

Is PillCam COLON Capsule Endoscopy Ready for Colorectal Cancer Screening? A Prospective Feasibility Study in a Community Gastroenterology Practice

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- OBJECTIVES:** Colorectal cancer (CRC) screening with colonoscopy was introduced into the National Cancer Prevention Program in Germany in 2002. As compliance for screening is low (around 3% per year), colon capsule endoscopy (CCE) could be an alternative approach. In this study, feasibility and performance of CCE were evaluated in comparison with colonoscopy in ambulatory patients with special attention to a short colon transit time.
- METHODS:** CCE was prospectively tested in ambulatory patients enrolled for colonoscopy who presented for screening or with positive fecal occult blood test. Study subjects underwent colon preparation and ingested the capsule in the morning. Colonoscopy was performed after excretion of the capsule. Colonoscopy and CCE were performed by independent physicians who were blinded to the results.
- RESULTS:** In total, 38 patients were included. One patient was excluded because the capsule remained in the stomach during the entire period of examination. Another patient had limited time and the procedure had to be stopped when the capsule was still in the transverse colon. We therefore report the results of 36 patients (30 men and 6 women; mean age 56 years, range 23–73 years) who successfully completed CCE and the conventional colonoscopy examination. The capsule was excreted within 6 h in 84% of the patients (median transit time 4.5 h). If oral sodium phosphate was excluded from the preparation, the colon transit time increased to a median of 8.25 h. In total, 7 of 11 small polyps (<6 mm) detected by colonoscopy were identified by CCE. One small polyp detected by CCE was not identified by colonoscopy. In this series, no large polyps were found. One CRC was detected by both methods. The mean rates of colon cleanliness (range from 1 = excellent to 4 = poor) in the cecum (2.1), transverse colon (1.6), and in the descending colon (1.5) were significantly better than in the rectosigmoid colon (2.6), and the overall mean rate during colonoscopy was significantly better than during CCE. No adverse effects occurred.
- CONCLUSIONS:** CCE appears to be a promising new modality for colonic evaluation and may increase compliance with CRC screening. To achieve a short colon transit time, sodium phosphate seems to be a necessary adjunct during preparation. The short transit time is a prerequisite to abandon the delay mode of the capsule. With an undelayed PillCam COLON capsule, a “pan-enteric” examination of the gastrointestinal tract would be possible. Further studies are needed to improve the cleanliness, especially in the rectum and to evaluate the method as a potential screening tool.

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INTRODUCTION

Germany is among the countries with the highest incidence (73/100,000 in men and 50/100,000 in women with 71,400 new cases per year) and mortality (30,000 deaths per year) of colorectal cancer (CRC) (1,2), which constitutes a major public health burden. Screening colonoscopy was introduced into the National Cancer Prevention Program in Germany in 2002 (ref. (3)). A first evaluation of screening colonoscopy showed high prevalence of colorectal neoplasia in Germany (4) and other countries (5,6). The prevalence of advanced neoplasia was higher in men than in women (4–6). Early diagnosis and treatment of adenomas and cancer reduce the disease-specific mortality (7,8). In Germany, screening colonoscopy is cost saving resulting from the prevention of CRC, which compensates for the costs of screening and surveillance (9). Despite its wide accessibility, screening colonoscopy is not fully accepted by the average German population, with a compliance rate of only 3% per year (10).

The PillCam COLON capsule endoscope (Given Imaging Ltd, Yoqneam, Israel) was developed as a safe, minimally invasive method to visualize the colon without requiring sedation. In two pilot studies from Israel (11) and Belgium (12), PillCam COLON capsule endoscopy (CCE) showed promising accuracy for the detection of significant lesions.

The primary objective of this study was to evaluate the feasibility of CCE for CRC screening in a community practice of gastroenterology. The procedure was aimed at shorter transit times as in most ambulatory practices same day CCE readings and colonoscopies are not practical. Secondary objectives were the efficacy of colon cleaning and the detection rate of colon neoplasia by CCE compared with colonoscopy.

METHODS

Patients

In this prospective study, eligible subjects between 18 and 75 years of age were considered if they were scheduled for screening colonoscopy and with positive fecal occult blood test (FOBT) without abdominal complaints between August 2007 and February 2008. In total, 52 individuals were asked to participate. In total, 14 patients refused to participate (10 women and 4 men) because of the extensive colon cleansing procedure and the long time they had to stay in the practice. Overall, 38 subjects were included in the study. The demographic data of the individuals are shown in **Table 1**.

A power calculation of the sensitivity, on the basis of the existing literature, was not performed as the number of capsules provided by Given Imaging Ltd was limited.

Exclusion criteria were dysphagia, congestive heart failure, renal insufficiency, known or suspected bowel obstruction, the presence of a cardiac pacemaker or other implanted electro-medical device, and pregnancy.

Colon preparation

The day before the examination all subjects had a light breakfast (just a toasted bread and coffee or tea without milk) and then began the required “clear-liquid diet.” Between 1200 and 1800 hours, they ingested 3 l of a polyethylene glycol solution (Endofalk; Falk Pharma Inc., Freiburg, Germany) and another 0.5 l of this solution between 0600 and 0700 hours on the day of the examination. They arrived at the practice at 0745 hours and orally ingested 20 mg of domperidone (Motilium; Altana Pharma Inc., Konstanz, Germany) and 15 min later the PillCam COLON capsule (Given Imaging Inc., Hamburg, Germany) with a cup of water. After capsule ingestion, patients were required to walk around for the following 2 h. This was introduced because the first two individuals were sitting during the whole procedure and in these patients the transit time of the capsule was prolonged to 12 and 9 h, respectively. Individuals came back at 1000 hours for a boost dose of 22 ml sodium phosphate solution (Fleet; Ferring Inc., Kiel, Germany) together with 0.5 l of water, only if the capsule had passed the stomach as assessed with real-time viewing monitor (Rapid Access Real Time Tablet PC; Given Imaging Inc.). In case the capsule was still present in the stomach, the subjects received 10 mg of metoclopramide (MCP-ratiopharm SF; Ratiopharm Inc., Ulm, Germany) intravenously. If the capsule was still in the small bowel at 1200 hours, a second boost of 22 ml Fleet together with 0.5 l of water was administered. The preparatory steps are summarized in **Table 2**.

To simplify the procedure, we also evaluated a preparation without Fleet. Five capsules were provided for this reason. This preparation is also summarized in **Table 2**.

Colon cleanliness was graded for each of the following colonic segments: cecum and ascending colon, transverse colon, descending colon, and rectosigmoid colon. A four-point-scale grading system from 1 to 4 (excellent, good, fair, and poor) was used.

CCE

The PillCam COLON capsule endoscope measures 11 mm×32 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 restarts 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. Interpretation of the data was performed 1 day after colonoscopy by two investigators (KF and US) who were blinded to the results. The selected reading speed was around 8–12 frames per second. Segmental unblinding of the colon was not performed because the evaluation of the capsule videos was performed after colonoscopy.

Table 1. Demographic data of 38 individuals undergoing CCE and colonoscopy

Patient no.	Age	Gender	Weight (kg)	Height (cm)	Bowel preparation (A with Fleet; B without Fleet)	Reason for referral
1	33	M	130	196	A	Familiar risk of CRC
2	54	M	90	188	A	Positive FOBT
3	61	M	78	178	A	Screening
4	73	M	88	178	A	Positive FOBT
5	47	M	88	185	A	Positive FOBT
6	60	M	84	178	A	Screening
7	63	M	87	185	A	Screening
8	46	M	100	190	A	Positive FOBT
9	67	M	70	160	A	Positive FOBT
10	63	F	68	164	A	Positive FOBT
11	67	M	88	180	A	Screening
12	23	M	70	183	A	Positive FOBT
13	60	M	92	185	A	Screening
14	54	M	75	173	A	Positive FOBT
15	63	M	72	178	A	Screening
16	42	M	97	183	A	Positive FOBT
17	51	M	66	175	A	Positive FOBT
18	49	M	86	183	A	Familiar risk of CRC
19	62	M	82	179	A	Screening
20	38	M	103	182	A	Positive FOBT
21	52	F	64	169	A	Screening
22	68	F	62	164	A	Screening
23	43	M	68	165	A	Positive FOBT
24	60	F	79	159	A	Screening
25	62	M	115	176	A	Screening
26	60	M	90	178	A	Screening
27	63	F	79	168	A	Screening
28	62	F	80	180	A	Positive FOBT
29	58	M	60	177	A	Positive FOBT
30	49	M	75	175	A	Positive FOBT
31	66	M	78	173	A	Screening
32	66	M	97	180	A	Positive FOBT
33	64	M	84	178	A	Screening
34	62	M	76	176	B	Screening
35	53	M	74	182	B	Positive FOBT
36	64	M	87	175	B	Screening
37	64	W	95	158	B	Screening
38	66	M	85	175	B	Screening

CCE, colon capsule endoscopy; CRC, colorectal cancer; FOBT, fecal occult blood test.

Table 2. The PillCam Colon preparation and procedure regimen with and without Fleet

Time	Action	
	With Fleet	Without Fleet
Per day on all days at 1200–1800 hours	Clear liquid diet after a light breakfast and 3l Endofalk	
Examination day		
0600–0700 hours	0.5l Endofalk	0.5l Endofalk
0745 hours	20mg Motilium	20mg Motilium
0800 hours	PillCam COLON ingestion; walking for 2 h	PillCam COLON ingestion; walking for 2 h
1000 hours (boost no. 1) ^a	22ml Fleet+0.5l water	0.5l Endofalk
1200 hours (boost no. 2) ^b	22ml Fleet+0.5l water	
1430 hours	End of the procedure. Conventional colonoscopy was performed immediately after excretion of the capsule or at the latest at 1430 hours	

^aBoost 1 was administered only if the capsule has passed the stomach. If the capsule was delayed in the stomach as detected with real-time monitoring, the subjects received 10mg of metoclopramide (MCP-ratiopharm SF; Ratiopharm Inc., Ulm, Germany) intravenously and the procedure was continued after the capsule moved into the small intestine. ^bBoost 2 was administered only if the capsule was delayed in the small intestine at that time.

The location of polyps within the colon was determined with the help of the rapid localization feature. Eight electrodes were fixed on the abdomen of the individuals and connected with the recorder. Polyps were classified with respect to size (larger or equal to 6 mm or smaller), morphology (pedunculated, sessile, and flat), and colon segment location.

However, the estimation of the exact size of polyps is difficult. Interestingly, the size of polyps estimated by CCE did not differ significantly from that found by colonoscopy. All polyps were recorded as positive findings. Significant findings were defined as polyps larger than 6 mm and carcinomas. Other findings such as diverticuli, angiomas, proctitis, or hemorrhoids were noted but not considered as significant findings.

The excretion of the capsule was verified by peranal excretion.

Colonoscopy

All colonoscopies were performed by one experienced colonoscopist (AS) under conscious sedation with propofol (Propofol; Fesenius-Kabi Inc., Bad Homburg, Germany) administered by the endoscopy team (11). The colonoscopy began after excretion of the capsule or at the latest by 1430 hours. The capsule was not removed by the colonoscope and the recording of the CCE was continued until it was excreted or the battery was

exhausted. Digital pictures were recorded from each examination. Polyps seen at the time of conventional colonoscopy were recorded by size, location, and morphology, and were then removed.

The Mann–Whitney *U*-test was used for statistical comparison of the cleanliness of the different colon segments and for the comparison of the quality of cleaning at CCE and colonoscopy. Because of the small number of patients prepared without Fleet, no comparison was possible concerning the cleanliness of colon segments or total transition time.

RESULTS

Patients

From August 2007 until February 2008, 38 patients agreed to participate in the study, all of them were able to swallow the capsule without complaints. In one female patient (63 years), the capsule remained in the stomach for the entire examination time. The capsule was excreted in the morning after the examination. In one male subject (61 years) the recorder was disconnected after 6 h as he was limited in time. The capsule was present in the transverse colon at that moment. There was no technical capsule failure or failure of data transmission. We therefore report the results of 36 patients (30 men and 6 women; mean age 56 years, range 23–73 years) who successfully completed CCE and the conventional colonoscopy examination. Complete colonoscopy until the cecum was achieved in all cases.

Propulsion of the PillCam COLON capsule

If Fleet was used for colon preparation as indicated in **Table 2**, the mean total transit time was 4.6 ± 1.9 h (median 4.5 h) and the mean time the capsule remained in the colon (colon transit time) was 96 ± 66 min (median 72 min) (**Table 3**). With this regimen, 84% of the capsules were excreted 6 h after ingestion.

In four patients, Fleet was omitted from the preparation procedure (**Table 2**) and replaced by 0.5l of Endofalk. The mean total transit time in four subjects was 8.3 ± 1.6 h (range 6.5–10 h, median 8.3 h) and the colon transit time was 303 ± 134 min (mean 320 min) (**Table 3**). In no individual, was the capsule excreted within 6 h after ingestion.

Colon cleanliness

On the basis of the four-point-scale grading system (excellent, good, fair, and poor = 1–4), we found that colon cleanliness was between 1.5 and 2.6 (mean) in the different segments of the colon (**Table 3**). Compared with the rectosigmoid colon, the cleanliness of the proximal colon segments was significantly better. The rectum could not be adequately evaluated in 6 of the 38 patients. When Fleet was omitted from the preparation procedure, the colon was graded cleaner in the different segments (mean range 1.2–2.0). However, statistical comparison was not possible due to the small number of individuals (**Table 4**). The quality of colon cleanliness as assessed during

Table 3. Propulsion of the PillCam Colon capsule after preparation with and without Fleet as indicated in Table 2

	With Fleet	Without Fleet
<i>N</i>	32	4
Total transit time (h) mean±s.d.	4.6±1.9	8.3±1.6
Median	4.5	8.3
Range	2.5–12	6.5–10
Colon transit time (min) mean±s.d.	96±66	303±134
Median	72	320
Range	10–240	150–420
Percentage of capsules excreted within 6 h	84	0

Table 4. Colon cleanliness based on the four-point-scale system after preparation with and without Fleet

	With Fleet		Without Fleet
	Mean grading	<i>P</i> vs. rectosigmoid	Mean grading
<i>N</i>	32		4
Cecum/ascending colon	2.1	0.02	1.8
Transverse colon	1.6	<0.001	1.2
Descending colon	1.5	<0.001	1.5
Rectosigmoid colon	2.6		2.0

1, excellent; 2, good; 3, fair; 4, poor.

Table 5. Comparison of colon cleanliness as assessed at CCE and colonoscopy based up the four-point-scale system after preparation with Fleet in 32 patients

	CCE	Colonoscopy	<i>P</i>
Mean	1.9	1.2	<0.001
s.d.	0.6	0.4	

CCE, colon capsule endoscopy.
1, excellent; 2, good; 3, fair; 4, poor.

colonoscopy (1.2 ± 0.4) was significantly better than during CCE (overall cleanliness 1.9 ± 0.6) (Table 5).

CCE findings

In our series of 36 individuals, we detected only one significant lesion, a carcinoma in the transverse colon that was identified by CCE and colonoscopy (Figures 1 and 2). The carcinoma showed a villous-like surface and the capsule was retained at this place for 20 min because of spastic contraction of the colon wall. Polyps <6 mm were found in 12 subjects by either of the methods, 7 by CCE and 11 by colonoscopy. One small

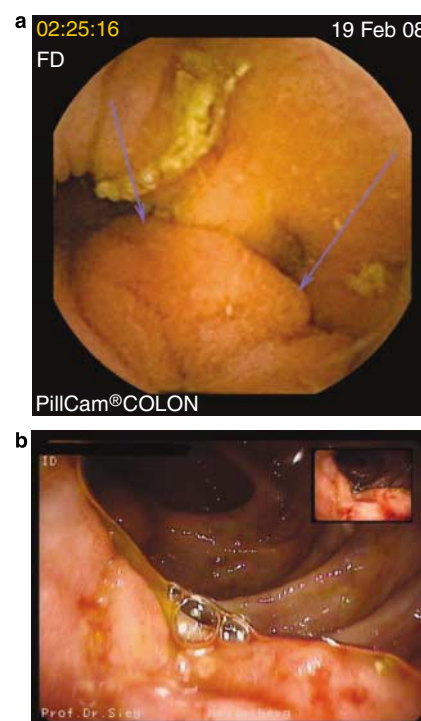


Figure 1. Carcinoma of the transverse colon. (a) Pillcam COLON capsule image. The carcinoma in the lower part of this figure showed a villous-like surface and the capsule was retained at this place for about 20 min because of spastic contraction. (b) Colonoscopy image. The carcinoma in the lower part was verified by biopsies.

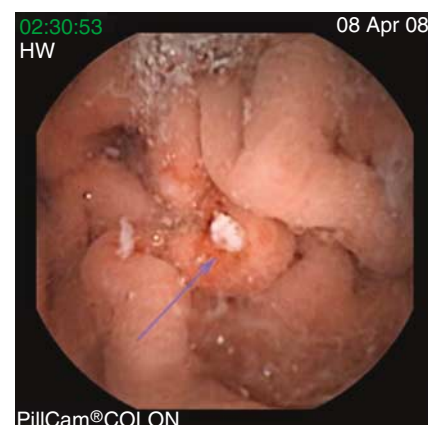


Figure 2. Pillcam COLON capsule image: gastric ulcer.

polyp was detected by CCE and colonoscopy was negative. Diverticuli were found in 10 subjects by CCE and in 9 subjects by colonoscopy. In one subject scheduled for colonoscopy because of positive FOBT, we suspected a gastric ulcer by CCE (Figure 2). This 64-year old man was on 100 mg of aspirin and agreed to a supplemental gastroscopy, where a *Helicobacter pylori*-negative ulcer was verified. The Z-line was visualized in 17 of 38 CCE examinations. The reason for the low visu-

alization rate was partly a fast movement of the capsule in the esophagus and partly too much foamy or clear fluid in the lower part of the esophagus at the time of the examination. In most instances, only one or two frames showing the Z-line were captured during CCE.

Adverse effects

No capsule endoscopy-related or conventional colonoscopy adverse effects were reported.

DISCUSSION

This is the first study showing the feasibility of the PillCam CCE in comparison with conventional colonoscopy in a routine and screening setting of a practice of gastroenterology. Although we detected only one significant lesion by both methods, the sensitivity toward small polyps is similar to both of the first feasibility studies in Israel (12) and Belgium (13). The capsule provides good-quality pictures of the entire colon with the exception of the rectum in a considerable number of individuals. This may constitute a significant limitation of the method for this minority of patients, as most of the colorectal neoplasms are present in the rectum. However, most of the findings seen at colonoscopy were detected by CCE. The two imagers of the capsule are an important feature, as some of the findings were detected only on one side of the recorder. Unfortunately, in our series of individuals no large polyps were detected by both the methods, although this is the primary goal of CRC screening. In only 45% of the CCE examinations, the Z-line was visualized. This was not the primary goal of our study and it seems that screening for Barrett's cannot be performed with the PillCam COLON capsule. The reasons for non-visualization of the Z-line were too fast movement of the capsule and too much foamy or clear fluid at the Z-line. Visualization of the Z-line may be improved by reducing the amount of fluid that the patients swallow together with the capsule.

We considered conventional colonoscopy to be the gold standard for the detection of colonic neoplasms. However, studies featuring tandem colonoscopies showed a miss rate of small polyps between 11 and 27% and a miss rate of large polyps ≥ 10 mm between 2 and 6% (14–18). This is comparable to virtual colonography with sensitivities for large polyps between 85 and 94% (19–22). Compared with computed tomographic virtual colonography performed in expert radiological centers, conventional colonoscopy was even found to be less sensitive for adenomatous polyps (19). On the other hand, meta-analysis on computed tomographic virtual colonography showed a sensitivity for small (< 6 mm) polyps of 70–86% (20,21). Unfortunately, we found no large polyps in our study. A sensitivity of CCE for large polyps of 70–77% was reported (12,13). It seems therefore that the sensitivity of CCE for advanced neoplasia is lower compared with virtual colonography.

The colon preparation was adapted to clean the colon and in the same time to facilitate the progression of the capsule with

one or two boosts of sodium phosphate. With our preparation, the capsule was excreted within 6 h by the majority of patients (84%). This proves that CCE can be performed in ambulatory patients and colonoscopy can be performed on the same day after evaluation of the data. With this kind of preparation, the pre-programmed delay mode may be unnecessary. One gastric ulcer was detected with the PillCam COLON. Duodenal and part of the gastric ulcers would have been missed with a capsule switching into sleep after 3 min. We also detected the Z-line in a considerable number of individuals. Therefore, with an undelayed PillCam COLON capsule a “pan-enteric” examination of the gastrointestinal tract would be possible.

The cleanliness from the cecum until the descending colon was good to excellent, even under conditions of a routine setting. Only the rectosigmoid colon was less clean mainly because of the large amount of green-coloured fluid being stored before excretion. Further studies are needed to improve the preparation regimen aiming for less volume and more propulsion. Colon cleanliness as assessed during colonoscopy was significantly better compared with CCE. This is caused by an extensive bowel preparation procedure after which we find only clear fluid inside the colon, which can be easily removed at colonoscopy.

In five patients, we omitted sodium phosphate to simplify the procedure. The cleanliness of the colon was even better with this regimen. However, the propulsion of the capsule was not satisfactory resulting in a doubled mean transit time. This means that colonoscopy cannot be performed on the same day in a practice of gastroenterology with this procedure.

Although this is a prospective study with blinding of the investigators to the capsule endoscopy and conventional colonoscopy results, there are, however, limitations to this study. This is only a single-center study and we did not find large polyps, which constitute the primary goal of CRC screening. Moreover, we did not compare CCE with alternative screening methods such as virtual colonography.

Despite these limitations, we consider this to be interesting findings as CCE was performed under conditions of a routine setting in a practice of gastroenterology. The time frame of CCE with this preparation allows colonoscopy on the same day. In addition, a multicenter trial using this method is currently being held. Under these conditions, CRC screening can be performed in patients able to drink a sufficient amount of polyethylene glycol solution. It is conceivable that patients perform CCE at home and bring back the recorder after excretion of the capsule (home examination). Hopefully, this method will expand the portfolio of screening methods available for the patient unwilling or unable to undergo conventional colonoscopy (23), although it may not be feasible for mass screening in high-volume centers. Interestingly, the majority of our patients were men who were predominantly interested in this new technology. Men show less compliance with CRC screening but are at higher risk for colorectal neoplasia (4,6). Obviously in this “high-risk” group of patients, CCE can raise the interest for CRC screening.

CONFLICT OF INTEREST

Guarantor of the article: Andreas Sieg, MD, PhD.

Specific author contributions: performed the colonoscopies and wrote the paper: Andreas Sieg; evaluation of the capsule colonoscopies, help in collecting the data and revision of the paper: Kilian Friedrich and Ulla Sieg.

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Potential competing interests: None.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Capsule colonoscopy (CCE) for CRC screening is feasible and safe with acceptable quality of cleansing.

WHAT IS NEW HERE

- ✓ CCE is also feasible in a gastroenterological practice setting.
- ✓ With an undelayed capsule, “pan-enteric” examination of the GI tract is possible.
- ✓ CCE may increase compliance among men for screening.

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