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Review

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Capsule endoscopy: clinical insights, challenges, and evolving perspectives in the 21st century

Akiyoshi Tsuboi[1], **Shiro Oka**[1], **Shinji Tanaka**[2]

[1]Department of Gastroenterology, Hiroshima University Hospital, Hiroshima 734-8551, Japan.
[2]Department of Gastroenterology, JA Onomichi General Hospital, Onomichi 722-0018, Japan.

Correspondence to: Dr. Akiyoshi Tsuboi, Department of Gastroenterology, Hiroshima University Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan. E-mail: atsuboi@hiroshima-u.ac.jp

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Abstract

Capsule endoscopy (CE) is widely employed in clinical practice owing to its minimally invasive nature and high diagnostic accuracy. It is the primary modality for evaluating suspected diseases of the small-bowel, as recommended by guidelines from various countries. Advancements in CE technology have introduced various models for evaluating not only the small-bowel but also the colon, esophagus, stomach, and the entire gastrointestinal tract. Moreover, colon CE enables early detection of colorectal polyps and cancers, as well as surveillance of inflammatory bowel disease. Furthermore, innovative developments, such as magnetically controlled CE, offer enhanced maneuverability, particularly in the stomach. Recent reports highlight the growing use of artificial intelligence in CE, with promising potential for reducing physician burden, and clinical implementation is anticipated. Furthermore, novel CE technologies are expected to enable the diagnosis of gastrointestinal diseases through a less invasive approach in the near future.

Key questions/aims: Herewith we provide a comprehensive review of the current status and clinical applications of CE while addressing the challenges that remain in its implementation in practice and highlighting the key areas for future research and development.

Keywords: Capsule endoscopy, small-bowel, magnetically controlled capsule endoscope, artificial intelligence

INTRODUCTION

Small-bowel capsule endoscopy (SBCE) was initially introduced in 2000 by Iddan *et al.*[1]. In recent years, it has gained widespread use owing to its minimally invasive nature and diagnostic yield. The primary indication for SBCE is small-bowel bleeding, and it has been endorsed as the first-line modality for this condition in the guidelines of reputable organizations, such as the American College of Gastroenterology (ACG)[2], European Society of Gastrointestinal Endoscopy (ESGE)[3], and Japanese Gastroenterological Endoscopy Society[4]. In Japan, obscure gastrointestinal bleeding (OGIB) is defined as bleeding from an unknown source, even after esophagogastroduodenoscopy (EGD), colonoscopy (CS), and, when appropriate, second-look endoscopy. However, with the widespread use of SBCE, the definition of OGIB has now changed to refer to bleeding from unknown sources even after enteroscopy. This distinction helps differentiate it from small-bowel bleeding or mid-gut bleeding in Europe and the United States[2,3]. Apart from diagnosing small-bowel bleeding, SBCE is also utilized to evaluate small-bowel tumors, such as Peutz-Jeghers syndrome, familial adenomatous polyposis, and inflammatory small-bowel diseases such as celiac disease and Crohn's disease[3,4]. The first SBCE device, known as M2A capsule, was developed in 2000 and later renamed PillCam™[5]. In the mid-2000s, other capsules such as Endocapsule, MiroCam, and OMOM capsules were introduced. In 2013, CapsoCam was developed, enabling 360-degree panoramic shots with four small cameras[6]. These devices have continued to improve, and various types of SBCEs are currently available.

Furthermore, capsule endoscopy (CE) is useful not only for observation of the small-bowel but also as an alternative to CS, known as colon capsule endoscopy (CCE). The first-generation CCE was developed in 2006[7]. With the development of second-generation devices and improvements in preparation, CCE is now used for applications ranging from colorectal cancer surveillance to monitoring disease activity in inflammatory bowel disease.

CE has been developed not only for the colorectal region but also for the upper digestive tract, including the esophagus and stomach. Esophageal capsule endoscopy (ECE) was first approved by the Food and Drug Administration (FDA) in the U.S. in 2004[8]. However, due to the wide anatomical lumen and blind spots in the stomach, magnetically controllable CEs have been developed.

With recent advancements in endoscopic technology, the development of artificial intelligence (AI) has been developed to assist in the reading of CE. Additionally, completely novel concepts such as ultrasound CE and sampling CE have been introduced in recent years.

The purpose of this paper is to provide an updated overview of the role of CE, including SBCE, CCE, and magnetically controlled capsule endoscopy (MCCE). A literature search was conducted using PubMed with the keyword "Capsule endoscopy". This review aims to provide a comprehensive overview of the current status and future prospects of CE.

CURRENT POSITIONING OF SBCE

In cases where small-bowel bleeding is suspected as the primary indication for SBCE, studies have reported a diagnostic yield ranging from 55% to 62%[9-11].

In prospective studies, SBCE has been consistently shown to demonstrate significantly superior diagnostic performance compared to alternative modalities such as computed tomography (CT) enterography[12] and CT angiography[13]. SBCE exhibits a detection rate for bleeding sources comparable to device-assisted enteroscopy (DAE)[10].

While SBCE is minimally invasive and highly accurate in detecting small-bowel lesions, it does not allow for pathological diagnosis through tissue sampling. In contrast, DAE is invasive but enables both pathological diagnosis via tissue sampling and endoscopic treatments, such as endoscopic hemostasis, endoscopic balloon dilation, and endoscopic resection. SBCE is recommended as the first-line modality for suspected small-bowel bleeding in the guidelines of the U.S, Europe, and Japan[2-4]. Further examination with DAE is recommended depending on the findings of SBCE. In patients with overt small-bowel bleeding, early examinations of SBCE following a bleeding episode yield higher diagnostic outcomes[14]. Uchida *et al.* conducted a meta-analysis and found that performing SBCE within two days of bleeding leads to elevated diagnostic and therapeutic yields (55.9% and 65.2%, respectively)[14]. Consequently, ESGE guidelines[3] recommend SBCE examination within 48 h of suspected small-bowel bleeding.

In terms of total enteroscopy rates, double-balloon endoscopy has been reported at 44%[15], single-balloon enteroscopy at 17%[16], and motorized spiral enteroscopy at 61%-70%[17,18]. On the other hand, the total enteroscopy rate of SBCE is reported to be 85%[19]. Thus, SBCE has a higher exploration rate of the entire small-bowel compared to other enteroscopy methods.

The total enteroscopy rate of DAE via the anterograde route was reported to be 1.6% for double-balloon enteroscopy[15] and 16.7% for motorized spiral enteroscopy[17]. Thus, physicians typically select the insertion route for DAE - antegrade or retrograde - based on physical findings and cross-sectional imaging in clinical practice. The usefulness of SBCE for selecting the DAE route has been reported[20-26]. In a recent meta-analysis, the localization of small-bowel lesions by SBCE was found to be useful; however, 3D localization technologies and tracking systems need to be developed to further improve accuracy[27].

The indications, contraindications, preparation, completeness, and safety profiles of SBCE

The indications and contraindications for SBCE vary among devices. Generally, the indication for SBCE is diagnosis and surveillance of small-bowel disease, including suspected small-bowel bleeding, chronic diarrhea, chronic abdominal pain, the detection and surveillance of small-bowel lesions associated Crohn's disease, celiac disease, graft versus host disease, collagen disease, and vasculitis. It is also indicated for detecting small-bowel lesions in polyposis syndromes, such as familial adenomatous polyposis and Peutz-Jeghers syndrome. An absolute contraindication, regardless of the model, is known or suspected gastrointestinal obstructions, strictures, or fistulas. SBCE devices that require radiofrequency for image transfer are contraindicated for patients with implanted cardiac devices, such as pacemakers or implantable cardioverter defibrillators (ICD). Although the manufacturer advises against using SBCE for patients with implanted cardiac devices, a meta-analysis showed that the examination in these patients was safe, and SBCE did not affect the devices[28]. Artifacts in SBCE images occurred in 5.8% of patients with left ventricular assist devices (LVAD)[28]. Although these artifacts did not affect the diagnostic yield, the number of patients with LVADs and ICDs is small. Thus, SBCE is not recommended for these patients. In fact, while the guidelines do not restrict the use of CE in patients with implanted pacemakers, they do not mention patients with LVADs or ICDs[29,30]. Patients with dysphagia are considered to have relative contraindications due to the risk of aspiration. However, endoscopic placement is effective for these patients to avoid aspiration, and the effectiveness of AdvanCE delivery device (US Endoscopy Inc., Mentor, OH, USA), a dedicated device that can be used for PillCam, has recently been reported[31]. SBCE during pregnancy is not recommended due to limited data.

The preparation for SBCE remains controversial. Initially, preparation was not recommended when SBCE was first developed. However, as SBCE moves through the gastrointestinal tract and captures images automatically, the visibility of the mucosa can be reduced by residual material and air bubbles.

Consequently, SBCE can directly affect the quality of the examination due to decreased visibility of the mucosa. Meta-analyses have concluded that consuming 2 L of polyethylene glycol (PEG) solution before capsule ingestion enhances the visibility of the small-bowel mucosa[32-36]. Several meta-analyses have also reported that the use of antifoam agents, such as simethicone, improves the visibility of the mucosa[37,38]. Although current guidelines often recommend bowel preparation before SBCE[29,39], a standardized protocol has not yet been established. In a recent meta-analysis, Marmo *et al.* revealed that the earlier the ingestion of SBCE capsule following the administration of laxatives, the better the visualization of the mucosa[40]. Furthermore, there have been reports in recent years indicating that laxatives taken immediately prior to examination lead to improved mucosal visibility[41,42]. Conversely, Lamba *et al.* reported that the administration of laxatives before SBCE does not improve the diagnostic rate or visibility and leads to decreased patient acceptability. Thus, further studies are needed to establish a pretreatment regimen[43].

For the completeness of the SBCE, a recent meta-analysis reported an observability rate of 87.6% for the entire small-bowel mucosa[11]. Westerhof *et al.* identified a history of small-bowel surgery, hospitalization, moderate or poor bowel cleansing, and a gastric transit time of > 45 min as independent risk factors for incomplete SBCE procedures[44]. Diabetes mellitus has also been reported to be related to incomplete SBCE[45]. Factors contributing to prolonged gastric transit time of SBCE include hospitalization, diabetes mellitus, cerebrovascular disease, older age, female sex, the use of psychotropic medications, and glucagon-like peptide-1 receptor agonists[46-48]. The usefulness of image confirmation with a real-time viewer for completing the SBCE examination has been reported[49]. Additionally, the endoscopic SBCE delivery method for patients with prolonged gastric transit time is useful for achieving complete SBCE[50].

From a safety perspective, the most common adverse event associated with SBCE is retention. Capsule retention is defined as a capsule remaining in the gastrointestinal tract for more than two weeks[9]. The incidence of SBCE retention has been reported to be 1.2%[9] to 4.6%[51]. Consequently, SBCE can be employed for safe and comprehensive small-bowel observation and is recommended as the preferred modality for enteroscopy according to European, American, and Japanese guidelines[2-4]. However, it is important to note that the retention rate is higher for patients with Crohn's disease. In a recent meta-analysis on capsule retention in patients with Crohn's disease, Pasha *et al.* reported retention rates of 4.63% for cases with established Crohn's disease and 2.32% for those with suspected Crohn's disease[51]. Therefore, evaluating the presence of gastrointestinal strictures in advance, especially with a patency capsule, is recommended for patients with Crohn's disease.

When capsule retention occurs without symptoms, medical treatment is prioritized. With conservative management, 10%-70% of capsules are naturally excreted[52-54]. If excretion does not occur, retrieval using DAE may be required, with oral insertion being an effective approach in such cases[55].

To ensure the quality of SBCE, it is essential to fully understand its indications, contraindications, safety profiles, and preparation regimens. Leighton *et al.* reported quality indicators for SBCE and DAE[56]. It is hoped that implementing these quality indicators in clinical practice will enhance the quality of examinations at each institution.

CURRENT STATUS OF SBCE DEVICES

A variety of SBCE devices are available, as listed in Supplementary Table 1. One notable device is the PillCam™ SB, developed by Given Image[5], which has evolved into its third generation known as PillCam™ SB3, measuring 26.2 mm in length and 11.4 mm in width. The first-generation PillCam™ captures two pictures per second with a 140° field of view. In contrast, the second-generation PillCam™ offers a wider

field of view (156°), a higher-resolution camera, and a longer battery life of approximately 12 h[57,58]. The third-generation SBCE automatically adjusts the imaging frame rate based on the capsule's speed as it passes through the small-bowel. Unlike the fixed two images per second in the second-generation SBCE, the third-generation SBCE can receive up to six images per second, depending on the capsule's speed. Hirata *et al.* reported that the third-generation PillCam™ SB3 with an Adaptive Frame Rate (AFR) showed improved diagnostic performance compared with the second-generation PillCam™ SB2[59]. Figure 1 displays endoscopic images of small-bowel angioectasia captured by each generation of the PillCam™, demonstrating enhanced image quality and visibility of the lesion and surrounding villous structures.

Another innovative CE is the CapsoCam Plus® (CapsoVision, Inc. Saratoga, USA), measuring 31.0 mm in length and 11.0 mm in width, which stands out due to its distinctive features. It features four small cameras that enable a 360-degree panoramic view [Figure 2] and includes flash memory within the capsule body to store all images internally. Since there is no need for image transmission, the CapsoCam Plus® can operate for extended periods, surpassing other SBCE modalities in battery life. The prototype panoramic-view CE was able to identify the Vater papilla, the only landmark in the small-bowel, at a high rate of approximately 70%[6]. Also, it demonstrated high total small-bowel observation rates due to its long-lasting battery[21].

Endocapsules were first reported in 2008[60]. Olympus subsequently released a second-generation SBCE device called the EndoCapsule 10[61], measuring 26.0 mm in length and 11.0 mm in width. This improved version featured better image quality, a larger angle of view, and a longer battery life compared to the first-generation capsule. However, no studies have yet compared the diagnostic yields of these SBCE techniques.

The MiroCam® (Introduction Medic, Seoul, Korea) functions differently, transmitting captured gastrointestinal images via human body communication to sensor pads attached to the patient's body. This unique image-transmission system enhances the battery life. The safety and efficacy of the MiroCam® were initially reported in a clinical trial in 2009[62]. The latest MiroCam® models, MC1600 and MC2000, measure 24.5 and 30.1 mm in length, respectively, and 11.0 mm in width. MC1600 offers a constant frame rate of 6 frames per second (FPS), while MC2000 boasts two cameras on each side of the capsule with a constant frame rate of 3 FPS. MC2000 is expected to improve diagnostic performance due to its wide viewing angle of 340°[63].

Finally, the OMOM capsules, developed by Jinshan Science and Technology (Chongqing, Yubei, China), have also resulted in significant advancements. The latest model, the OMOM HD capsule, measures 25.4 mm in length and 11.0 mm in width. With an AFR similar to that of the PillCam™ SB3, the OMOM HD capsule's frame rate can be adjusted to 10 FPS using an advanced sensor.

Comparison of diagnostic capability among SBCEs

The current section provides an overview of multiple SBCE modalities, including PillCam™, Endocapsule, MiroCam®, CapsoCam, and OMOM. Numerous studies have compared the diagnostic performance of these devices, particularly focusing on their diagnostic yields, reading times, and overall concordance rates in detecting small-bowel lesions and other gastrointestinal abnormalities.

PillCam™ *vs.* Endocapsule

Although the Endocapsule detected a slightly higher number of small-bowel lesions in two previous reports[64,65] (17 *vs.* 24 lesions in one study and 26 *vs.* 29 lesions in another), these differences were not statistically significant. Both devices exhibit similar diagnostic capabilities, suggesting that either modality can be effectively used in clinical practice for detecting small-bowel lesions.

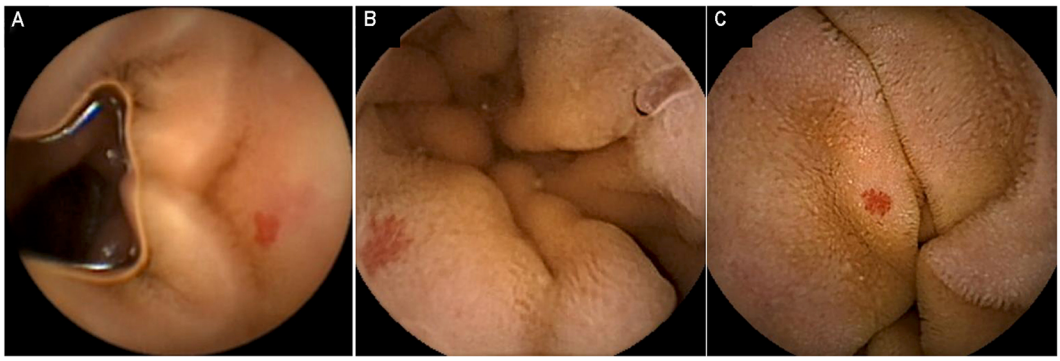

Figure 1. Images for small-bowel angioectasia captured by each generation of PillCam™. (A): The first-generation PillCam™; (B): The second-generation PillCam™; (C): The third-generation PillCam™. With advancements in technology across generations of PillCam™, image quality has significantly improved. Not only has the visibility of angioectasia increased, but the surrounding villous structures are also now clearly visible.X.

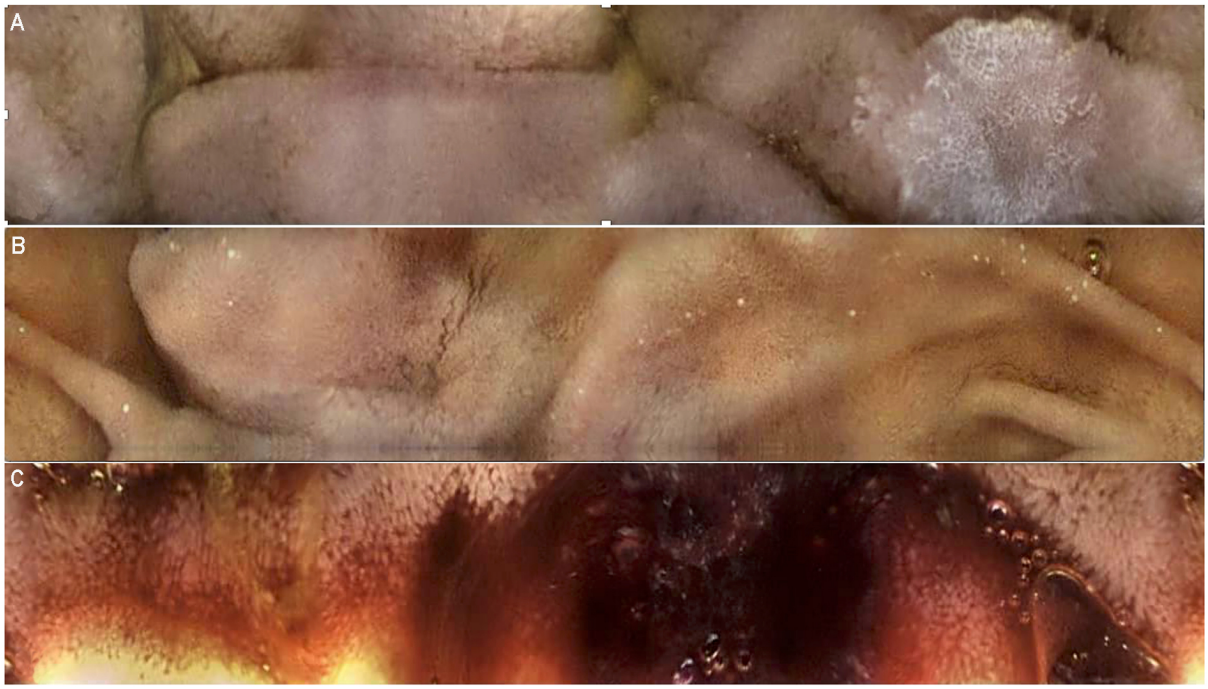

Figure 2. Images of CapsoCam Plus. (A): An endoscopic image of an adenomatous lesion of familial adenomatous polyposis; (B): An endoscopic image of a gastrointestinal stromal tumor of the jejunum; (C): An endoscopic image of an active bleeding from the small bowel.

PillCam™ *vs.* MiroCam®

Comparisons between PillCam™ and MiroCam® demonstrate similar overall diagnostic yields[66-68], although MiroCam® exhibited a slightly higher diagnostic rate in one study (95.2% *vs.* 78.6% for PillCam SB2)[68]. However, MiroCam® was associated with significantly longer reading times[68] (40.3 minutes *vs.* 25.4 minutes for PillCam™ SB2), which could impact its clinical utility, particularly in time-sensitive cases.

PillCam™ *vs.* CapsoCam

When comparing PillCam™ with CapsoCam, several studies have demonstrated similar diagnostic yields between the two devices[69-72]. However, reading times were consistently longer for CapsoCam[69,70,72]. Thus,

while both devices are effective for lesion detection, PillCam™ may offer advantages in terms of efficiency.

PillCam™ *vs.* OMOM

A single study comparing PillCam™ SB3 with OMOM2 found no significant difference in the diagnostic rates for detecting bleeding sources (88.6% for PillCam™ *vs.* 77.3% for OMOM2)[73]. These findings suggest that both devices can be effectively used for detecting small-bowel bleeding.

MiroCam® *vs.* Endocapsule

In a study comparing MiroCam® and Endocapsule, no statistically significant difference was observed in the diagnostic yields of the two devices (50% for MiroCam® *vs.* 48% for Endocapsule)[74]. These results suggest that both modalities offer comparable diagnostic capabilities.

Meta-analysis of each modality

A recent meta-analysis of these studies concluded that there are no significant differences in the diagnostic performance of the various SBCE modalities[75]. However, it is important to note that many of these studies involved older SBCE models, particularly as newer generations of SBCE devices, such as PillCam™ SB3, continue to evolve. In fact, some studies have indicated that PillCam™SB3 exhibits a higher diagnostic ability for small-bowel and esophageal lesions than PillCam™ SB2[59,76]. Consequently, future comparative studies of currently available CE devices are anticipated.

CURRENT STATUS OF CCE

First-generation CCE was developed in 2006[7], followed by the second-generation CCE (CCE2) PillCam™ Colon 2 (Medtronic, Minneapolis, MN, USA) in 2009[77]. Measuring 31.5 mm in length and 11.6 mm in diameter, CCE2 employs two cameras and an AFR that automatically adjusts the frame rate from 4 to 35 FPS depending on the capsule's movement speed. Endoscopic images of CCE2 are shown in Figure 3. Although the CS remains the gold standard for colorectal cancer screening, CCE has emerged as a promising alternative due to its minimally invasive nature and high patient acceptability. Meta-analyses have reported that, when compared to CS, CCE-2 exhibits sensitivity and specificity of 87% and 95%, respectively, for polyps larger than 10 mm, and 87% and 88%, respectively, for polyps larger than 6 mm[78-80]. Computed tomography colonography (CTC) is an alternative to CS for colorectal cancer screening. In comparison to CTC, CCE showed a better detection yield, particularly for diminutive colorectal polyps ≥ 6 mm[81,82]. González-Suárez *et al.* reported that the sensitivity and specificity for the neoplastic lesions ≥ 6 mm of CCE were 96.1% and 88.2%, whereas that of CTC was 79.3% and 96.3%, respectively[81]. Cash *et al.* reported that the sensitivity and specificity of CCE for polyps ≥ 6 mm were 79.2% and 96.3%, while that of CTC was 26.8% and 98.9%, respectively[82].

Many studies have reported the usefulness of CCE not only in diagnosing colorectal tumors but also in evaluating colonic mucosal inflammation in ulcerative colitis[83-95]. In previous reports using CCE-1 for ulcerative colitis, the diagnostic accuracy of CCE-1 was found to be insufficient. Consequently, these reports concluded that CCE-1 is considered an inadequate alternative to CS[83-85].

The first report on CCE-2 for ulcerative colitis was published in 2013 by Hosoe *et al.*[86] Hosoe *et al.* reported a high correlation (P = 0.797) between CCE-2 and CS findings[86]. The sensitivity, specificity, positive predictive value, and negative predictive value of CCE-2 for assessing disease activity were reported to be 95%-96%, 100%, 100%, and 85%-92%, respectively, in previous reports[87,95]. Shi *et al.* also reported that the measuring of Mayo endoscopic score (MES) and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) derived from CCE-2 images correlated well with CS findings[92]. However, there is concern that the

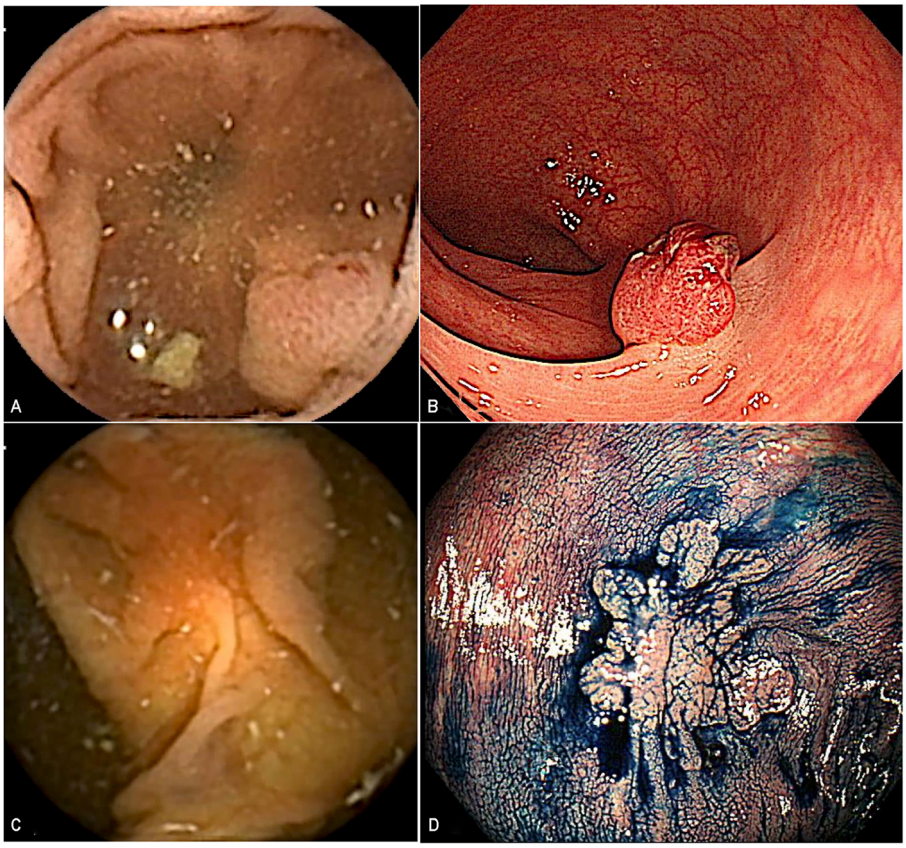

Figure 3. Images of colon tumors by colon capsule endoscopy. (A): The endoscopic image of a 0-Is lesion located in the sigmoid colon using colon capsule endoscopy (PillCam™ CCE2); (B): A conventional colonoscopy image of the same lesion detected by CCE2; (C): An endoscopic image of 0-IIa lesion located in transverse colon by CCE2; D: A conventional chromoendoscopy image of the same lesion detected by CCE2. CCE: Colon capsule endoscopy.

MES and UCEIS are based on CS images and are not specific scoring systems for CCE. To address this, Hosoe *et al.* developed Capsule Scoring of Ulcerative Colitis (CSUS), a scoring system based on CCE-2, which they reported correlates with fecal calprotectin, the Lichtiger index, and UCEIS[91]. Matsubayashi *et al.* reported a higher relapse rate in patients with ulcerative colitis in remission who had a CSUC score higher than 1 compared to those with a CSUC score of 0[93]. Based on the above, CCE-2 can serve as an alternative examination to CS for disease assessment in ulcerative colitis. However, there are no reports on the usefulness of CCE-2 regarding neoplasia associated with ulcerative colitis, and further case accumulation will be needed.

Although CCE is a minimally invasive modality with a high diagnostic yield, it has several limitations. The first problem is the detection rate of flat and diminutive lesions. It has been reported that lateral spreading tumors and sessile serrated lesions in the right-sided colon are more likely to yield false negatives[96,97]. While the diagnostic accuracy for polyps larger than 6 mm is adequate, there are insufficient studies on the detection of smaller lesions. The second issue is the lengthy reading time; physicians need to examine images captured by the two cameras separately, requiring 50 to 60 min of reading time[98,99]. Thus, compared with the CS, CCE can be time-consuming and burdensome for physicians. Furthermore, CCE is expensive compared to other modalities, such as CS and CTC, costing approximately 100,000 yen in Japan. Another challenge is the extensive bowel preparation required for CCE, involving laxatives for both bowel cleansing and promoting capsule excretion. To ensure the detection of colorectal polyps, CCE necessitates the use of 2

to 4 L of liquid laxatives such as PEG solution. In a recent meta-analysis, PEG laxative and sodium phosphate (NaP) boosters were the most commonly used regimens. However, this regimen was not associated with a higher complete examination rate or bowel cleansing level[100]. Another meta-analysis reported that routine prokinetics specifications and split-dose PEG were associated with complete examinations[101]. Ohmiya *et al.* reported the effectiveness of castor oil as a booster of CCE[102]. They reported that the capsule excretion rate of castor oil was significantly higher than that without castor oil (97% and 81%, respectively; $P < 0.0001$). In a recent meta-analysis, the castor oil has the potential for improvement of excretion rates in CCE[103]. To address these issues, the Japanese Association for Capsule Endoscopy (JACE) recommends castor oil as the standard preparation regimen for CCE. Mizukami *et al.* reported that encapsulation of castor oil increased patient tolerability while maintaining the capsule excretion rate[104]. However, patient acceptance is poor because of the unpleasant flavor of castor oil. On the other hand, for patients with ulcerative colitis, the same rigorous preparation required for colorectal tumors is not necessary to observe mucosal inflammation. Okabayashi *et al.* reported that a reduced dose of laxatives is possible[88]. In fact, in JACE, the recommended regimens are separated for patients with ulcerative colitis and colorectal tumors.

We summarized the current issues for SBCE and CCE in Table 1.

CURRENT STATUS OF ECE

ECE was developed as a non-invasive diagnostic tool based on SBCE technology, aimed at visualizing the esophagus without the need for sedation or invasive procedures associated with traditional endoscopy. The first generation of esophageal capsules, such as the PillCam ESO (Given Imaging Ltd., Yoqneam, Israel), was approved in 2004. The second generation of ECE, which has been improved and available since 2007, shares a similar size, shape, and weight with the small-bowel capsule (PillCam™ SB2), measuring 26 mm × 11 mm. It is equipped with cameras on both ends that capture images at 18 FPS, compared to the 2-3 FPS of small-bowel capsules, providing a wider 169° angle of view. The third-generation ECE, PillCam™ ESO3, features an even wider 174° angle of view and a higher recording rate of 35 FPS.

ECE was designed specifically to evaluate esophageal conditions, including gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), and esophageal varices. ECE operates by capturing high-speed images of the esophagus as the capsule travels through the gastrointestinal tract, offering a patient-friendly alternative to standard endoscopic examinations. Currently, ECE is primarily used for screening and monitoring esophageal varices, BE, and detecting other esophageal lesions in patients who are at high risk or unwilling to undergo conventional endoscopy. A meta-analysis conducted by Bhardwaj *et al.* revealed that the pooled sensitivity and specificity for the diagnosis of BE for all studies were 77% and 86%, respectively[105]. According to a recent meta-analysis by McCarty *et al.*, the diagnostic pooled sensitivity and specificity for esophageal varices were 83% and 85%, respectively[106]. In a multicenter prospective ECE study for pediatric patients by Cardey *et al.*, the sensitivity, specificity, and accuracy for esophageal varices using a modified classification were 100 %, 93 %, and 97 %, respectively[107]. ECE is a well-tolerated and safe procedure, making it a viable alternative to EGD in infants suspected of having esophageal varices or in cases where EGD is declined, such as pediatric patients.

Recent improvements, such as the ability to transmit images in real-time, have enabled more immediate interpretation, facilitating quicker clinical decision-making. Despite its advantages, ECE faces challenges, including limited maneuverability compared to conventional endoscopes, the potential for incomplete examinations due to rapid transit times, and the need for further validation in detecting early-stage neoplasms. Additionally, image interpretation requires significant expertise, highlighting the need for

Table 1. Current state of SBCE and CCE

(1) Clinical indications of SBCE and CCE
SBCE
Suspected small-bowel bleeding
Inflammatory conditions (i.e., Crohn's disease, Celiac disease, small-bowel lesions associated with vasculitis or collagen disease)
Diagnosis of small-bowel tumors (including gastrointestinal polyposis syndromes, such as familial adenomatous polyposis and Peutz-Jeghers syndrome)
CCE
Detection of colorectal neoplasm
Evaluation of ulcerative colitis
(2) Current challenges/ limitations to diagnosis
SBCE
Risk of oversight (especially in jejunal lesions)
No consensus of preparation regimen
Burden on the physician
CCE
Need for improved preparation regimens
Burden on the physician
False negative of flat or diminutive lesions
Novel CE modalities
AI-assisted diagnosis reduces the risk of missed diagnoses and alleviates the burden on physicians.
Using a 360° viewing angle may reduce the risk of oversight.
MCCE allows physicians to capture the region of interest
MCCE and ECE help reduce the burden on patients

AI: Artificial intelligence; CE: capsule endoscopy; CCE: colon capsule endoscopy; ECE: esophageal capsule endoscopy; MCCE: magnetically controlled capsule endoscopy; SBCE: small-bowel capsule endoscopy.

standardized training programs to optimize diagnostic performance.

As technology advances, the indications for ECE are likely to expand beyond screening and surveillance to include comprehensive diagnostic evaluations of esophageal motility disorders and more precise assessments of inflammatory conditions, thereby broadening its clinical utility.

Educational program for CE reading

It is important to establish an educational program or e-learning enrollment system for junior physicians and nurses with limited experience. The importance of training in CE reading has been extensively reported in the literature, with numerous studies highlighting the beneficial effects of training programs on the performance of physicians[108-114]. It is widely recognized that completion of a formal and structured CE training program, aligned with the core CE curriculum guidelines, is essential before granting certification of competence in performing CE[109,115,116]. Attending the educational program is important, but enhancing participants' understanding of the content during their participation is equally crucial. Several reports have assessed proficiency levels within educational programs[109,115,116]. Incorporating evidence-based training programs, assessment tools, and certification for junior physicians and nurses is essential to ensure proper selection of indications for CE and to enhance diagnostic yield through improved lesion recognition and interpretation.

CURRENT STATUS OF AI FOR CE

Interpreting SBCE requires approximately 30 min[117], while CCE reading may take 50 to 60 min[98,99]. A technical review by the ESGE recommends up to 10 FPS in single-view mode and up to 20 FPS in double- or multiple-view modes for reading SBCE[39]. The optimum reading speed for CCE is controversial, but in clinical practice, a speed of approximately 10 FPS is considered appropriate [118]. The number of images captured by SBCE exceeds 60,000, and CCE, with its dual cameras, further increases the number. Maintaining focus while reviewing numerous images can be challenging, particularly because CE is a

passive procedure without the added stimuli of instrument manipulation or patient interaction. In addition, because CE automatically captures images that move physiologically, the entire lesion may be difficult to visualize or may only be visible at the edges of the image. These factors may increase the risk of missed lesions during the physicians' reading process. To address this concern, assistive reading technologies have been incorporated into the reading software for each CE model.

For instance, QuickView mode has been included in RAPID™ software since ver. 6.0. It is a function that automatically extracts images with a high probability of abnormal findings using a specific algorithm. Although the use of QuickView mode is expected to reduce the number of images read and shorten the reading time, it is not recommended for primary reading, as many reports indicate that it is not sensitive enough to detect abnormal findings[119-122]. In addition to Quick view mode, RAPID™ software ver. 9.0 introduced the "TOP 100" feature, which automatically selects the 100 images most likely to contain abnormalities. Studies have demonstrated the effectiveness of such assistive features. Arieira *et al.* reported that TOP 100 correctly identified all sites of active bleeding and detected a majority of significant lesions (83.5%), including angioectasia, a frequent source of small-bowel bleeding, with 95% accuracy[123]. Gomes *et al.* evaluated the Express-View mode for MiroCam®, which achieved a diagnostic accuracy of 91%[124]. The per-patient sensitivity was 83.1% for all clinically significant lesions and 56.2% for all lesions. For the OMOM capsules, the images were reviewed using Vue Smart Software (Jinshan Science & Technology Co.). The Vue Smart Software system uses AI-based diagnostic assistance technologies. It deletes up to 90% of the captured images and automatically selects images of suspected abnormal lesions.

Computer-aided diagnosis (CAD) combines AI, computer vision, and pathology image processing to automatically detect abnormalities and assist physicians in providing more accurate diagnoses. Convolutional neural networks, a form of deep learning, are highly beneficial in endoscopy[125-128].

Numerous studies have reported the usefulness of AI in CE. Various studies have reported the automatic detection of lesions, such as erosions, ulcers[129] [The area under the receiver operating characteristic curve Receiver Operating Characteristic - Area Under the Curve (ROC-AUC): 0.958, sensitivity: 88.2%, specificity: 90.9%], angioectasia[130] (ROC-AUC: 0.998, sensitivity: 98.8%, specificity: 98.4%), blood[131] (ROC-AUC: 0.9998, sensitivity: 96.6%, specificity: 99.9%), and various protruded lesions[132] (ROC-AUC: 0.911, sensitivity: 90.7%, specificity: 79.8%). AI assistance has also been shown to impact reading time[133] and has been compared with assistive systems, including RAPID software[134]. Aoki *et al.* reported that the reading time of SBCE after the first screening of AI reading was significantly shorter compared to only physicians reading (expert: 3.1 min *vs.* 12.2 min, trainee: 5.2 min *vs.* 20.7 min)[133]. Aoki *et al.* evaluated the detection capability of their construction AI system compared to Quick View mode equipped with RAPID software[134]. They reported that the detection rate of the AI system was significantly higher than QuickView mode (99% *vs.* 89%, respectively). The reading time of AI systems is astonishingly fast. Reports indicate that the use of AI for reading can significantly reduce the reading time [134-140]. This reduction in reading time is particularly pronounced for trainees, and it also alleviates the psychological stress associated with the reading process[141]. SBCE reading with AI assistance could maintain a diagnostic yield comparable to that of expert physicians and reduce the reading time. In a small-bowel follicular lymphoma assessment, AI has proven useful for disease progression evaluation[142].

Furthermore, the application of AI in CCE has been reported. AI has shown promise in detecting colorectal polyps[143,144] (ROC-AUC: 0.902-0.97, sensitivity: 79.0-90.7%, specificity: 87.0-92.6%), erosions, ulcers[145] (ROC-AUC: 1.00, sensitivity: 96.9%, specificity: 99.9%), and blood[146] (sensitivity: 97.2%, specificity: 99.9%) in the colon. In CCE, the reading time can be lengthy, and AI has been demonstrated to reduce this reading time while maintaining high sensitivity[147].

Despite the potential benefits, several challenges remain in the clinical application of AI for CE: (1) determining the timing of AI support - before, during, or after physician reading through real-time assistance or double-checking; (2) addressing the wide variety of small-bowel lesions; and (3) managing the decrease in the number of images of interest with AI assistance. Currently, the timing of AI assistance for CE remains to be determined. Real-time AI-assistance systems are already available for CS and EGD. Additionally, the small-bowel presents a diverse range of lesions, which are often challenging even for expert physicians. The development of AI systems with high sensitivity may increase the number of images selected for physician review, potentially prolonging the reading time. It is essential to develop an AI system that integrates various small-bowel lesions for prospective validation in the future.

MCCE

Conventional CE is not suitable for observing the stomach, which has a wide lumen, as the capsule is moved by physiological peristalsis and automatically captures images. To address this limitation, MCCE was described by Carpi *et al.* in 2006[148]. In 2010, Rey *et al.* reported the first study utilizing MCCE to observe the human stomach[149]. The MCCE uses magnetic force to control the position of the capsule, offering a less invasive and mentally burdensome alternative to the conventional EGD. A list of currently available MCCE devices is presented in Supplementary Table 2. Recent reports on the MCCE[150-153] demonstrate a diagnostic consistency of 86.8% to 96.2% with conventional EGD, a high complete examination rate of gastric anatomical landmarks ranging from 85% to 97%, and improved tolerability[154]. In addition, MCCE can detect both gastric and small-bowel bleeding. MCCE is a novel modality that significantly differs from conventional CE, directly influencing the quality of examination. To ensure competent performance and interpretation of MCCE findings, medical staff must undergo standardized training at professional institutions and acquire necessary qualifications.

Amid the spread of COVID-19, concerns regarding droplet exposure during conventional EGD have risen. The MCCE offers a convenient alternative, as patients simply swallow the capsule, minimizing the risk of droplet exposure to CE operators. This feature has garnered attention as a valuable option during the COVID-19 pandemic. Remote-controlled MCCE, which completely avoids patient-examiner contact, proves particularly useful in upper gastrointestinal endoscopic practice during these challenging times[155]. Zhu *et al.* developed a remote-control MCCE system and reported comparable completion rates, safety, and diagnostic performance to conventional MCCE[156]. Adequate training is crucial for effective interpretation of MCCE results. In this context, the usefulness of AI using images has been reported[157,158]. The availability of AI for MCCE in the near future could further expand the utilization of this modality.

Novel CE

In recent years, various novel types of CE, such as ultrasound CE and sampling CE, have been developed to enhance the diagnosis and monitoring of gastrointestinal conditions, offering improved features compared to traditional capsule endoscopes.

Endoscopic ultrasonography (EUS), which combines ultrasound and endoscopic technologies, provides high-resolution, real-time imaging of the gastrointestinal wall layers and surrounding extramural structures. However, EUS is an invasive procedure that carries potential risks, including perforation and bleeding. To address these concerns, several groups have proposed the concept of capsule endoscopy using ultrasound (USCE) and have explored its feasibility for subsurface imaging of the gastrointestinal tract[159-164]. However, these reports have primarily focused on laboratory or animal studies. Qiu *et al.* developed a novel USCE for esophageal lesions and reported its use and safety in humans[165]. They concluded that their novel USCE is comfortable for patients, easy to operate, and cost-effective, with the potential for widespread clinical application.

A recent advancement in CE technology is the emergence of the smart capsule, which functions primarily as a passive imaging tool. The smart capsule incorporates advanced technologies with diagnostic and therapeutic functions, expanding its potential for evaluating gastrointestinal disorders.

A smart capsule capable of measuring pH, temperature, pressure, and other biochemical parameters has been developed to assess gastrointestinal tract function. These measurements provide valuable data for diagnosing conditions such as GERD, small intestinal bacterial overgrowth (SIBO), and motility disorders, allowing for a more detailed understanding of the pathophysiological processes occurring within the gastrointestinal tract.

The three smart capsules currently approved by the FDA are SmartPill® (Medtronic, Minneapolis, MN)[166-169], Bravo® (Medtronic, Minneapolis, MN)[170-173], and Vibrant® (Hakochav, Yokneam, Israel)[174,175].

SmartPill® is designed to be ingested by the patient and travels through the gastrointestinal tract, collecting data on pH, temperature, and pressure. This device is used to evaluate gastroparesis, chronic constipation, and whole gut dysmotility. Studies comparing SmartPill® data with gastric scintigraphy have shown a strong correlation, with a sensitivity of 87% and specificity of 92% for detecting delayed gastric emptying in patients with gastroparesis[166]. Research comparing SmartPill® with radiopaque markers (ROM) demonstrated comparable results, with a specificity of 95% for identifying slow colonic transit in constipated patients[168]. The capsule has shown good agreement with other diagnostic methods, with studies reporting correlation coefficients ranging from 0.66 to 0.74 compared to ROM for whole gut transit times[167].

The Bravo pH Monitoring System is a wireless, catheter-free device used for diagnosing GERD. It offers an innovative approach to measuring esophageal pH levels over an extended period, providing more comprehensive data compared to traditional catheter-based pH monitoring methods. Bravo has shown higher patient tolerance and diagnostic yield due to extended monitoring. In a previous report, Sweis *et al.* indicated that increased acid exposure detection rates occur when data is collected over 48 to 96 h compared to the traditional 24-h recording period[173]. Hasak *et al.* reported that prolonged wireless pH monitoring has clinical value, showing that the acid burden from extended studies correlates with the presence and severity of reflux symptoms when off therapy[170]. In addition to its usefulness for pH monitoring, this modality has good patient tolerability. Wenner *et al.* reported that the smart capsule caused significantly less discomfort than catheter-based systems, contributing to improved adherence and fewer test-related activity restrictions[171].

The Vibrant Capsule is a smart capsule designed for the treatment of chronic idiopathic constipation. It represents a novel, non-pharmacological approach that uses mechanical vibrations within the gastrointestinal tract to stimulate colonic motility and promote bowel movements. In a pivotal Phase 3, double-blind, placebo-controlled trial involving 312 patients, the Vibrant Capsule significantly increased the number of complete spontaneous bowel movements (CSBMs) compared to placebo (39.3% *vs.* 22.1%, $P = 0.001$). Improvements were observed as early as the second week of treatment and were sustained throughout the trial period[175].

Smart capsules currently under investigation include the intestinal fluid sampling capsule (Capscan®, Envivo, California, USA)[176,177], the Smart Capsule Bacterial Detection System (Biora Therapeutics, San Diego, CA)[178], and the gas sensing capsule device (ATMO Biosciences, Australia, USA)[179]. A new vibrating capsule, Vibrabot (AnX Robotica, Texas, USA)[180], is also under development. Additionally, the NaviCap

and Biojet capsules (Biora Therapeutics, San Diego, CA) are being explored for drug administration.

Furthermore, smart capsules with biopsy capabilities combine diagnostic imaging with tissue sampling, offering a less invasive alternative to traditional endoscopic biopsies[181,182]. These capsules may be less burdensome to patients, safer, and more acceptable than conventional endoscopic methods.

CONCLUSION

CE has proven to be a minimally invasive and highly effective diagnostic tool. Nevertheless, certain challenges remain, including the time-consuming reading process, high cost, and extensive preparation required for CCE. The integration of AI in clinical practice as an assistive reading tool may alleviate the burden on physicians and address these issues effectively. Thus, with the potential for AI-driven assisted reading, CE can further enhance its diagnostic capabilities in the field of gastroenterology. Furthermore, the clinical development of novel CEs is underway, which will enable the diagnosis of gastrointestinal diseases through a less invasive approach in the near future.

DECLARATIONS

Authors' contributions

Study's conception and design: Tsuboi A, Oka S, Tanaka S
Writing the paper: Tsuboi A
Provided administrative, technical, and material support: Tsuboi A

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Not applicable.

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Consent for publication

Not applicable.

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