Capsule endoscopy compared with conventional colonoscopy for detection of colorectal neoplasms

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Abstract
Colon capsule endoscopy (CCE) may be a means to overcome the low adherence to colorectal cancer screening. The device is an ingestible capsule with a video camera at both ends that can take photographs as it progresses through the gastrointestinal tract. PillCam colon (PCC1) may be used for structural evaluation of the large bowel following an adequate cleansing procedure. PCC1 measures 11 mm × 31 mm and has dual cameras that enable the device to acquire video images from both ends with a wide coverage area, automatic light control and a frame rate of four frames per second. The system includes a sensor array and data recorder connected to the patient during the procedure. The recorded data are downloaded to the Given Imaging Rapid workstation for review of the colon video. The second generation of PillCam Colon (PCC2) is similar to PCC1 and incorporates new developments. The angle of view has been increased to 172 degrees. It has an adaptive frame rate, alternating from 35 frames per second while in motion to 4 images when virtually stationary. The new RAPID® software now includes a simple graphic interface tool for polyp size estimation. The procedure of bowel cleansing until capsule ingestion is similar to that used for traditional colonoscopy. However it is more rigorous as the bowel cleanliness for capsule colonoscopy has to be excellent or at least good to result in an adequate sensitivity of the method. Briefly, it consists of 3.5-4 L of split dose polyethylene glycol. Oral NaP boosters are administered after 1-2 h if the capsule has entered the small bowel. Sodium phosphate (NaP) seems to be a necessary adjunct to the regimen because the total transit time is doubled without NaP. The cleansing level was considered to be good to excellent in 72%-88% in studies with PCC1. The sensitivity for significant polyps (> 6 mm or more than 3 polyps >3 mm) ranged from 63%-88% with specificities between 64%-94%. PCC2 showed an improved sensitivity of 89% and a specificity of 76%. CCE seems to be a safe and effective method of visualizing the colonic mucosa through colon fluids without the need for sedation or insufflation of air. The sensitivity of CCE to detect polyps, advanced adenomas and cancer is lower compared to optical colonoscopy but improvements will be made in the near future. With an increased recording duration, even a panenteric examination of the whole gastrointestinal tract may be possible.

Key words: Colon capsule endoscopy; Colorectal cancer; PillCam colon; Conventional colonoscopy

INTRODUCTION
Colorectal cancer is the second leading cause of cancer...
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death in North America[1] and Western Europe. Screening colonoscopy was introduced in the National Cancer Prevention Program in Germany in 2002[2], even though results from randomised controlled studies on its effect on incidence and mortality of colorectal cancer were not yet available. A first evaluation of screening colonoscopy in Germany showed a detection rate of adenomas of 20%, advanced adenoma 6% and colorectal cancer 0.7%, similar to the detection rates in Poland[3]. However, the participation in colonoscopy screening is as low as 3%-4%[3]. In the US, a decrease in incidence and mortality of colorectal cancer may be attributed partly to an increased screening activity[4].

A means to overcome the low screening activity might be to introduce new convenient methods to reduce people’s resistance. One of these methods might be colon capsule endoscopy (CCE). Small bowel capsule endoscopy has been used successfully to visualize the upper gastrointestinal tract and small bowel. The instrument is an ingestible capsule with a video camera at one end that can take photographs as it progresses through the gastrointestinal tract. The main indication for use of the small bowel capsule is obscure gastrointestinal bleeding[5] and it has been shown to be feasible and cost saving as an outpatient procedure[6]. The newly developed PillCam colon (PCC1) may be used for structural evaluation of the large bowel following an adequate cleaning procedure.

DEVICE DESCRIPTION OF THE COLON CAPSULE

PCC1

PCC1 capsule endoscope (Given Imaging Ltd., Yoqneam, Israel) was the first capsule with a battery life that enables visualization of the colon[7]. The capsule measures 11 mm × 31 mm and has dual cameras that enable the device to acquire video images from both ends with a wide coverage area, automatic light control and a frame rate of four frames per second. The operation time is approximately 10 h and after an initial image transmission of 3 min, the capsule enters a delay mode (of approximately 2 h), after which it spontaneously “wakes up” and starts the transmission of images. The system includes a sensor array and data recorder connected to the patient during the procedure. The recorded data are downloaded to the Given Imaging Rapid workstation for review of the colon video. The localization display of the RAPID® software enables the physician to identify the location of findings, i.e. right, transverse or left colon segments once the main anatomical landmarks (first cecal image, hepatic flexure, splenic flexure and exit of the capsule) have been selected. RAPID® Access RT by Given Imaging allows real time visualization of capsule images. This allows localization of the device and consequently an intervention to optimize the procedure during the ongoing examination. One example is that the patient has to drink a small amount of sodium phosphate 2 h after ingestion of the capsule in order to push the capsule through the small bowel. However, he should only drink sodium phosphate if the capsule has passed the stomach because sodium phosphate may delay gastric emptying time.

PCC2

The second generation of PillCam Colon (PCC2), Given Imaging Ltd., Yoqneam, Israel, is similar to PCC1 and consists of an ingestible video capsule measuring 11.6 by 31.5 mm and has two imagers, one at each end of the capsule. The second-generation system incorporates new developments to the capsule, the data recorder and the RAPID® software[8].

The angle of view has been increased to 172 degrees (from 156 in PCC1). In order to conserve battery energy, the capsule captures images at an adaptive frame rate, alternating from 35 frames per second while it is in motion (such as in the transverse colon) to 4 images when it is virtually stationary. After swallowing, the capsule works with a low frame rate of 14 per minute until it automatically identifies the small bowel.

The new data recorder also assists and guides the medical staff and patient through the procedure. It buzzes, vibrates and displays instruction numbers in order to alert the patient to take the laxative booster or that the procedure has terminated.

The new RAPID® software now includes a simple graphic interface tool for polyp size estimation. After marking the distance from one side of the polyp to the other, the RAPID® software calculates the distance and displays the polyp size in millimetres.

PROCEDURE AND CLEANLINESS

The procedure of bowel cleansing until capsule ingestion is similar to that used for traditional colonoscopy. However, it is more rigorous as the bowel cleanliness for capsule colonoscopy has to be excellent or at least good to result in an adequate sensitivity of the method. The reason for the rigorous procedure is that with a capsule, unlike a colonoscope, fluid cannot be aspirated. If the fluid is unclear, the bowel mucosa may not be seen by CCE.

The reason for the combination of PEG with laxatives is to maintain the colon cleanliness and facilitate progression of the capsule through the gastrointestinal tract.

Briefly, it consists of a clear liquid diet with/without a small breakfast on the day before capsule ingestion and 3.5-4 L of split dose polyethylene glycol (PEG). Oral NaP boosters are administered after 1-2 h if the capsule has entered the small bowel and again 2-3 h later, followed by the administration of a bisacodyl suppository two hours after the second boost if the capsule has not been excreted (Table 1). The procedures for PCC1[9,10,12] and for the newly developed PCC2[12] are similar.

With this regimen 69%-84% of the capsules were excreted within 6-8 h[8,12] and 92.8% within 10 h[10]. If only conventional colonoscopy preparation was used, the excretion rates were as low as 20%. Sodium phosphate (NaP) seems to be a necessary adjunct to the regimen. In two studies, NaP was omitted from the regimen and replaced by PEG[12,13]. This resulted in a low excretion rate and the total transit time was doubled, without improvement of the
Table 1  Procedure protocols and cleansing levels

| Authors | Eliakim 2006[8] | Schoofs 2006[9] | Sieg 2009[10] | Van Gossum 2009[11] | Eliakim 2009[12] |
|---------|----------------|----------------|--------------|---------------------|----------------|
| Device  | PCC1           | PCC1           | PCC1         | PCC1                | PCC1           |
| Day 2   | Low fibre diet | -              | -            | -                   | -              |
| Day 1   | 7-8 pm         | 6-9 pm         | 1-6 pm       | 6-9 pm              | evening        |
|         | PEG 2 L        | PEG 3 L        | PEG 3 L      | PEG 3 L             | PEG 2 L        |
| Day 0   | 6-7 am         | PEG 1 L        | PEG 1 L      | PEG 1 L             | PEG 2 L        |
|         | 8-9 am         | Capsule ingestion | Capsule ingestion | Capsule ingestion | Capsule ingestion |
|         | Tegaserod 6 mg | Domperidone 20 mg | Domperidone 20 mg | Domperidone 20 mg | Domperidone 20 mg |
|         | NaP 30 mL      | NaP 22 mL      | NaP 22 mL    | NaP 22 mL           | NaP 22 mL      |
|         | +              | NaP 45 mL      | NaP 45 mL    | NaP 45 mL           | NaP 45 mL      |
| 10:00 am| 12 am-1 pm     | Tegaserod 6 mg | NaP 30 mL    | NaP 22 mL           | 1-2 h later NaP 45 mL |
|         | 02:00 pm       | NaP 15 mL      | NaP 22 mL    | NaP 22 mL           | 2 h later NaP 22 mL |
|         | 04:30 pm       | Bisacodyl supp 10 mg | Bisacodyl supp 10 mg | Bisacodyl supp 10 mg | Bisacodyl supp 10 mg |
|         | 84.4           | 88            | 72          | 72                  | 78             |
|         |                 |                |             |                     | 55/55          |

Table 2  Sensitivity and specificity of colon capsule endoscopy for polyps 6 mm or larger performed with PCC1 and PCC2

| Authors | Eliakim[8] | Schoofs[9] | Van Gossum[10] | Spada[11] | Pilz[12] | Gay[13] | Sacher-Huvelin[14] | Eliakim[15] |
|---------|------------|------------|----------------|-----------|----------|---------|-------------------|------------|
| Year    | 2006       | 2006       | 2009           | 2010      | 2010     | 2010    | 2010              | 2009       |
| Device  | PCC1       | PCC1       | PCC1           | PCC1      | PCC1     | PCC1    | PCC1              | PCC1       |
| N       | 84         | 36         | 328            | 49        | 36       | 128     | 545               | 98         |
| Sens (%)| 63         | 76         | 64             | 63        | 50       | 88      | 39                | 89         |
| Spec (%)| 94         | 64         | 84             | 87        | 76       | 76      | 88                | 76         |

PCC1: PillCam Colon 1 (Given Imaging Ltd, Yoqneam, Israel); PCC2: Second generation of PillCam Colon (Given Imaging Ltd, Yoqneam, Israel).

Detection of Lesions

The long-term objective of colon capsule endoscopy (CCE) is screening of the average population. In the first feasibility studies, the sensitivity for significant polyps (> 6 mm or more than 3 polyps >3 mm) was evaluated in patients with an indication for colonoscopy and ranged from 63%-88% with specificities between 64%-94%[8,10,11,13,15,18] (Table 2). In a small study under routine screening conditions from Switzerland, the sensitivity of significant findings was only 50% (95% CI: 19-81)[14] and in a study from France in patients at average and increased risk, the sensitivity was 39% (95% CI: 30-48)[16]. CCE was successfully used in an ambulatory practice of gastroenterology with a median transit time of 4.5 h[12]. In patients with short transit time, a panenteric examination of the upper, mid and lower gastrointestinal tract would be possible. In patients with excellent or good colon cleanliness, the sensitivity was significantly higher than in patients with poor cleanliness[11].

Meta-analyses on PCC1 with 626 patients[17] and 837 patients[18] found sensitivities for significant polyps of 69% and 76%, with specificities of 86% and 82% respectively.

A second generation capsule (PCC2) showed an improved sensitivity of 89% and a specificity of 76% in 98 patients aged 18 to 57 years scheduled to undergo colonoscopy for suspected or known colonic disease[19]. The sensitivity described is higher than with any other CCE so far but still has to be established in further studies.

To date, conventional colonoscopy is the gold standard for the detection of significant polyps or colon cancer.
for detection of colorectal neoplasia, offering the ability to remove detected polyps and obtain biopsy samples with one examination in contrast to all diagnostic procedures. However, standard colonoscopy only detects about 90% of polyps 10 mm or larger\textsuperscript{[10-20]}. Some studies also suggested that colonoscopy may be protective only for cancers\textsuperscript{[25]} and advanced adenomas\textsuperscript{[26]} in the distal but not proximal colon. The effectiveness of all screening programs depends on the quality of colonoscopy because colonoscopy is used to evaluate positive screening tests in all programs. A highly qualified colonoscopy with an adequate withdrawal time\textsuperscript{[28]} is a prerequisite for all screening programs.

**SAFETY**

No capsule or laxatives-related adverse effects occurred during the first feasibility studies\textsuperscript{[8-12]} and only mild to moderate adverse effects were reported in a multicenter trial\textsuperscript{[31]}. Only 4 of 582 patients (0.7%) were unable to swallow the capsule\textsuperscript{[8,12]}.

**COST EFFECTIVENESS**

Cost-effectiveness of CCE was evaluated in a recent paper based on a mathematical Markov model\textsuperscript{[30]}. With equal compliance rates, colonoscopy was more cost-effective than CCE. With a 30% increase in compliance, CCE becomes more cost-effective than colonoscopy. Moreover, future generations of capsules may improve the detection rate of polyps and thereby increase the cost-effectiveness. When both procedures are offered, patients prefer colonoscopy because of the higher sensitivity and that there is no need for a second test\textsuperscript{[31]}.

**CONCLUSION**

CCE seems to be a safe and effective method of visualizing the colonic mucosa through colon fluids without the need for sedation or insufflation of air. Colon cleanliness significantly influences the sensitivity for polyps and cancer. The sensitivity of CCE to detect polyps, advanced adenomas and cancer is lower when compared to optical colonoscopy. Improvements in capsule technology increased the sensitivity for colorectal neoplasms in PCC2 and, with the new generation of capsules, a similar sensitivity of CCE and colonoscopy may be accessible in the future. Currently, a large study on a standard screening population is not yet available. The future range of CCE in CRC screening will depend not only on sensitivity, but also on these issues: 1) Bowel preparation: The bowel preparation for CCE is more extensive than for colonoscopy as only clear liquids are allowed. Therefore, PEG and laxatives restrict its applicability. 2) Reading time: The reading time of colon capsule endoscopy usually ranges between 30 and 60 min. This is a time-consuming procedure that lasts longer than a colonoscopy. Future developments may shorten the reading time by an automatic detection of polyps and/or a pre-reading by trained technicians; and 3) Costs: The actual costs of a colon capsule endoscopy in Germany exceed the costs for colonoscopy by about 6 times. CCE is not yet reimbursed by most of the insurance companies. The high price of CCE represents an obstacle to mass screening.

Nevertheless, a non-invasive method for CRC screening may be of interest for those reluctant to undergo colonoscopy because of its perceived inconvenience, discomfort or embarrassment as CCE seems to be a more adequate alternative. The examination can even be performed in the privacy of a patient’s home at the weekend, avoiding the need to take time off work. I believe that CCE will have a place as an additional screening tool for CRC in a selected and limited population.

As CCE has still some limitations (cannot insufflate air, clean or take biopsies), future capsule prototypes seem to be necessary. An increase of frame rate, angle of view and duration of the procedure seem likely\textsuperscript{[8-12]}. With an increased recording duration, even a panenteric examination of the whole gastrointestinal tract may be possible. Improvement of visualization of the small bowel by a computed color enhancement system (FICE)\textsuperscript{[31]} is under evaluation and possibly could be applied to CCE. A smart capsule with motion control and 360 degree view (Capsovision, Saratoga CA) is also under evaluation. Remote control movement will improve with the use of magnets or electrostimulation. Even an active endoscopic robot seems to be possible according to animal experiments\textsuperscript{[34]}.

**REFERENCES**

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. CA Cancer J Clin 2008; 58: 71-96
2. Richtlinien des Bundesausschusses der Ärzte und Krankenkassen über die Früherkennung von Krebserkrankungen. Dtsch Ärztebl 2002; 11: 518-521
3. Sieg A, Theilemeier A. [Results of colonoscopy screening in Germany: 2005—Internet-based documentation]. Dtsch Med Wochenschr 2006; 131: 379-383
4. Regula J, Rupinski M, Kraszewska E, Polkowski M, Pachlewski J, Orlowska J, Nowacki MP, Butruk E. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. N Engl J Med 2006; 355: 1863-1872
5. Knöppel J, Allentäfeler H, Brenner G. [Epidemiologic and health economic significance of colorectal cancers in Germany]. Internist (Berl) 2003; 44: 268-274, 276-277
6. Nakamura T, Terano A. Capsule endoscopy: past, present, and future. J Gastroenterol 2008; 43: 93-99
7. Soncini M, Russo A, Campi E, Lanzi P, Colombo A, Pometta R, Colucci A, Gasparini P. Capsule endoscopy of the small bowel in the clinical practice: outpatient management is feasible and cheaper. Minerva Gastroenterol Dietol 2010; 56: 383-387
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8 Eliakim R, Fireman B, Graînek IM, Yassin K, Waterman M, Kopelman Y, Lachter J, Koslowsky B, Adler SN. Evaluation of the PillCam Colon capsule in the detection of colonic pathology: results of the first multicenter, prospective, comparative study. *Endoscopy* 2006; 38: 963-970
9 Schoofs N, Devière J, Van Gossum A. PillCam colon capsule endoscopy compared with colonoscopy for colorectal cancer: a prospective pilot study. *Endoscopy* 2006; 38: 971-977
10 Eliakim R, Yassin K, Niv Y, Metzger Y, Lachter J, Gal E, Saponnikov B, Konikoff F, Leichtmann G, Fireman Z, Kopelman Y, Adler SN. Prospective multicenter performance evaluation of the second-generation colon capsule compared with colonoscopy. *Endoscopy* 2009; 41: 1026-1031
11 Van Gossum A, Munoz-Navas M, Fernandez-Urien I, Carretero C, Gay G, Delvau M, Lapalus MG, Ponchon T, Neuhaus H, Philipper M, Costamagna G, Riccioni ME, Spada C, Petruzzelli L, Fraser C, Postgate A, Fitzpatrick A, Hagenmuller F, Keuchel M, Schoofs N, Devière J. Capsule endoscopy versus colonoscopy for the detection of polyps and cancer. *N Engl J Med* 2009; 361: 264-270
12 Sieg A, Friedrich K, Sieg U. Is PillCam COLON capsule endoscopy ready for colorectal cancer screening? A prospective feasibility study in a community gastroenterology practice. *Am J Gastroenterol* 2009; 104: 848-854
13 Spada C, Riccioni ME, Hassan C, Petruzzelli L, Cesaro P, Costamagna G. PillCam colon capsule endoscopy: a prospective, randomized trial comparing two regimens of preparation. *J Clin Gastroenterol* 2011; 45: 119-124
14 Pilz JB, Portmann S, Peter S, Beglinger C, Degen L. Colon Capsule Endoscopy compared to Conventional Colonoscopy under routine screening conditions. *BMC Gastroenterol* 2010; 10: 66
15 Gay G, Delvau M, Frederic M, Fassler I. Could the colonic capsule PillCam Colon be clinically useful for selecting patients who deserve a complete colonoscopy?: results of clinical comparison with colonoscopy in the perspective of colorectal cancer screening. *Am J Gastroenterol* 2010; 105: 1076-1086
16 Sacher-Huvelin S, Coron E, Gaudric M, Planche L, Benamouzig R, Maunoury V, Filiocco B, Frederic M, Saurin JC, Subtil C, Lecleire S, Cellier C, Courmaros D, Heresbach D, Galmiche JP. Colon capsule endoscopy vs. colonoscopy in patients at average or increased risk of colorectal cancer. *Aliment Pharmacol Ther* 2010; 32: 1145-1153
17 Rokkas T, Papaxoinis K, Triantafyllou K, Ladas SD. A meta-analysis evaluating the accuracy of colon capsule endoscopy in detecting colon polyps. *Gastrointest Endosc* 2010; 71: 792-798
18 Spada C, Hassan C, Marmo R, Petruzzelli L, Riccioni ME, Zullo A, Cesaro P, Pilz J, Costamagna G. Meta-analysis shows colon capsule endoscopy is effective in detecting colorectal polyps. *Clin Gastroenterol Hepatol* 2010; 8: 516-522
19 Hisson LJ, Fennerty MB, Sampliner RE, Garewal HS. Prospective blinded trial of the colonoscopic miss-rate of large colorectal polyps. *Gastrointest Endosc* 1991; 37: 125-127
20 Rex DK, Cutler CS, Lemmel GT, Rahmani EY, Clark DW, Helper DJ, Lehman GA, Mark DC. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. *Gastroenterology* 1997; 112: 24-28
21 Shehadeh I, Rebala S, Kumar R, Markert RJ, Barde C, Gopal-swamy N. Retrospective analysis of missed advanced adenomas on surveillance colonoscopy. *Am J Gastroenterol* 2002; 97: 1143-1147
22 van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. *Am J Gastroenterol* 2006; 101: 343-350
23 Rockey DC, Paulson E, Niedzwiecki D, Davis W, Bosworth HB, Sanders L, Yee J, Henderson J, Hatten P, Burdick S, Sanyal A, Rubin DT, Sterling M, Akerkar G, Bhutani MS, Binmoeller K, Garvie J, Bini EJ, McQuaid K, Foster WL, Thompson WM, Dachman A, Halvorsen R. Analysis of air contrast barium enema, computed tomographic colonography, and colonoscopy: prospective comparison. *Lancet* 2005; 365: 305-311
24 Pickhardt PJ, Choi JR, Hwang I, Butler JA, Puckett ML, Hildebrandt HA, Wong RK, Nugent PA, Mysliwiec PA, Schindler WR. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med* 2003; 349: 2191-2200
25 Cotton PB, Durkaliski VL, Pineau BC, Palech YY, Mauldin PD, Hoffman B, Vining DJ, Small WC, Affronti J, Rex D, Kopecy KK, Ackerman S, Burdick JS, Brewington C, Turner MA, Zlass A, Wright AR, Iyer RB, Lynch P, Sivak MV, Butler H. Computed tomographic colonography (virtual colonoscopy): a multicenter comparison with standard colonoscopy for detection of colorectal neoplasia. *JAMA* 2004; 291: 1713-1719
26 Johnson CD, Chen MH, Toledano AY, Heiken JP, Dachman A, Kuo MD, Menias CO, Siewert B, Cheema JL, Obregon RG, Fidler JL, Zimmerman P, Horton KM, Coakley K, Iyer RB, Hari AK, Halvorsen RA, Casola G, Yee J, Herman BA, Burgart LJ, Limburg PJ. Accuracy of CT colonography for detection of large adenomas and cancers. *N Engl J Med* 2008; 359: 1207-1217
27 Baxter NN, Goldwasser MA, Paszat LF, Sasaki R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. *Ann Intern Med* 2009; 150: 1-8
28 Brenner H, Hoffmeister M, Arnold V, Stegmaier C, Altenhofen L, Haug U. Protection from right- and left-sided colorectal cancer. *Ann Intern Med* 2008; 149: 89-95
29 Barclay RL, Vicari JJ, Doughty AS, Johanson JF, Greenlaw RL. Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. *N Engl J Med* 2006; 355: 2533-2541
30 Hassan C, Zullo A, Winn S, Morini S. Cost-effectiveness of capsule endoscopy in screening for colorectal cancer. *Endoscopy* 2008; 40: 414-421
31 Imaeda A, Bender D, Fraenkel L. What is most important to patients when deciding about colorectal screening? *J Gen Intern Med* 2010; 25: 688-693
32 Swain P. The future of wireless capsule endoscopy. *World J Gastroenterol* 2008; 14: 4142-4145
33 Pohl J, Aschmeini I, Schuhmann S, Ell C. Computed image modification for enhancement of small-bowel surface structures at video capsule endoscopy. *Endoscopy* 2010; 42: 490-492
34 Li H, Yan G, Ma G. An active endoscopic robot based on wireless power transmission and electromagnetic localization. *Int J Med Robot* 2008; 4: 355-367

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