 hours of ingestion.[2] For the minority of patients who are unable to swallow the capsule or have known gastroparesis or anatomic abnormalities, a capsule loading device (AdvanCE, US Endoscopy) is available. This device is loaded through the working channel of the endoscope, and the capsule is placed in a cup at the tip of the endoscope. The endoscope and loading device are then advanced into the duodenum, where the capsule can be released. A wireless motility capsule (SmartPill, Given Imaging) that utilizes pH, temperature, and pressure measurements to evaluate patients for regional and generalized GI motility disorders has also been developed and is approved for use in many countries. This article will focus on the recent advances, current limitations, and future expectations in VCE technology and its use in clinical practice.

Technological Advances in Video Capsule Endoscopy Software

The VCE system has 3 main components: the capsule, which contains a camera; the data recorder, which is attached to sensors on the outside of the patient; and a computer with software for downloading and analyzing data from the recorder. Accurate interpretation of a VCE study is time consuming and requires concentrated, undivided attention, as abnormalities may be present on only a few frames.[3] On average, it takes approximately 1 hour to visualize all of the images (usually more than 50,000).[4,5] An effort has been made by manufacturers to develop software that reduces the time required to analyze the results of VCE while also minimizing the possibility of missing lesions.

Suspected Blood Indicator and QuickView

The first software designed to improve the interpretation of a VCE study was the Suspected Blood Indicator (Given Imaging), a system that identifies frames containing several red pixels, which can theoretically detect bleeding lesions and lead to a more focused examination. However, the accuracy of this tool is suboptimal at present, as it is sometimes oversensitive and may miss lesions that are not actively bleeding; thus, this software should be used only as a supportive tool.[6-11]

Next came QuickView (Given Imaging), a software tool that samples frames at a rate determined by the reader and selects images based on their pattern and color in order to create a short video. Although the reading time is significantly reduced and lesion detection rates are reasonable, the miss rate has been shown to be as high as 12%; therefore, this tool is not recommended for use at this time without complete capsule evaluation.[12-14]

An express mode function in the EndoCapsule has had similar results, and the OMOM pill has a comparable picture elimination mode with promising results from a clinical and reading time point of view.[15,16]

Virtual Chromoendoscopy

Flexible spectral imaging color enhancement (FICE, Fujinon) has been added to the Given Imaging software and

uses a spectral estimation technology, narrowing the bandwidth of white light that permits an automatic reconstruction of the endoscopic images into virtual images with different wavelengths of red, green, and blue.[17] Data available thus far on the use of virtual chromoendoscopy in small bowel VCE are limited, with conflicting reports regarding its value in clinical practice.[18-22] Most studies support its use to improve the evaluation of the mucosal patterns and borders of different lesions, but whether this leads to an increased diagnostic yield or accuracy is not clear.[21,23]

Three-Dimensional Reconstruction Software

Reports have found that 3-dimensional reconstruction can enhance the current reading software in capsule endoscopy by improving lesion demarcation and highlighting the textural features of ulcers, angioectasias, and polyps.[24,25] Software algorithms (shape-from-shading) have been developed to reconstruct 3-dimensional images from 2-dimensional images obtained with VCE.[26,27] In one small study, the use of a 3-dimensional reconstruction of a standard 2-dimensional video reading platform was shown to significantly increase the performance of novice VCE readers in distinguishing masses from bulging, but no improvement was seen in the performance of expert VCE readers.[28] In the near future, it is possible that capsule endoscopes will be equipped with stereoscopic cameras that will enable 3-dimensional VCE. Space limitations, low depth resolution of stereoscopic cameras, and power consumption issues are currently the main obstacles in the development of this technique.[29] Additionally, 3-dimensional reconstructions do not necessarily offer increased or improved resolution over more traditional 2-dimensional images, at least in other areas such as radiology.

Technological Advances in Video Capsule Endoscopy Hardware

There have been numerous technological developments in VCE hardware since its introduction into clinical practice. Improvements in lens quality and design, in addition to the introduction of adaptive illumination, have led to enhanced image quality and a wider angle of view. Power management strategies have increased VCE study duration and quality. Real-time images can be displayed on the data recorder screen while an examination is being performed, which can enable earlier termination of the procedure once the capsule is seen in the colon. Presently, the capsule moves through the GI tract by peristalsis, which can be unpredictable and can lead to incomplete examinations and missed lesions. Recently, there has been a drive to develop new capsule devices that can be actively manipulated in situ, which could potentially enable careful inspection of an area of interest, tissue acquisition, and targeted drug delivery.

Remote Manipulation

The first report of successfully controlling the movement of a capsule was achieved by using an external handheld magnet along with a modified PillCam COLON capsule that had one of its cameras replaced with neodymium boron iron cylindrical magnets. In this report, the capsule could be manipulated within the stomach and esophagus relatively easily.[30] More recently, a small blinded nonrandomized study compared gastric visualization using joystick-controlled, magnetically guided capsule endoscopy vs conventional gastroscopy. Similar diagnostic yields were achieved with both methods, but fewer missed findings were seen with magnetically guided capsule endoscopy.[31] One of the major difficulties with using external magnets is that the magnetic force exerted on the capsule varies inversely to the fourth power of the distance between the external magnet and the capsule. Therefore, this method is less effective when the capsule is in a distant position from the external magnet or if the patient is obese. Self-propelled capsules have also been evaluated and may allow movement to a region of pathologic interest with stabilization of the position for improved diagnostic and potential therapeutic capabilities.[24] Prototype capsules with propellers, paddles, and legs have been used in vitro and in vivo with limited success in moving through the GI tract.[32-34] Robotic control for magnetic steering has been shown to be more precise and reliable than manual operation.[35] However, there remains a large gap between the battery power currently available and the power required for the next generation of capsules.[36]

Tissue Acquisition

With the development of real-time viewing and remote manipulation, the possibility of capsule devices that can obtain biopsies and deliver targeted drug therapy becomes feasible. Several biopsy mechanisms have been described, including a rotational biopsy device that has been used to sample rabbit intestinal epithelial tissue, a spring-driven microdevice with barbed spikes, and a modified Crosby capsule biopsy. However, each of these mechanisms lack the ability to navigate, precisely target, or extract multiple samples.[37-39] Another prototype has been designed to overcome some of these problems by utilizing a magnetically actuated, soft capsule endoscope combined with a large number of microgrippers. In a study, multiple tissue biopsies of the stomach were successfully obtained in an ex vivo porcine model.[40] The NEMO (Nano-Based Capsule Endoscopy With Molecular Imaging and Optical Biopsy) and VECTOR (Versatile Endoscopic Capsule for Gastrointestinal Tumor Recognition and Therapy) projects aim to develop an advanced capsule device that has both diagnostic and therapeutic capabilities, particularly for use in early GI cancer screening.[41,42]

Drug Delivery and Therapeutics

The development of a drug delivery system for VCE is currently an exciting field of research due to its potential application in numerous clinical scenarios, particularly in the management of bleeding lesions and local therapy for Crohn's disease. One study has described targeted administration of 1 mL of medication using a needle within a capsule device while resisting peristalsis with a holding mechanism.[43] In another study, a prototype capsule equipped with magnets and a nitinol clip was steered with an external magnet to the site of an iatrogenic bleed in a porcine model, and the clip was successfully deployed to achieve hemostasis.[44] A coagulation capsule has also been described that produces heat by way of an exothermic reaction caused by the interaction between calcium oxide and water.[45]

The GI tract represents a challenging environment for the development of an effective drug delivery system for capsule endoscopy.[46] Factors such as capsule size constraints and GI transit time variability need to be considered. For a drug delivery system with a passive release mechanism, particularly one dependent on fluid availability, regions of low fluid such as the colon can be problematic.[47] Therefore, an anchoring system to actively control the transit of the capsule is desirable to manage factors such as timing, release rate, number of doses, and targeted location.

Colon Capsule

Colon capsule endoscopy (CCE) was first introduced in 2006 as another method to image the colon with the advantage of being a minimally invasive, pain-free procedure requiring no sedation.[48] However, the need for extensive bowel preparation to achieve adequate mucosal visualization and polyp detection rates, the high cost, the inability to obtain biopsies or insufflate the colon, and the well-established role of colonoscopy as the gold standard of colonic investigation have meant that CCE has not found a niche as readily as small bowel VCE. Currently, the main indication for CCE is colorectal cancer surveillance in average-risk patients refusing conventional colonoscopy or patients with a previously incomplete colonoscopy.[49] The sensitivity of the first-generation PillCam COLON capsule endoscopy device for colorectal cancer detection was suboptimal when compared with conventional colonoscopy.[50-55] A second-generation PillCam COLON capsule endoscopy device was released in 2009 and features 2 cameras, each with a 172-degree angle of view, which enables a near 360-degree view of the colon. The images are captured at a rate of 4 to 35 images per second, compared with a fixed frame rate of 4 images per second for the first-generation device.[56] The adaptive frame rate of the second-generation device enables conservation of battery power when the capsule is stationary and the capture of up to 35 pictures per second when the capsule is mobile. These developments, in addition to a more standardized bowel preparation regimen, have led to more promising results for second-generation CCE with improvements in both the polyp and colorectal cancer detection rates.[57,58] Insufflation techniques, which may improve mucosal visualization, have been described. These prototype capsules use a magnetic controlled drug delivery system with 2 compartments containing reactants that create a simple chemical reaction when activated to form carbon dioxide.[59,60]

Mucosal healing has become one of the most significant endpoints in inflammatory bowel disease research studies and clinical practice. The utility of CCE in this setting has been evaluated in a few studies with mixed results.[56] One small study found that the sensitivity and specificity of CCE for detecting active mucosal inflammation in ulcerative colitis was 89% and 75%, respectively, when compared with colonoscopy,[61] whereas another study concluded that CCE was significantly inferior and could not be recommended for the assessment of inflammation in ulcerative colitis.[62] CCE appears to be a safe, well-tolerated, noninvasive method for visualizing the colon, but at present has a somewhat limited role. Discussion of its use as an alternative investigation can be considered, when available, for colorectal cancer screening in patients who refuse colonoscopy or when colonoscopy is incomplete or not possible.

Summary

Multiple trials have proven the efficacy of VCE as a diagnostic test, and it has become a first-line investigative tool for obscure GI bleeding. Despite having good safety profiles and patient tolerability, VCE beyond the small bowel is currently not equivalent to conventional gastroscopy or colonoscopy in terms of cost-effectiveness and diagnostic yield; therefore, it is not routinely used clinically. As discussed in this article, technology in the field of VCE is advancing rapidly since its introduction 15 years ago. Numerous capsule devices are available, developed by different companies, each with various specifications and features. VCE software and hardware innovations have already led to significant improvements in image quality, study completion rates, lesion recognition, and reductions in missed lesions. At present, the inability to control the movement of the capsule to selectively acquire tissue or deliver therapy remains the major barrier to VCE bridging the gap between being a diagnostic tool and becoming a therapeutic device. Research is ongoing in these areas, but it will likely take time for these technological advances to transform the management of patient care.

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