Review

Colon capsule endoscopy for colorectal cancer screening in patients with the positive fecal occult blood test (FOBT) in Japan

Konosuke Nakaji*

Endoscopy Center, Aishinkai Nakae Hospital, Wakayama, Japan

*Corresponding author: Konosuke Nakaji, MD, FACP, Endoscopy Center, Aishikai Nakae Hospital, 30-1 Funadokoro Wakayama 640-8461, Tel:+81-73-451-0222; Fax: +81-73-541-0837; E-mail: parupurikopui@yahoo.co.jp

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Abstract

Screening for colorectal cancer (CRC) has been shown to be effective in reducing mortality from the disease. Unfortunately, however, while the decrease in CRC mortality is mainly due to the contribution of the recommended colonoscopy, its acceptability is still low. Therefore, less-invasive screening modalities with equivalent sensitivity and specificity for the detection of polyps and cancer are desired. Colon capsule endoscopy (CCE) was first introduced in 2006 as a wireless, non-invasive technique for imaging of the large bowel that does not require sedation or X-ray exposers. In this review, the current role of CCE for patients with the positive fecal occult blood test (FOBT) in Japan will be discussed.

Keywords: colon capsule endoscopy, colorectal cancer screening, positive fecal occult blood test (FOBT)

Introduction

Colorectal cancer is the leading cause of death worldwide [1], and increased incidence in the Japanese population [2] with Westernized-Japanese diet habits. Today, it is the first leading cause of cancer deaths in women and the second for both men and women in Japan [3]. Japanese CRC screening programs for colorectal cancer based on fecal occult blood testing (FOBT) started in 1992. It is an annual two-day FOBT method, and offered to those 40 years of age and over, and a total colonoscopy is performed for those with at least one positive FOBT [4]. There has been sufficient evidence of colorectal cancer screening programs using FOBT and colonoscopy reducing the motility of CRC [5]. However, participation rates are only 41.4% for men and 34.5% for women in Japan so far [6]. There may be several reasons the recommended colonoscopy is refused, including perceptions of discomfort, pain, or being worried about anal intubations especially for women, and the invasive nature of colonoscopies that include perforations and bleeding. Recently, the second-generation colon capsule endoscopy (CCE) (PillCam Colon 2: Medtronic Minneapolis, USA) began to be covered by Japanese health insurance. It is an easy and non-invasive method for screening colorectal cancer and

only involves swallowing a capsule. Thus, this newer CCE is thought to be useful for detecting colorectal lesions in patients with FOBT who are unsuitable or unwilling to undergo a colonoscopy. However, to our knowledge, there have been no reports so far on the role of CCE in the FOBT-based Japanese population cohort. Therefore, in this article, we will review the current works of literature and present our trials on this issue in Japan.

Technical characteristics, indications, and cost-effectiveness

The PillCam COLON2 capsule (Medtronic, Minneapolis USA) (Figure 1), which records digital images on 2 camera heads (31 mm×11 mm, weight 2.9 g) with wide visualization (172° for each camera; 344° for both) at a rate ranging from 4 to 35 frames per second in accordance with the speed of the capsule, which has an adaptive frame rate (AFR) and an approximately 10-hour procedure time, was used. The images were transmitted to a recording device (DR3) wirelessly carried by the patient with sensors attached to the patient's skin (Figure 2). The data were transferred from the device to a computer that uses software (RAPID v.8.3 now available) (Figure 3) to

compile a video that was then analyzed by a board-certified technical assistant and later confirmed by a board-certified gastroenterologist. We sometimes found that only one thumbnail (picture) represented an important finding, so a training system for CCE is necessary. Several reader education programs for technical assistants and gastroenterologists such as computer-based learning (E-learning) and hands-on seminars have been reported in both Europe and Japan [7] [8]. In Japan, the indication for CCE is either a failed total colonoscopy or the presumption that a colonoscopy would be difficult to conduct due to adhesion after an operation on the abdomen and so on. We use patency capsules (a soluble dummy capsule for small bowel capsule endoscopies) for some patients if a patient is worried about retention. Contraindications of CCE are almost the same as with the small bowel capsule, including patients with intestinal obstructions, dysphasia, implanted electric devices, and confirmed or suspected pregnancy. CCE examination has been estimated to cost approximately between ¥10,000 and ¥30,000 with medical insurance in Japan. At our institute, all CCE has been performed in an outpatient setting because it was not covered by Japanese social insurance in the inpatient unit. One study described the introduction of CCE to CRC screening in Japan showed it to be more cost-effective than conventional screening (20% or more) with the quality-adjusted life years using the Markov model [9].

Bowel preparation for CCE

Unlike conventional colonoscopy, adequate bowel preparation is essential to obtaining an accurate CCE diagnosis because a cleaning procedure is not available. Table 1 shows a recent bowel preparation regimen we did for

CCE. In summary, the day before the examination, the patient followed a low-residue diet and ingested a hypertonic magnesium citrate solution. On the day of the examination, we used polyethylene glycol that contained ascorbic acid (Moviprep: EA pharma, Tokyo, Japan) as both the preparation and the booster with 10 mg of metoclopramide were given intravenously after capsule ingestion. Patients are then required to walk up and down stairs during the examination in the hospital until they excrete the capsule to accelerate bowel movements [10]. A glycerin enema was used in cases of delayed excretion. In our prospective and multicenter (9 institutes in Japan) study of this regimen (n=82, 45 male patients, average age of 60.0±13.8 years old), the capsule was excreted 85% of the time and excellent visualization of the entire colon was achieved 82% of the time. The average colon transit time was 172 ±95 minutes and the average total water intake was 3,605±518 mL. A glycerin enema was used in 33% of the cases. A sodium phosphate solution is commonly used as a booster in Europe [11] but has limited use in the US and is not available in Japan due to concerns about renal toxicity. Several boosters and prokinetics for CCE have been tried such as Gastrografin (a contrast medium for the digestive tract) [12], Daikenchuto (Tsumura, Tokyo, Japan: a Japanese herbal medicine) [13], Neostigmine (0.25 mg intramuscular administration) [10] in Japan, and the Japanese association for capsule endoscopy recently recommended aromatic castor oil as a prokinetic [14]. Linaclotide, which activates the cell surface receptors of guanylate cyclase 2C (GC-C), may also act as a prokinetic. Our recent study showed the colon transit time was significantly shorter in the Linaclotide (L) group (n=11) than in the non-Linaclotide (NL) group (n=37) (P<0.001).

Table 1. Bowel preparation regimen with ascorbic acid containing polyethylene glycol (Moviprep) for colon capsule endoscopy.

Day	Time	Action	Dose of Solution	Total amount of solution
Day before exam	Noon, Evening, Between these meals	Low- residue diet		
	Evening	Magcorol P hypertonic solution 180 mL	180mL	
	Bedtime	Laxoberon	10mL	
Day of exam	Wake up	Mosapride 20mg		
	-2hrs before capsule ingestion	Moviprep 1200mL Water 600mL	1800mL	1800mL
		Capsule Ingestion Metoclopramide 10mg IV	200mL	2000mL
	Reaching small Bowel	Magcorol P isotonic solution 900mL	900mL	2900mL
	+1 hrs, from reaching small bowel	Moviprep 400mL Dimethicone solution 200mL	600mL	3500mL
	+2 hrs, from reaching small bowel or reaching colon	Moviprep 400mL water 200mL	600mL	4100mL
	+1 hrs, from reaching colon	Light meal		
	+3 hrs from reaching colon or 16:00	Glycerine enema 120mL

Figure 1. PillCam Colon 2 capsule

Figure 2. DR3 and sensors

Figure 3. Rapid for PillCam software R8.3

Figure 4. An advanced colonic cancer with positive FOBT patients detected by second-generation colon capsule endoscopy

The fluid intake was significantly smaller in the L group than in the NL group ($P<0.001$). The acceptability was significantly higher in the L group than in the NL group ($P=0.04$). Also, in our transit times study for CCE, male patients, exercising during CCE, and patients who do not have diabetes mellitus showed a significantly shorter colon transit time [10]. Despite these efforts, an ideal preparation method that has a sufficient cleansing level, high excretion ratio, and is well-tolerated by CCE patients has yet to be determined.

CCE for detection of colon polyps

The first-generation colon capsule, which was released in 2006, had limited sensitivity (64 %) and specificity (84%) for detecting colon polyps (≥ 6 mm) [15]. In addition, sensitivity and specificity for advanced adenoma were 73% and 79%, respectively [15]. However, with the newer second-generation colon capsule, which provides AFR with wider visualization as mentioned above, the sensitivity and specificity have increased [16-21], and one recent study showed ($n=50$) for ≥ 6 mm polyps it was 93% sensitivity and 80% specificity and ≥ 10 mm it was 100% sensitivity and 100% specificity [21]. A multicenter study in Japan held in 2105 ($n=66$) showed the sensitivity for clinically significant polyps (≥ 6 mm) was 94% with the second-generation CCE [22]. A study on 165 Japanese patients for whom the second-generation capsule was used for polyp detection between Nov. 2013 and Dec. 2017 in our institute for significant polyps (>6 mm) showed the positive predictive value (PPV) was 93% as compared to colonoscopy. As mentioned above, the sensitivity and specificity of the second generation CCE for polyp detection have improved remarkably compared with that of the first generation, which led simultaneously to its approval by the U.S. Food and Drug Administration and coverage by Japanese health insurance in 2014. In addition, CCE has been adopted as an option for screening CRC every 5 years by the U.S. Preventive Services Task Force. Furthermore, second-generation CCE may detect small polyps (<5 mm) or sessile polyps better compared to other modalities; CS/CTC due to no inflation of the intestinal lumen [23].

CCE for colorectal cancer screening in patients with the positive fecal occult blood test (FOBT)

To the best of our knowledge, only a few trials have been conducted evaluating second-generation CCE in patients with positive FOBT. In 2014, Grainne Holleran et al. [24] of Ireland reported that a colonoscopy followed by CCE the next day for patients who are FOBT positive ($n=62$) detected at least one polyp in 58%, significant lesions in 29%, and cancer in 2% of them. The negative-predictive value of CCE was high both for any polyps (90%) and significant lesions (96%). They concluded there was a strong correlation between CCE and colonoscopy for any lesions and significant lesions. In 2104, Rondonotti [25] of Italy reported comparisons of

CCE and CT colonography (CTC) for positive FOBT patients. CCE identified the polyps with 88.2% sensitivity and 87.8% specificity. CTC identified the polyps with 88.2% sensitivity and 84.8% specificity. They indicated that CCE seems better tolerated than CTC, and CCE could be a reliable alternative to CTC for positive FOBT. In 2018, Mathieu Pioche et al. [26] of France also compared CCE and CTC on positive FOBT patients, and reported that the 84% of CCE patients ($n=16/19$) were positive. CCE detected 60% of potentially neoplastic lesions (6 adenomas or cancers, 6 clinically significant polyps). On the other hand, CTC detected positive findings of 46.4 % (13/28), and 8 potentially neoplastic lesions (28.6%). They concluded there were more potentially neoplastic lesions diagnosed in the CCE group than in the CTC group ($p=0.04$). We enrolled 35 Japanese patients (15 males, 20 females, with a mean age of 61.6 ± 12.8 years old) with an asymptomatic positive FOBT result at three institutes in a cohort study. It was assumed that thirty-one patients would have difficulty with a conventional colonoscopy due to colonic adhesion as the result of previous abdominal surgery. Our study showed that the positive rate was 94.3% with a completion rate of 86.6%. Of these, 40 polyp lesions were detected (an average of 1.1 lesions in each case). The average water intake was $3,706 \pm 684$ mL, the average colon transit time was 164.5 ± 88.3 min., and the adequate cleansing rate including excellent and good was 71.4%. Subsequently, 21 significant lesions were endoscopically resected within 3 months of the CCE. There were 15 adenomas, 3 hyperplastic lesions, and 3 cancerous ones (1 advanced and 2 early) (Fig 4, 5a and 5b). The colon transit time was significantly shorter and the liquid intake was significantly smaller ($P<0.001$) in positive FOBT patients than those of the other indications of 130 patients. There were no adverse events. Based on these results with their reasonable predictive value, safety, and good acceptability, CCE could be a suitable alternative to colonoscopy for patients with positive FOBT in whom it is not technically feasible to undergo a conventional colonoscopy in the Japanese colorectal cancer screening program. We propose a new screening algorithm for the CRC program using CCE as shown Figure 6.

Future perspectives for CCE

With participation in the colorectal screening program increasing with FOBT, an increase in the number of colonoscopies for these patients is inevitable. However, today, there are too few colonoscopists to conduct the screening colonoscopies for these patients especially in rural areas in Japan. To compensate for this, CCE will play an important role in detecting CRC. With improving device technology such as detection of the top 100 significant lesions with newer software, CCE will be a more solid modality that is used to evaluate CRC. Further prospective randomized studies with large numbers of subjects are necessary to establish the role of CCE in diagnostic

Figure 5a, b. An early colonic cancer with positive FOBT patients found by second-generation colon capsule endoscopy.

Figure 6. Algorithm for colorectal cancer screening with colon capsule endoscopy.

algorithms for colorectal cancer screening for FOBT positive patients.

Disclosure Statement

There are no conflicts of interest to declare.

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