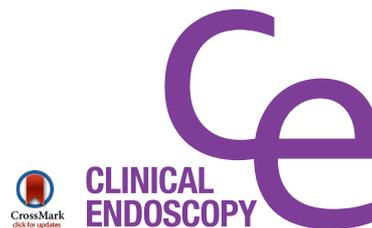


REVIEW

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Colon Capsule Endoscopy: Where Are We and Where Are We Going

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Colon capsule endoscopy (CCE) is a noninvasive technique for diagnostic imaging of the colon. It does not require air inflation or sedation and allows minimally invasive and painless colonic evaluation. The role of CCE is rapidly evolving; for example, for colorectal screening (colorectal cancer [CRC]) in average-risk patients, in patients with an incomplete colonoscopy, in patients refusing a conventional colonoscopy, and in patients with contraindications for conventional colonoscopy. In this paper, we comprehensively review the technical characteristics and procedure of CCE and compare CCE with conventional methods such as conventional colonoscopy or computed tomographic colonography. Future expansion of CCE in the area of CRC screening for the surveillance of polyps and adenomatous lesions and for assessment of inflammatory bowel disease is also discussed. **Clin Endosc 2016;49:449-453**

Key Words: Capsule endoscopy; Colonoscopy; Colonography, computed tomographic

INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy in women and men worldwide.¹ It is a lethal disease with 500,000 deaths per year, accounting for 8.4% of cancer-related death.^{1,2} Colonoscopy is a very effective tool for CRC prevention, as it allows removing premalignant adenomas.³⁻⁶ As screening with conventional colonoscopy prevents progression to CRC and enables detection of early CRC, the incidence and mortality rates of CRC have been declining.^{7,8}

Colonoscopy is relatively safe, and severe colonoscopy-related complications are rare. However, major complications such as perforation, hemorrhage, and even mortality can be induced by colonoscopy. Consequently, colonoscopy is usually considered a painful and invasive procedure. Because the fear of complications and anxiety about pain can make healthy

individuals reluctant to undergo colonoscopy, screening rates for CRC are remain below target.^{3,9,10} According to a previous report, 27.7% of adults between 50 and 75 years of age have never been screened.¹¹ Another weak point of colonoscopy is the possibility of an incomplete examination. Factors such as poor bowel preparation, tortuous or redundant colon, acute angulation, and obstruction can result in a failed cecal intubation. The completion rate of colonoscopy has been reported as 91.1%.¹²

Colon capsule endoscopy (CCE) is a noninvasive technique for diagnostic imaging of the colon. The first generation of CCE (PillCam-Colon; Given Imaging Ltd., Yoqneam, Israel) was released in 2006.¹³ In a meta-analysis, CCE showed a sensitivity of 69% and specificity of 86% for detecting significant polyps; that is, a polyp ≥ 6 mm in size or three or more polyps.¹⁴ The second generation of CCE (PillCam-Colon 2; Given Imaging), which provides an adaptive frame rate and wider angle of view, is now available.¹⁵ This newer capsule showed improved accuracy for detecting polyps that were ≥ 6 mm, with a sensitivity of 84% and a specificity of 88%.¹⁶ It does not require air inflation or sedation and thus allows a minimally invasive and painless colonic evaluation. The European Society of Gastrointestinal Endoscopy (ESGE) proposed that CCE can be used for CRC screening in average-risk patients, in patients with an incomplete colonoscopy, in patients refusing

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a conventional colonoscopy, and in patients with contraindications for conventional colonoscopy.¹⁷

In the present paper, we comprehensively review the previous literature and discuss the potential application and future expansion of CCE.

CURRENT STATUS OF CCE

Technical characteristics of CCE

The novel capsule, PillCam Colon 2, is 31.5×11.6 mm in size and equipped with two cameras with a 172° angle of view, covering almost 360° of the colon. CCE uses a bi-directional communication system with a data recorder.¹⁸ Acquired images are transmitted to the data recorder, which analyzes the transmitted images and determines the frame rate, which ranges from four images per second when stationary to 35 images per second while in motion, which enhances visualization of the colon and saves on battery life. Once the capsule enters the small bowel, the data recorder recognizes the small bowel mucosa and sends a message to the patient using visual and audio signals. With ringing signals and vibrations, instructions are shown on a liquid crystal display of the data recorder. Patients are instructed to ingest the booster to accelerate the capsule transit along the small bowel and colon. When the examination is completed, data are uploaded to the RAPID workstation for image viewing and processing. The resolution of the CCE image is <0.1 mm and magnification scale is up to ×8. Additional software helps to enhance visualization and to estimate the size of the detected lesion.

CCE procedure

Adequate bowel preparation is crucial for successful CCE. In contrast to conventional colonoscopy, additional cleaning

maneuvers such as washing and suctioning during the procedure is not available. Even small amounts of fecal material could interfere with the identification of colonic polyps. Additionally, colon preparation is important to promote capsule propulsion and excretion.^{19,20} The preparation solution fills the lumen with clear fluid and distends the colonic wall, which allows close observation of the colonic mucosa and facilitates capsule propulsion.

For successful CCE, subjects are recommended to begin a low-residue diet 2 days before CCE and a clear-liquid diet the day before CCE. As the regimen for conventional colonoscopy (polyethylene glycol [PEG] solution only) exhibited an inadequate ingestion rate, a new colon preparation regimen was applied to maintain a clean colon and clear capsule image. In previous studies, the regimen including a PEG solution and boosters with sodium phosphate resulted in a satisfactory bowel preparation.^{21,22} A split regimen of PEG on the evening before the examination and on the morning of the examination is usually preferred, although a recent study showed equivalent efficacy of a non-split regimen.²³ Boosters are required for capsule excretion and completion of the exam. A sodium phosphate booster is effective to accelerate transit time.^{21,24} As there have been concerns about sodium phosphate toxicity, such as acute kidney injury and electrolyte imbalance, other boosters such as ascorbic acid and magnesium citrate were investigated, but they resulted in low capsule excretion and completion rates.^{25,26} Currently, a low volume of sodium phosphate is used as a booster, 40 mL of sodium phosphate with 1 L of water to be drunk when the capsule has reached the small bowel and 20 mL of sodium phosphate with 500 mL of water 3 hours after the first booster. Additional agents may also be administered; for example, prokinetics for delayed gastric emptying and a suppository in case of delayed capsule expulsion.

Table 1. Diagnostic Accuracy of CCE in Detecting Polyps ≥6 mm

Study	Type of colon capsule	No. of patients	Sensitivity, %	Specificity, %
Eliakim et al. (2006) ¹³	CCE-1	84	50	83
Schoofs et al. (2006) ²⁸	CCE-1	36	77	70
Van Gossum et al. (2009) ²¹	CCE-1	320	64	84
Eliakim et al. (2009) ¹⁵	CCE-2	98	89	76
Sacher-Huvelin et al. (2010) ²⁴	CCE-1	56	79	54
Gay et al. (2010) ²⁹	CCE-1	126	87.5	76
Sacher-Huvelin et al. (2010) ²⁴	CCE-1	545	39	88
Spada et al. (2011) ¹⁶	CCE-2	109	84	64
Rex et al. (2015) ²⁷	CCE-2	695	81	93

CCE, colon capsule endoscopy; CCE-1, first generation colon capsule endoscopy; CCE-2, second-generation colon capsule endoscopy.

Comparison with conventional method

Several studies compared the accuracy of CCE with that of conventional colonoscopy (Table 1).^{13,15,16,21,24,27-29} Since second-generation CCE was developed for improved performance and a more standardized bowel cleansing method was established, the accuracy of CCE in polyp detection has increased. Two prospective studies reported sensitivities and specificities ranging from 84% to 89% and 64% to 76%, respectively, for detection of significant polyps (≥ 6 mm or three or more polyps).^{16,27} These studies showed considerably high sensitivity; furthermore, CCE succeeded in diagnosing all 10 CRCs detected by conventional colonoscopy. The relatively low specificity was mainly owing to size discrepancy rather than true false-positive results. Although the technical performance characteristics of CCE have markedly improved, some problems remain, such as cost, practical implementation, and patient preference.³⁰ Because CCE needed a higher level of bowel preparation than conventional colonoscopy, a significant number of patients experienced technical failure. In addition, patients should also undergo conventional colonoscopy in case of a positive CCE, which reduced the merit of CCE. A recent prospective study showed a preference to undergo conventional colonoscopy rather than CCE because of reluctance to repeat the bowel preparation.³¹

In case of incomplete colonoscopy, an alternative method to evaluate the non-visualized colon is needed. CCE was proven to identify additional conditions such as carcinoma, inflammatory bowel disease (IBD), telangiectasia, and others that might influence treatment decisions (Table 2).³²⁻³⁶ CCE and computed tomographic (CT) colonography exhibited comparable efficacy with respect to completion of the colon exam. However, the diagnostic yield of CCE was superior to that of CT colonoscopy and CCE seemed to be more tolerable than CT colonoscopy.^{36,37}

Contraindications for CCE and safety issues

Contraindications for CCE are comparable to those of small bowel capsule endoscopy.³⁸ CCE should not be performed in patients with a swallowing disorder because of the risk of

aspiration. Because of the microwaves transmitted by CCE, pregnancy is a contraindication for CCE. Known or suspected bowel obstruction or stricture is another contraindication because of the risk of CCE retention. Magnetic resonance imaging should be examined after the capsule is discharged from the gastrointestinal tract. Because of potential interference between CCE and a cardiac pacemaker or implantable cardiac defibrillator, CCE should not be done in patients with those devices.

FUTURE EXPANSION OF CCE

Screening modality for CRC detection

CCE has limitations as a first-line diagnostic examination for CRC screening, because tissue samples cannot be taken and individuals with significant findings on CCE still need to be referred for conventional colonoscopy. However, CCE might have a potential role as a filter test. The fecal occult blood test was proven to be a useful screening tool, but the false-positive rate is relatively high. Because a large proportion of individuals with positive results on the occult blood test do not have advanced adenoma or neoplasia on colonoscopy, this induces an economic burden and potential risk for colonoscopy-related complications. In a recent trial, CCE was performed after a fecal occult blood test for selecting individuals who needed to undergo conventional colonoscopy. CCE was proven to be effective for detecting malignancies and polyps in individuals with a positive fecal occult blood test and reducing unnecessary conventional colonoscopy by 71%.³⁹ To establish the role of CCE in CRC screening, large prospective trials involving hundreds of participants are now in progress in Europe. These studies will provide answers regarding whether CCE is really helpful in CRC screening by evaluating the accuracy of CCE in detecting CRC and advanced adenoma in fecal occult blood-positive patients or in the primary general population.

The next question would be when to perform a colonoscopy in patients with a positive CCE. Performing a colonoscopy

Table 2. CCE for Incomplete Colonoscopy

Author	Type of colon capsule	No. of patients	Complete colon visualization, %	Additional significant findings, %
Pioche et al. (2012) ³²	CCE-1	107	93	34
Alarcón-Fernández et al. (2013) ³³	CCE-1	34	85	23
Triantafyllou et al. (2014) ³⁵	CCE-1	75	91	44
Negreanu et al. (2013) ³⁴	CCE-2	67	90	34
Spada et al. (2015) ³⁶	CCE-2	100	98	25

CCE, colon capsule endoscopy; CCE-1, first generation colon capsule endoscopy; CCE-2, second-generation colon capsule endoscopy.

immediately after CCE has merit because patients do not have to repeat the bowel preparation. To establish this process, several conditions are required. First, a system to review CCE results in a short time is needed to determine the necessity of conventional colonoscopy on the same day. Specific software to guide a quick overview of CCE images has been developed, but the accuracy of this software requires validation.⁴⁰ Another issue is that the colon transit time of CCE should be homogenous and relatively short to predict the timing of conventional colonoscopy. As colon transit time has a high level of individual variation with the current bowel preparation regimen, a new regimen with an adequate cleansing level and more consistent transit time is desirable.

To improve patient compliance, a trial offering an out-of-clinic CCE procedure was conducted.⁴¹ Boosters and supplementary agents (metoclopramide, sodium phosphate, and bisacodyl) were given to and taken by patients according to detailed data-recorder instructions. Patient compliance to the data-recorder instructions was 100%, which showed that CCE is feasible and easily performed as an out-of-clinic procedure.

Diagnosis and surveillance of IBD

Data regarding the use of CCE in patients with IBD are insufficient. The role of CCE as a primary diagnostic tool in IBD is limited, because biopsy and histological diagnosis is mandatory for the diagnosis of IBD. The possible role of CCE in the area of IBD is examining mucosal healing in the course of monitoring disease activity. Mucosal healing is an important goal of medical treatment of IBD for an improved clinical outcome, which means reducing rates of hospitalization and surgical resection.⁴²⁻⁴⁴ Several studies have examined the usefulness of CCE in the monitoring of mucosal inflammation. According to a previous report, the sensitivity and specificity of first generation CCE for detecting active ulcerative colitis was 89% and 75%, respectively.⁴⁵ Some other studies reported that CCE is safe but insufficient to replace conventional colonoscopy for monitoring disease extent and activity.^{46,47} These previous studies dealt with first generation CCE, and recently, the diagnostic accuracy of second-generation CCE was evaluated in pediatric patients.⁴⁸ The sensitivity and specificity for disease activity were 96% and 100%, respectively, and positive and negative predictive values were reported as 100% and 85%, respectively. Considering these previous results, the ESGE guidelines recommended that second-generation CCE may be helpful for monitoring mucosal inflammation in patients with ulcerative colitis. Further studies especially in adults using second-generation of CCE are expected to support this strategy.

CONCLUSIONS

CCE has some shortcomings compared with conventional colonoscopy; for example, an inability to take biopsy samples and to predict histology during the examination. Furthermore, it is not economic, considering that the average cost of a CCE has been estimated at approximately \$950 in the United States and €700 in Europe.⁴⁹ CCE is considered a complementary test because its diagnostic accuracy is still less than that of conventional colonoscopy.

Beyond these limitations, CCE appears to be a promising novel modality for colonic evaluation. It is a noninvasive and painless modality that directly monitors the colonic mucosa. CCE can provide additional information in cases of incomplete colonoscopy and in cases of patients unwilling or unable to undergo colonoscopy. Because CCE is well tolerated by patients and can be performed even in an outpatient setting, its use could increase patient compliance. The sensitivity of the second-generation CCE for polyp detection has been remarkably improved compared with that of first generation CCE, which led to its approval by the U.S. Food and Drug Administration in 2014. Considering the rapidly developing technologies, the future of CCE is promising in the area of CRC screening for the surveillance of polyps and adenomatous lesions and for the assessment of IBD.

Conflicts of Interest

The authors have no financial conflicts of interest.

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