

Capsule Endoscopy for Colorectal Cancer Screening

An Evidence-Based Analysis

*Presented to the Ontario Health Technology
Advisory Committee in August, 2008*

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List of Abbreviations

AUC	Area under the curve
CI	Confidence interval(s)
IY	Incremental yield
MAS	Medical Advisory Secretariat
NPV	Negative predictive value
OR	Odds ratio
OHTAC	Ontario Health Technology Advisory Committee
PillCam ESO	PillCam for esophagus
PillCam SB	PillCam for small bowel
PPV	Positive predictive value
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
SROC	Summary receiver operating characteristic

Glossary

Average risk for colorectal cancer	The risk of developing colon cancer among people 50 years of age and older who do not have any other risk factor for colorectal cancer
Cecum	The proximal section of the colon
Neoplasia	Abnormal growth of cells that may be benign or malignant
Segmental unblinding	A technique used in virtual colonoscopy studies for cases of discrepancy between the results of CT colonography and colonoscopy. In the technique, findings of CT colonography are revealed to the endoscopist after initial examination of each colonic segment. If a lesion is found through CT colonography but not at the initial colonoscopy, the endoscopist re-examines that segment to see whether the CT colonography finding is a true or false positive result.
Sigmoid colon	The distal section of the colon
Virtual colonoscopy	A method used to detect colorectal cancers and polyps using CT or MR colonography

Background

The colorectal cancer (CRC) screening project was undertaken by the Medical Advisory Secretariat (MAS) in collaboration with the Cancer Care Ontario (CCO).

In November 2007, the Ontario Health Technology Advisory Committee (OHTAC) MAS to conduct an evidence-based analysis of the available data with respect to colorectal cancer diagnosis and prevention. The general purpose of the project was to investigate the effectiveness, cost effectiveness, and safety of the various methods and techniques used for colorectal cancer screening in average risk people, 50 years of age and older.

The options currently offered for colorectal cancer screening were reviewed and five technologies were selected for review:

- Computed tomographic (CT) colonography
- Magnetic resonance (MR) colonography
- Wireless capsule endoscopy (PillCam Colon)
- Fecal occult blood test (FOBT)
- Flexible sigmoidoscopy

In this review, colonoscopy was considered as the “gold standard” technique by which the effectiveness of all other modalities could be evaluated. An economic analysis was also conducted to determine cost-effectiveness of different screening modalities.

Evidence-based analyses have been prepared for each of these technologies, as well as summary document that includes an economic analysis, all of which are presented at the MAS Web site: http://www.health.gov.on.ca/english/providers/program/mas/tech/tech_mn.html

Objective

The aim of this review was to determine the effectiveness and safety of capsule endoscopy in the identification of cancers and adenomatous polyps in the colon and rectum of average risk people, 50 years of age and older, in the context of colorectal cancer (CRC) screening.

Colorectal Cancer Screening

The objective of CRC screening is to reduce the burden of CRC and thereby the morbidity and mortality rate of the disease. It is believed that this goal can be achieved by regularly screening the average-risk population, enabling the detection of cancer at early, curable stages, and polyps before they become cancerous. Several methods of CRC screening have been proposed by various organizations, each with their own advantages and disadvantages. There is no single infallible technique for detection and thus there is an ongoing need for improvement of screening methods. However, as with other screening tests, an effective screening technique for CRC should, at a minimum, be feasible, accurate, safe, acceptable, and cost-effective.

Existing techniques for CRC screening generally fall into the following three categories:

Endoscopic techniques:

- Optical colonoscopy
- Flexible sigmoidoscopy (FS)

Stool-based techniques:

- Fecal occult blood test (FOBT)
- Fecal Immunochemical Test (FIT)
- Fecal DNA testing

Imaging techniques:

- Virtual colonoscopy techniques using:
 - a) Computed tomographic colonography (CT colonography)
 - b) Magnetic resonance colonography (MR colonography)
- Wireless capsule endoscopy (PillCam Colon)
- Double-contrast barium enema (DCBE)

Optical Colonoscopy

Optical colonoscopy is currently considered the gold standard for detection of colorectal neoplasia, providing visualization of the interior lining of the colon from anus to cecum and allowing for a high rate of detection of potentially curable CRCs and precancerous adenomatous polyps. The advantage of colonoscopy is that it enables detection, biopsy, and removal of identified lesions in a single, convenient session. In addition, the longer interval between screening colonoscopy (10 years) enables a reduction in cost compared to other methods.

The drawback of the technique is that it is invasive and is associated with clinically important complications such as bleeding and/or perforation, but the likelihood of these risks are small and they are more commonly associated with polypectomy and/or biopsy. (1) The risk of perforation is higher in the presence of conditions such as active colitis, inflammation, diverticular or ischemic disease, and prior irradiation. Although colonoscopy is not routinely indicated for patients with inflammatory bowel disease, it may be indicated for patients with ulcerative colitis of more than 10 years' duration because of an increased risk of carcinoma.

In a study conducted among the United States' Medicare population, the risk of colonic perforation following screening colonoscopy and sigmoidoscopy was shown to be approximately 1.3/1,000. A separate Swedish study (3) involving 6,066 diagnostic and therapeutic colonoscopies, showed that bleeding and perforation occurred in 0.2% and 0.1% of patients, respectively, with no colonoscopy related mortality. It should also be noted that colonoscopy does fail to reach the cecum in 5% to 10% of average-risk people due a variety of reasons such as tortuosity or malrotation of the loops, bowel spasm, diverticulitis or diverticulosis, ischemic colitis, colonic configuration from previous surgery, obstructive tumors, external compression from masses or hernia. (4)

Capsule Endoscopy

Capsule endoscopy is a new technology that has been introduced into clinical practice for the diagnosis of gastrointestinal diseases. As of December 2008, three different capsule types (PillCam devices) have been developed for the exploration of the small bowel (PillCam SB), the esophagus (PillCam ESO), and the colon (PillCam Colon). The latter is a major advance in visualization of the entire colon. The technology has the potential to be used as a CRC screening modality as the examination is minimally invasive, painless, and does not require administration of sedation. Patients can, therefore, continue their normal daily activities immediately following the procedure. This could lead to greater compliance rates relative to more invasive procedures. Clinical trials are under way to provide sufficient evidence for the diagnostic performance of PillCam Colon compared with conventional colonoscopy and virtual colonoscopy.

The PillCam Colon (manufactured by Given Imaging Ltd., Yoqneam, Israel) device itself is a swallowable capsule measuring 11 mm × 31 mm – roughly the size of a vitamin pill. After being swallowed, the capsule navigates the digestive tract and a tiny camera contained at each end of the capsule captures four images of the colon per second for a total of 144,000 coloured images in a typical procedure. The images are transmitted via sensors secured to the patient’s abdomen to a data recorder. With the help of special software, this data and images are later downloaded by the physician for interpretation. Within 10 hours, most patients then excrete the capsule, which is then discarded.

Table 1 lists the 3 commercially available PillCam devices produced by Given Imaging and their current licensing statuses.

Table 1: Licensing Status of PillCam Devices

Product	Approval by Health Canada	Approval by FDA	Size (mm)
PillCam SB	2001	2001	11 × 26
PillCam ESO	2004	2004	11 × 26
PillCam Colon	2007	Pending	11 × 31

ESO indicates esophagus; FDA, United States Food and Drug Administration; SB, small bowel.

Evidence-Based Analysis of Effectiveness

Research Questions

1. What is the accuracy of capsule endoscopy in the detection of CRCs and polyps in individuals 50 years of age and older, compared with the gold standard of optical colonoscopy?
2. How safe is the capsule endoscopy procedure?

Methods

Outcome Measures

- Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of capsule endoscopy for detection of colorectal cancers and polyps compared with the reference standard colonoscopy
- Incremental yield (IY) (yield of capsule endoscopy minus yield of colonoscopy) and 95% confidence interval for detection of colorectal cancers and polyps

Inclusion Criteria

- Prospective studies comparing accuracy of capsule endoscopy with optical colonoscopy in detection of colorectal cancers and polyps

Exclusion Criteria

- Retrospective studies
- Studies of areas other than the colon
- Studies addressing other diseases of the colon
- Studies addressing technical, educational, or other aspects
- Studies that did not report accuracy data

Method of Review

Studies meeting inclusion criteria were selected from the database of search results. Data on the study characteristics, patient characteristics, primary and secondary outcomes, and adverse events were abstracted.

Statistical Methods

A meta-analysis of diagnostic yield using Review Manager (RevMan 4.1) software was performed. The incremental yield (IY) was calculated by subtracting the yield of colonoscopy from that of PillCam Colon, and a 95% CI was determined. A fixed-effect model was applied if there was no heterogeneity, and a random effect model (DerSimonian-Laird) was applied if there was heterogeneity in reported sensitivities between the studies.

Results of Literature Search

A search of electronic databases (OVID MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, The Cochrane Library, and the International Agency for Health Technology Assessment) was undertaken to identify evidence published from January 1, 2003, to October 11, 2008. The search was limited to English-language articles and human studies. The search strategy is detailed in Appendix 1. The literature search identified 507 citations, of which two met the inclusion criteria (see Table 2). The search was updated in July 28, 2008. An additional 115 citations were identified, from which none was a newly published study meeting the inclusion criteria.

Table 2: Quality of Evidence of Included Studies

Study Design	Evidence Level	Number of Eligible Studies
Large RCT, systematic review of RCTs	1	0
Large RCT unpublished but reported to an international scientific meeting	1(g)	0
Small RCT	2	0
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls*	3a	2
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modeling	4d	0
Case series presented at international conference	4(g)	0

RCT refers to randomized controlled trial; g, grey literature.

*Each individual was to serve as his or her own control.

Results of Evidence-Based Analysis

Performance

Two studies (5;6) compared the performance of PillCam Colon with conventional colonoscopy for the diagnosis of colorectal polyps and cancer (summarized in Table 3). Both studies employed a double-blind design without segmental unblinding.

The study by Eliakim et al. was a multicentre trial that prospectively tested the diagnostic performance of PillCam Colon. The authors also tested the use of a novel colon-preparation regimen to clean the colon, improve the movement of the capsule through the colon, and provide clearer images. Study subjects ingested the PillCam Colon capsule on the morning of the examination and conventional colonoscopy was performed on the same day following excretion of the capsule or by the end of the day, whichever came first. Physicians performing the colonoscopy were blinded to the results of those working from the imaging results recorded by capsule endoscopy and vice versa. All conventional colonoscopies were recorded on videotape.

The capsule images were initially reviewed by the principal investigators. A second review was performed by an external review service and the results of the two readings were used as a basis for a third evaluation by an expert panel consisting of three investigators. If a colonic lesion was identified by the capsule, but the colonoscopy did not identify any significant findings, the expert panel decided acted to make a final decision.

Eighty-four patients completed both the capsule and colonoscopy procedures. One patient was unable to swallow the capsule, two failed to adhere to the procedural guidelines, and in one patient the capsule remained in the stomach for the entire examination time. Technical failure occurred in three cases. Seventy-three percent of patients completing the study were over the age of 50.

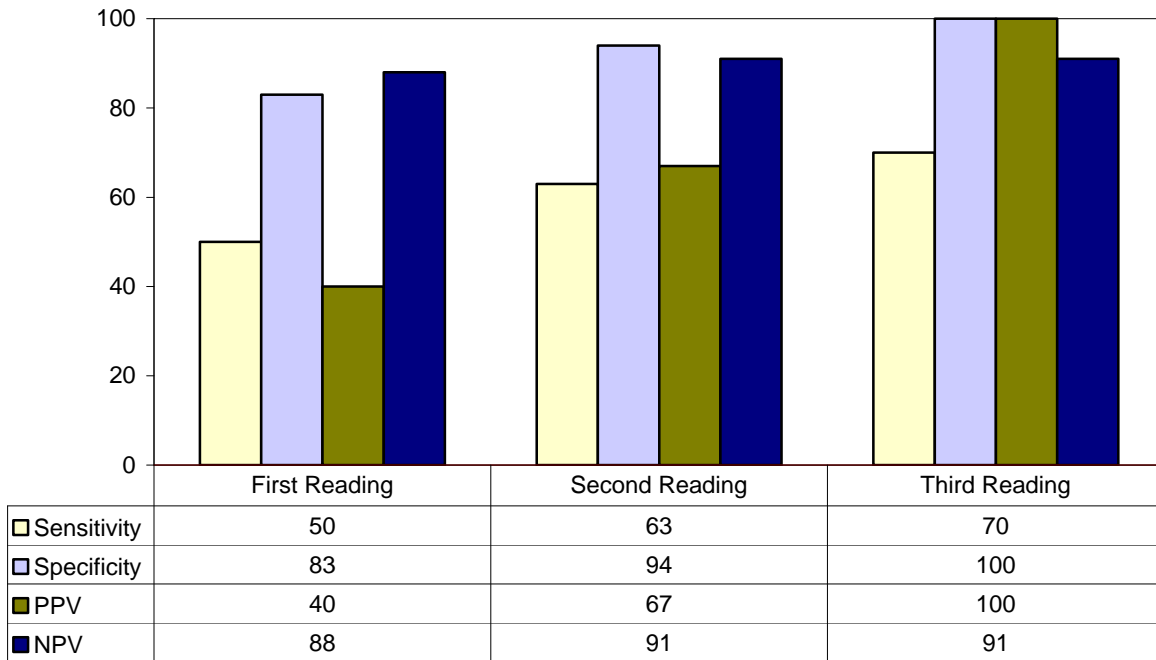
Forty-five patients were found by either method to have a polyp of 'any size', among which 20 patients had a significant polyp (predefined as at least one polyp larger than 6 mm, or at least three polyps of any size). PillCam Colon and conventional colonoscopy identified significant polyps in 14 patients (70%) and 16 patients (80%), respectively, and polyps of any size in 34 (76%) and 36 patients (80%), respectively.

The performance of the capsule for the detection of any polyp and significant polyps improved with the second and third readings. Figures 1 and 2 display the diagnostic performance of the PillCam Colon versus conventional colonoscopy for the detection of significant polyps (Figure 1) and any polyps (Figure 2). Conventional colonoscopy did not initially identify any polyp in four cases in which the PillCam Colon showed positive findings. These cases were counted as false positives for PillCam Colon. However, when patients underwent repeat colonoscopy, the capsule findings were confirmed in 3 of 4 cases. In two cases, repeat colonoscopy identified polyps seen by the capsule (5 mm and 8 mm in size). In the third case, the repeat colonoscopy identified one of the three polyps seen by PillCam colon. This polyp was less than 6 mm in size. In the fourth case, repeat colonoscopy failed to identify a 6–9 mm polyp seen using the PillCam Colon.

The propulsion of the PillCam Colon capsule was then compared in patients who received a single booster dose (n=44) versus those who received a double booster dose (n=46) of oral sodium phosphate in their colon-preparation regimen. The capsule was excreted within 10 hours in 70% of the patients who received a single dose and in 78% of those who received a second dose. In the second group, however, all the capsules remaining in the colon were in the sigmoid and rectum (see Figure 3).

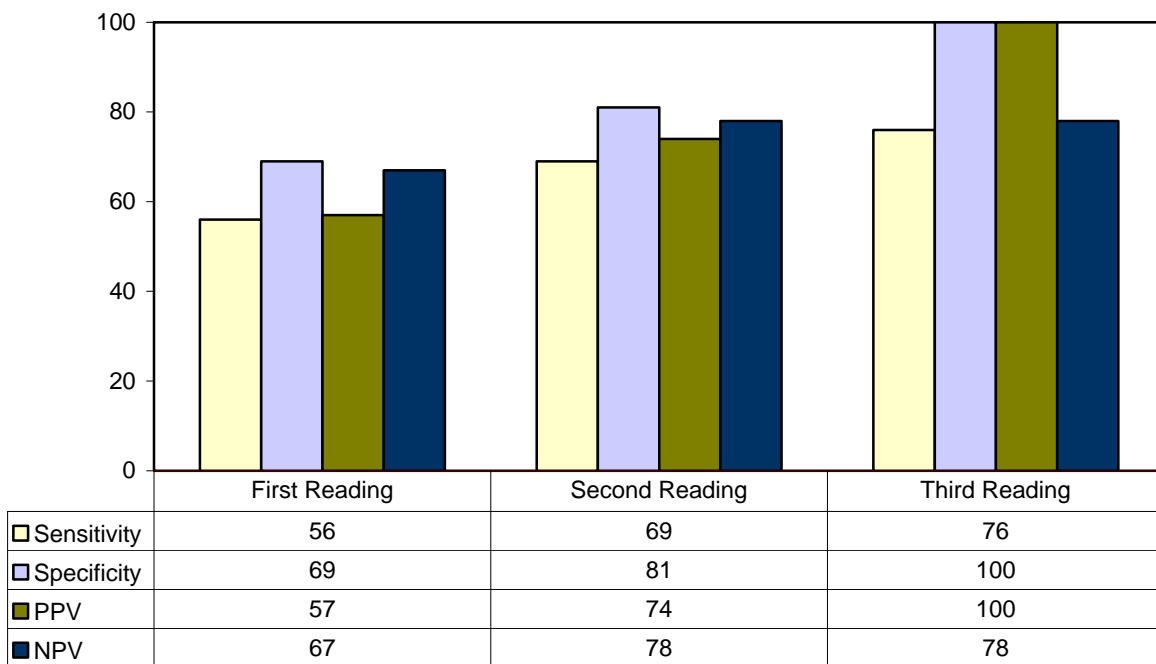
Table 3: Characteristics of Studies on PillCam Colon

Study	Country	Patients Included (Evaluated)	Age Mean, SD (Range)	Inclusion Criteria	Exclusion Criteria
Eliakim et al. 2006, (5) Multicentre	Israel	91 (84) Male: 55 Female: 36	57±11 (26–75)	<ul style="list-style-type: none"> ▪ CRC screening 43% ▪ Post-polypectomy surveillance 26% ▪ Rectal bleeding 14% ▪ Iron deficiency anemia 8% ▪ Other reasons 9% 	<ul style="list-style-type: none"> ▪ Age <18 years ▪ Dysphagia (difficulty in swallowing) ▪ Known/suspected bowel obstruction ▪ Implanted electromedical devices ▪ Pregnancy ▪ Patients expecting to do an MRI within 7 days ▪ Contraindication for use of bowel preparation agents ▪ Allergy to rectal suppositories used in this study ▪ Patients at high risk for capsule retention
Schoofs et al. 2006, (6) Single centre	Belgium	41 (36)	56 (26–75)	<ul style="list-style-type: none"> ▪ Patients scheduled for screening colonoscopy 41% ▪ Abdominal symptoms (pain, rectal bleeding, and altered bowel transit time) 59% 	<ul style="list-style-type: none"> ▪ Age <18 years ▪ Dysphagia ▪ Congestive heart failure ▪ Renal insufficiency ▪ Intestinal obstruction ▪ Implanted electromagnetic devices ▪ Pregnancy ▪ Abdominal surgery in the past 6 months ▪ Inability to understand patient information/consent ▪ Presence of a life-threatening condition ▪ Current participation in another clinical study



NPV indicates negative predictive value; PPV, positive predictive value.

Figure 1: Performance of PillCam Colon vs. Colonoscopy for Detection of Significant Polyps



NPV indicates negative predictive value; PPV, positive predictive value.

Figure 2: Performance of PillCam Colon vs. Colonoscopy for Detection of 'Any Polyps'

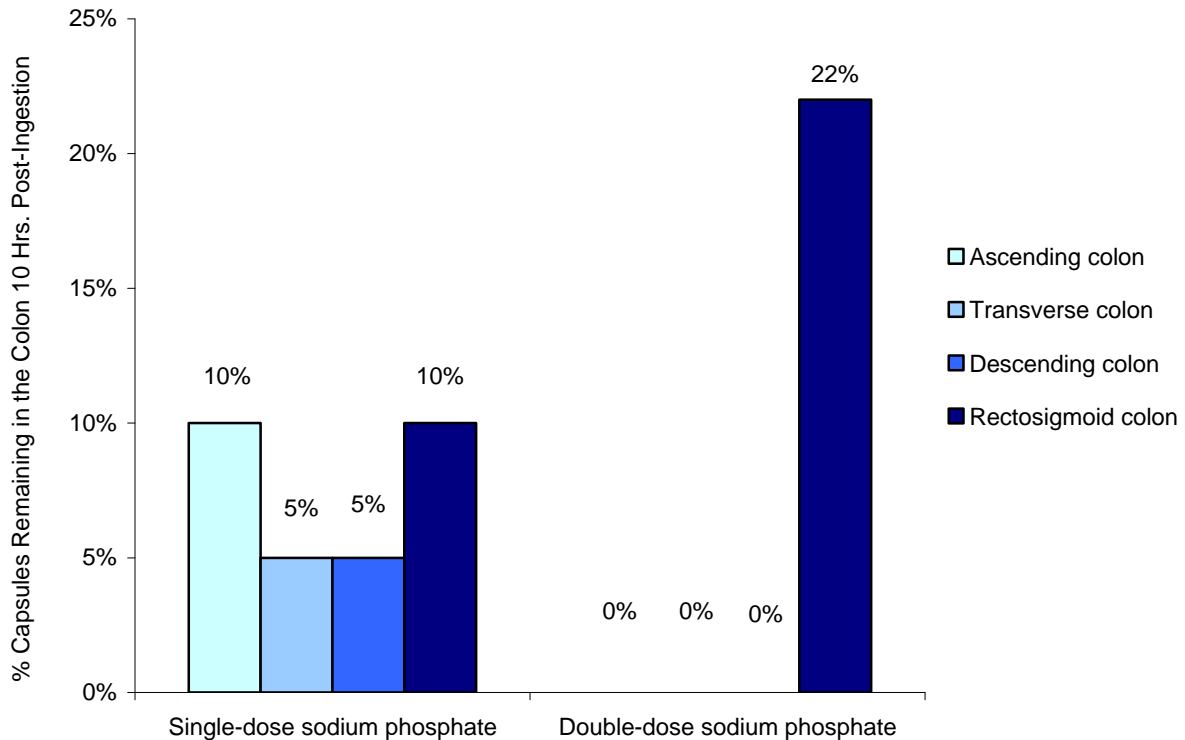


Figure 3: PillCam Capsule Propulsion After 10 Hours: Single- vs. Double-Dose Sodium Phosphate

Schoofs et al. (6) reported the results of a pilot study of the safety, feasibility, and performance of the PillCam Colon compared with conventional colonoscopy (the study characteristics are summarized in Table 3). Patients underwent conventional colonoscopy by an experienced colonoscopist on the same day after the expulsion of the capsule or when the battery was exhausted. All colonoscopy examinations were recorded on videotape, and all the polyp characteristics were entered into a case report form. The physician who performed the capsule study and the colonoscopist were blinded to each other’s findings.

All polyps at any size were considered positive findings. In the case of a positive finding by capsule and negative finding by colonoscopy, no repeat colonoscopy was performed to confirm the capsule finding. Polyps larger than 6 mm and/or at least three polyps of any size, and/or a suspected tumor were considered as significant findings. All other lesions were noted but not considered in the analysis.

A total of 36 patients were included in the analysis. One patient could not swallow the capsule, while four were excluded due to technical problems. Capsule findings were positive in 23 patients and negative in 13 patients. Colonoscopy findings were positive in 25 patients and negative in 11 patients. The capsule did not identify polyps in six out of 25 patients with positive colonoscopy. Colonoscopy did not identify four out of 23 patients with positive findings by Pillcam Colon. For the detection of polyps larger than 6 mm, or at least three polyps of any size, the capsule did not identify three out of 13 polyps identified by colonoscopy. Colonoscopy did not identify seven out of 17 polyps identified by the capsule. The Per-patient sensitivity, specificity, PPV, and NPV of PillCam colon for detection of polyps compared with colonoscopy as the gold standard are summarized in Table 4.

Table 4: Performance of PillCam Colon vs. Colonoscopy for Polyp Detection

	Polyps >6 mm or ≥3 Polyps of Any Size, %	Polyps >6 mm, %	Any Polyp, %
Sensitivity	77	60	76
Specificity	70	73	64
PPV	59	46	83
NPV	84	83	54

ESO indicates esophagus; FDA, United States Food and Drug Administration; SB, small bowel.

In Schoofs et al., two reviewers interpreted the images of capsule endoscopy and the inter-observer agreement of significant lesions was calculated to be 80.5%. In six patients, the capsule was not expelled within 10 hours, while in four it was located in the recto-sigmoid colon and could be excreted within a few hours. Figures 4 and 5 display the pooled sensitivity and specificity, respectively, of the PillCam.

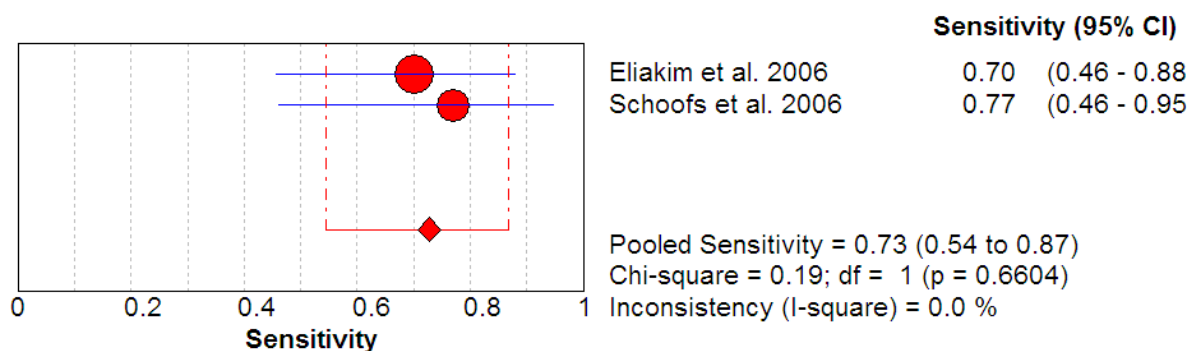


Figure 4: Pooled Sensitivity of PillCam Colon for Detection of Significant Polyps

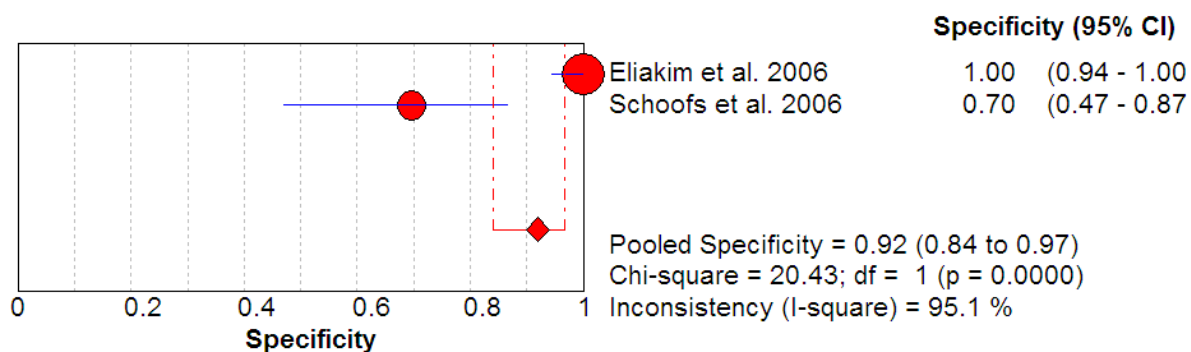


Figure 5: Pooled Specificity of PillCam Colon for Detection of Significant Polyps

Considering that no segmental unblinding¹ was performed to clarify positive PillCam findings with a negative colonoscopy, and that in the study by Eliakim et al. (5) several ostensibly false positive findings of PillCam Colon were in fact polyps missed by colonoscopy, we conducted a meta-analysis of the diagnostic yield of PillCam Colon and colonoscopy. The incremental yield (IY), defined as yield of PillCam Colon minus yield of colonoscopy, and 95% confidence interval were calculated using a fixed-effect model. No study heterogeneity was identified across the two studies. PillCam Colon had a 31% yield for detection of significant polyps compared with a 29% yield for colonoscopy with a IY of 0.05 (95% CI, -0.14 to 0.24, $P = .6$). For the detection of ‘any polyp’, PillCam colon had a 57% yield compared with 61% yield for colonoscopy [IY, -0.05 (95% CI, -0.18 to 0.07), $P = .4$] (see Figures 6 and 7).

Review: PillCam Colon
 Comparison:01 Yield of Capsule Endoscopy and Colonoscopy
 Outcome: 01 For Detection of Polyps >=6 mm or >=3 Polyps

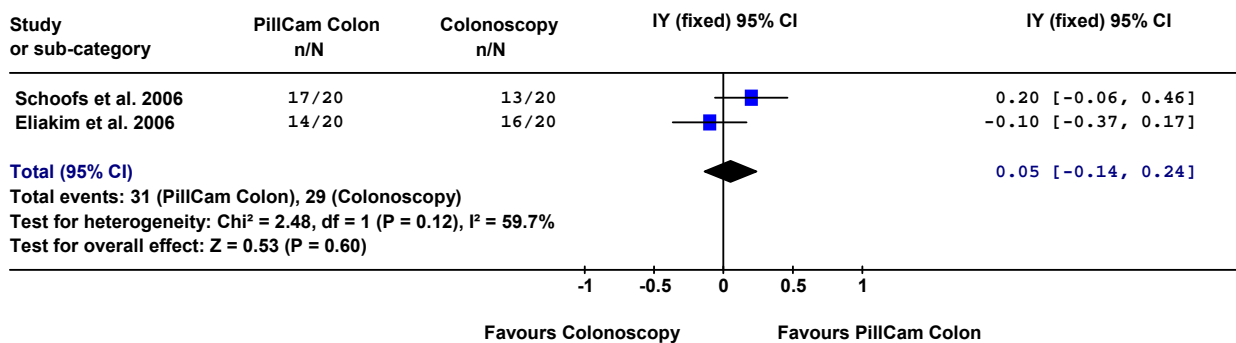


Figure 6: Yield of Capsule Endoscopy and Colonoscopy for the Detection of Significant Polyps

Review: PillCam Colon
 Comparison:01 Yield of Capsule Endoscopy and Colonoscopy
 Outcome: 02 For Detection of Polyp of any Size

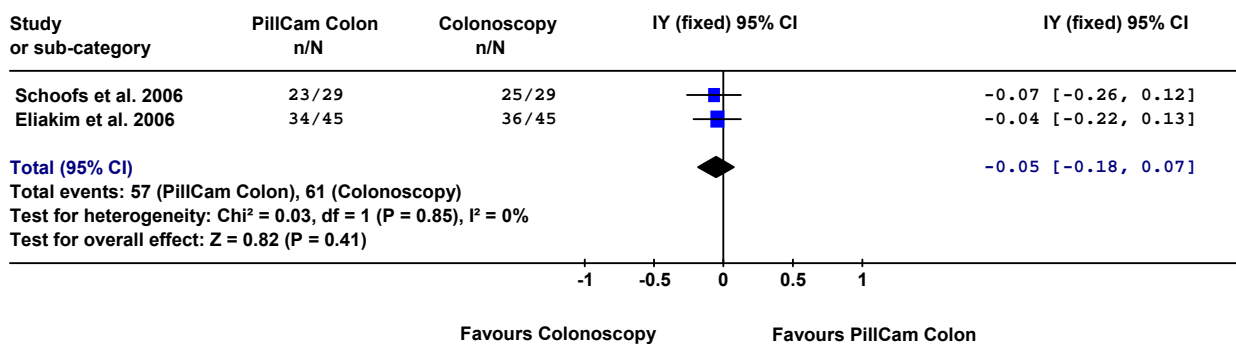


Figure 7: Yield of Capsule Endoscopy and Colonoscopy for the Detection of ‘Any Polyps’

¹ After the endoscopist has completed the evaluation of a given segment of the colon, a study coordinator or a nurse reveals the results of the new technique for the previously examined segment. If a lesion was seen using the new technique but not in the initial colonoscopy, the endoscopist closely re-examines that segment, using the images from the new technique for guidance. This method allows for the assessment of false negative results on colonoscopy that would otherwise have been recorded as false positive results of the new technique.

An important point in these studies is that both capsule and colonoscopy procedures were performed on the same day, using the same preparation. This allowed for a fair comparison of the two techniques. The improvement in performance of the PillCam Colon with the second and third reading in Eliakim et al. (5) probably represents the effect of a learning curve in the reading and interpretation of the images.

Safety

Both studies reported that no adverse events were related to the capsule procedures and that all patients tolerated the colon-preparation regimen.

Summary of Findings

Performance

- PillCam Colon is a non-invasive method for identifying colorectal polyps. It has, however, lower sensitivity and specificity than colonoscopy and its accuracy in the detection of cancer has not been studied.
- For the detection of significant polyps (defined as >6 mm or ≥ 3 polyps), the pooled sensitivity is 73% (54%–87%) and pooled specificity is 92% (84%–97%).
- There were no significant differences in the yield of PillCam Colon and colonoscopy.
- Considering that no segmental unblinding was performed in these studies, it is possible that the diagnostic accuracy of PillCam Colon was underestimated.
- Higher sensitivity, specificity, PPV, and NPV have been reported when an experienced physician interpreted the images.

Safety

- Swallowing of the capsule was accepted by the patients in the two studies.
- No adverse events related to the procedure have been reported by the two studies.

Advantages and Disadvantages

- Interpretation of findings is an important aspect of capsule procedures and the learning curve is an important issue for interpretation of images.
- Interpretation of the images requires special training.
- A large number of images must be viewed.
- A disadvantage of capsule endoscopy is that it does not offer any therapeutic capability for detected lesions.

Appendix: Literature Search Strategy

Capsule Endoscopy

Search date: October 11, 2007

Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, Cochrane Library, INAHTA/CRD

Database: Ovid MEDLINE(R) <1996 to October Week 1 2007>

Search Strategy:

- 1 exp Capsule Endoscopy/ (178)
- 2 (capsule\$ adj2 (endoscop\$ or Enteroscop\$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (785)
- 3 exp Capsule Endoscopes/ (32)
- 4 (pillcam or EndoCapsule or (video adj2 pill) or Sayaka Capsule or (capsule adj2 camera)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (28)
- 5 m2a.mp. (104)
- 6 or/1-5 (858)
- 7 limit 6 to (humans and english language and yr="2003 - 2007") (675)
- 8 (systematic\$ review\$ or meta-analysis or metaanalysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (31364)
- 9 7 and 8 (11)
- 10 7 (675)
- 11 limit 10 to (case reports or comment or editorial or letter or "review") (373)
- 12 10 not 11 (302)
- 13 9 or 12 (308)

Database: EMBASE <1980 to 2007 Week 40>

Search Strategy:

- 1 exp Capsule Endoscopy/ (842)
- 2 (capsule\$ adj2 (endoscop\$ or Enteroscop\$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1146)
- 3 exp Capsule Endoscope/ (114)
- 4 (pillcam or EndoCapsule or (video adj2 pill) or Sayaka Capsule or (capsule adj2 camera)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (37)
- 5 m2a.mp. (129)
- 6 or/1-5 (1232)
- 7 limit 6 to (human and english language and yr="2003 - 2008") (908)
- 8 (systematic\$ review\$ or meta-analysis or metaanalysis).ti,ab. (24452)
- 9 7 and 8 (13)
- 10 7 (908)
- 11 limit 10 to (editorial or letter or note or "review") (368)
- 12 case report.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (966554)
- 13 10 not (11 or 12) (370)
- 14 9 or 13 (380)

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