Capsule Endoscopy - 2011

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1. Introduction

The gold standard for evaluating pathologies of the large bowel, including screening for colorectal cancer, is optical colonoscopy, in spite of the fact that it is an invasive procedure and needs to be performed by an expert endoscopist. Colon capsule endoscopy is a new minimally invasive diagnostic procedure for exploring the large bowel. It does not require sedation, air insufflation or intubation. The few available clinical studies on this device have shown levels of safety, feasibility and performance as being comparable to those of optical colonoscopy. Colon capsule endoscopy is also well tolerated by the patients and it is currently considered an acceptable alternative for cases of "incomplete" colonoscopy, as well as for subjects unwilling to undergo the optical colonoscopy procedure, or those with contraindications for an invasive procedure. This raises the question of whether colon capsule endoscopy can eventually replace optical colonoscopy as a diagnostic tool. On the one hand, its has the advantage of being highly likely to increase compliance for undergoing colorectal cancer screening among asymptomatic individuals. On the other hand, its preparation protocols are even more stringent than those for optical colonoscopy, and the detection of suspected or obvious pathology mandates that the individuals return to undergo optical colonoscopy. Moreover, since the capsule does not expulse by 10 hours (the maximum battery life) for various reasons in approximately 8% of the cases, the colon will not have been examined in its entirety. We believe that colon capsule endoscopy will eventually replace optical colonoscopy as a first-line procedure when solutions are found for those drawbacks.

2. Colorectal cancer screening

Colorectal cancer (CRC) is the second leading cause of cancer death, and accounts for approximately 9% of cancer deaths overall (Jemel, 2010) Optical colonoscopy (OC) is a procedure in widespread use and the one advocated as the procedure of choice for screening and prevention of CRC by many authors (Brenner et al', 2010; Baxter et al' 2009) In spite of its being the gold standard for CRC screening, OC has several limitations: only an experienced endoscopist is qualified to perform it (Rex, 2002), limited endoscopy resources may limit its application for large, population-based screening programs, it must examine the entire colon, including cecum intubation (Shah, 2007; Rex, 2006), and it is an invasive procedure that requires sedation, with discomfort and embarrassment to the patient, leading
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to low compliance rates (Bujanda, 2007). Moreover, previous studies (Barclay, 2006; Bensen, 1999) have documented variations in OC procedures, adenoma detection rates and colonoscope withdrawal times among examiners (Rex, 1997; Barclay, 2006). The overall reported miss rate for neoplastic polyps ranges from 8-24% (Bensen, 1999; Rex, 1997). Several Canadian case control and cohort studies found that colonoscopy reduced the incidence and mortality of distal but not proximal CRC (Singh, 2010a; Singh, 2010b; Lakoff, 2008). There are other drawbacks associated with OC. The need for sedation requires that the examinee have an escort home, it increases the costs, and it may induce complications, such as cardiac arrhythmias, hypotension, oxygen desaturation, and others. OC also carries the risk of perforation of about one in 1,000 cases and death in about one in 5,000 cases (Orsoni, 1997; Weitzmann, 2001). It may fail to demonstrate the entire colon in 10-15% of cases, and may miss up to 10-20% of polyps <1 cm in size (Shah, 2007; Rex, 2006; Bressler, 2004; Picakardt, 2004; Heresbach, 2008). Finally, the miss rate of OC for large adenomas and malignancy has been shown to be about 12% and 5%, respectively (17-19). All these negative factors can impact on the compliance in asymptomatic subjects who consider OC for colorectal screening.

3. Colon Capsule Endoscopy (CCE)

CCE represents a new diagnostic technology for colonic exploration. Its objectives are to pass through the entire colon while transmitting images similar to OC, as well as to identify colonic pathologies. The ultimate goals are for it to complement or eventually replace the diagnostic OC for CRC screening and for diagnosing obscure gastrointestinal (GI) bleeding, the cause of positive fecal occult blood tests, iron deficiency anemia, and suspected inflammatory bowel disease (i.e., determining the disease extent or even monitoring mucosal healing in established cases). It is also intended to provide information in cases of incomplete colonoscopy and be applicable when OC poses a significant risk or is contraindicated, such as for patients with co-morbidities which preclude sedation or bowel preparation.

3.1 Technical description and operational data

The CCE system (Given Imaging Ltd., Yoqneam, Israel) consists of a battery-powered video capsule with two imagers, one at each end of the capsule. The capsule transmits signals through an antenna-lead array to a small data recorder worn around the waist of the examinee. The data can then be uploaded to a personal computer-based workstation and viewed with the RAPID® software.

The first generation Pillcam Colon capsule is 11 X 31 mm in size and has two wide-angle (156 degrees) imagers, one at each end. The frame acquisition is set at a constant rate of 4 per second (i.e., 2 frames per second per camera). The capsule's activity starts automatically upon removal from its packaging. Three minutes after being swallowed, the capsule enters into a "sleep" mode for one hour and 45 minutes, after which it becomes activated and starts recording.

The second generation Pillcam Colon 2 (Figure 1) is 11.6 X 31.5 mm in size and has two wide-angle (176 degrees) imagers, one at each end, yielding an almost 360° coverage. It is equipped with an adaptive frame rate (AFR) feature of 4-35 frames that vary depending on its rate of movement. The Pillcam Colon 2 captures images at an initial constant rate of 14 frames per second until the small bowel is reached.
When it identifies the small bowel, the AFR feature is activated and the image acquisition function switches to the variable rate mode. The adaptive frame rate feature maximizes tissue coverage, optimizes the length of recording, conserves battery power and provides a smooth video replay. The main differences between the two models are summarized in Table 1.

| Parameter                  | Pillcam Colon 1st generation | Pillcam Colon 2nd generation |
|----------------------------|------------------------------|------------------------------|
| Communication              | One-way                      | Bidirectional                |
| Frame rate (per second)    | Constant (4 per second)      | Adaptive (4-35)              |
| Polyp size estimation      | Two click process            | Simple Multi-step            |
| Field of view              | 156°                         | 176°                         |
| Light control              | Automatic                    |                              |
| Optics                     | 1st generation               | Advanced                     |
| Data recorder              | Storage of capsule video     | Real-time image rate control |
|                           |                              | Guidance (medical staff, patient) |

Table 1. The differences between the two colon capsule.

The data recorder within the capsule of a CCE system has several important features: bidirectional communication ability that helps control the frame rate, a notification feature which alerts and helps guide the patient through the process, and a real-time viewing capability by means of a liquid crystal diode display (Eliakim, 2006).

### 3.2 Clinical data

Despite the great enthusiasm generated by this new technique, there are only a few clinical studies in the literature (Eliakim, 2006, 2009, 2010, Schoof, 2006; Van Gossum, 2009; Sacher-Huvelin, 2010; Rokkas, 2010; Sieg, 2010; Pilz, 2010, Spade, 2010, 2011a, 2011b, Fireman, 2007), and the reported results in the initial ones on the first CCE generation (Eliakim, 2006, Schoof, 2006; Van Gossum, 2009) showed low sensitivity, specificity and predictive values.
The first two pilot studies (Eliakim, 2006; Schoof, 2006) demonstrated the feasibility and safety of CCE, however, a multicenter study that evaluated the detection of polyps and malignancy reported that the sensitivity of the technique was limited (Van Gossum, 2009). The published data on the sensitivity and specificity are summarized in Tables 2-6.

| Reference                        | CCE               | No. Patients | Sensitivity (%) | Specificity (%) |
|----------------------------------|-------------------|--------------|-----------------|-----------------|
| Sacher-Huvelin et al.            | 1st generation    | 545          | 58              | 71              |
| Pilz et al.                      | 1st generation    | 59           | 79              | 54              |
| Van Gossum et al.                | 1st generation    | 328          | 72              | 78              |
| Rokkas et al.                    | 1st generation    | 626          | 73              | 89              |
| Spada et al. (2010)              | 1st generation    | 837          | 71              | 75              |

CCE, colon capsule endoscopy

Table 2. Sensitivity and specificity for any type and size of polyp

These reported results were analyzed and grouped in different subgroups, according to the size and type of polyp. For "any" polyp, the sensitivity and specificity ranged between 58-79% and 54-89%, respectively (Table 2). For polyps ≥6 mm in size, the sensitivity and specificity were 39-69% and 73-88%, respectively, for the first generation CCE (Eliakim, 2006, 2010; Schoof, 2006; Van Gossum, 2009; Sacher-Huvelin, 2010; Rokkas, 2010; Pilz, 2010; Spada, 2010, 2011), and 89% and 76%, respectively, for the second generation CCE (27) (Table 3).

| Reference                  | CCE               | No. Patients | Sensitivity (%) | Specificity (%) |
|----------------------------|-------------------|--------------|-----------------|-----------------|
| Sacher-Huvelin et al.      | 1st generation    | 545          | 39              | 88              |
| Van Gossum et al.          | 1st generation    | 328          | 64              | 84              |
| Pilz et al.                | 1st generation    | 59           | 50              | 76              |
| Eliakim et al. (2009)      | 1st generation    | 91           | 58              | 83              |
| Schoofs et al. (2022)      | 1st generation    | 41           | 60              | 73              |
| *Rokkas et al. (2025)      | 1st generation    | 626          | *69             | *86             |
| *Spada et al. (2011)       | 1st generation    | 837          | 68              | 82              |
| Spada et al. (2011)        | 1st generation    | 40           | 63              | 87              |
| Eliakim et al. (2009)      | 2nd generation    | 104          | 89              | 76              |

CCE, colon capsule endoscopy

Table 3. Sensitivity and specificity for polyps ≥6 mm

*Significant polyp: >6 mm or ≥3 polyps of any size.
The sensitivity and specificity of CCE for advanced adenoma ranged between 72-73% and 57-79%, respectively (Table 4), and the sensitivity and specificity for malignant lesions ranged between 60-76% and 74-100%, respectively (Table 5).

| Reference                | CCE                  | No. Patients | Sensitivity (%) | Specificity (%) |
|--------------------------|----------------------|--------------|-----------------|-----------------|
| Sacher-Huvelin et al.    | 1st generation       | 545          | 72              | 57              |
| Van Gossum et al.        | 1st generation       | 328          | 73*             | 79*             |

CCE, colon capsule endoscopy; Advanced adenomas (≥6 mm)

Table 4. Sensitivity and specificity for advanced adenoma

| Reference                | CCE                  | No. Patients | Sensitivity (%) | Specificity (%) |
|--------------------------|----------------------|--------------|-----------------|-----------------|
| Sacher-Huvelin et al.    | 1st generation       | 545          | 60              | 100             |
| Van Gossum et al.        | 1st generation       | 328          | 74              | 74              |
| Spada et al. (2010)      | 1st generation       | 837          | 76              |                 |

CCE, colon capsule endoscopy; Meta-analysis

Table 5. Sensitivity and specificity for colorectal cancer

OC considered the gold standard, in this context it is important to understand that there are various limitations, for example the fact that the findings that were demonstrated on CCE and not on OC were considered as false positive, a fact which could account for an artificial low specificity. The latter is due to the possibility that at least in some cases the capsule endoscopy identified lesions that colonoscopy missed. Indeed, in a large multi-center French study (Sachuer-Huvelin, 2010) that offered a repeat colonoscopy for these patients the differences in accuracy between CCE and optical colonoscopy were minimized. So that the CCE specificity might practically represent the supremacy of the CCE over OC. Another cofactor is the fact that in most studies the majority of subjects included were known to have an established or suspected colonic disease (past history of adenomas or colon cancer, abnormal imaging findings etc.) or a high clinical suspicion of colonic disease (rectal bleeding, hematochezia, melena, positive occult blood, change in bowel habits, diarrhea or constipation). An example of such study is the one reported by Van Gossum et al (Van Gossum, 2009). In other studies, the total number of subjects that were recruited was limited and the percentage of subjects that were referred for screening was small. For example the article by Eliakim et al. (Eliakim 2009) recruited about 104 patients, of whom 32% were referred for screening. Pilz et al. (Pilz, 2010), a total of 59 subjects were recruited of whom only 41% were referred for screening. A study which examined the issue of screening and surveillance in a more targeted fashion (Sacher-Huvelin, 2010) included 545 subjects of whom about 30% were at an average risk (screening) and 70% were at an increased risk (surveillance) failed to demonstrate non inferiority in relation to colonoscopy. Sensitivity and specificity in this sample was about
39% and 88% respectively for polyps of 6 mm or larger. The researchers concluded that the CCE cannot yet replace the optical colonoscopy as a first choice for screening and surveillance purposes.

It should be noted that the reported sensitivity of CT colonography for detecting polyps ≥6 mm as reported in an article by Johnson et al. (Johnson, 2008) is about 78%, a figure which is higher than most of those reported for sensitivity for the first generation CCE, however, for the second generation CCE. Eliakim et al. (Eliakim, 2009) and Spada et al. (Spada, 2011) reported for sensitivity 89% and 84% respectively (Table 6).

| Study          | 1st generation | 2nd generation# |
|---------------|----------------|-----------------|
|               | Van Gossum     | Eliakim(2009)   | Spada(2011)   |
| No site       | 8 European     | 5 Israeli       | 8 European    |
| No. Patients  | 320            | 98              | 109           |
| Polyp ≥6 mm   |                |                 |               |
| Prevalence    | 27%(87)        | 24%(35)         | 41%(45)       |
| Sensitivity   | 64%            | 89%             | 84%           |
| Specificity   | 84%            | 76%             | 64%/92%*      |
| Polyp ≥10 mm  |                |                 |               |
| Prevalence    | 16%(50)        | 14%(20)         | 29%(32)       |
| Sensitivity   | 60%            | 88%             | 88%           |
| Specificity   | 98%            | 89%             | 95%           |

*After unblinding

Table 6. The first vs. 2nd generation Colon Capsule

Thus, the sensitivity, specificity and accuracy are insufficient for recommending CCE for wide clinical use, as at least for the first generation CCE as concluded by Van Gossum et al (Van Gossum, 2009). The technological improvements of the second generation CCE show promising and encouraging results, as was shown by a recent publications (Eliakim, 2009, Spada, 2010) (Table 6). More in-depth studies on screening average-risk populations as well as surveillance of at-risk populations are warranted, with an eye towards extending the indications for CCE.

4. Preparation protocol

The colon must be clean of any residual material in order to perform CCE, unlike the case of OC where it is possible to suction it. A typical preparation protocol, as described in an article by Eliakim et al. (Eliakim, 2009) (Table 7), includes a diet based on clear liquids to be followed the day before the examination, a split dose of 4 liters of polyethylene glycol (PEG) solution (2 liters during the evening before the examination and 2 liters in the morning of the examination), oral sodium phosphate boosters and a bisacodyl suppository. The aim of the sodium phosphate and bisacodyl additions is to maintain a clean colon and expedite the passage of the capsule down the bowel and its excretion within 10 hours following capsule ingestion.
### DAY BEFORE EXAMINATION

| Time  | Activity                                      |
|-------|----------------------------------------------|
| All day | Clear liquid diet                            |
| Evening | 2 liters polyethylene glycol                  |

### EXAMINATION DAY

| Time   | Activity                                      |
|--------|----------------------------------------------|
| 07:00  | 2 liters polyethylene glycol                  |
| 10:00  | Capsule ingestion                             |
| 1
| 1st booster | 30 ml sodium phosphate and 1 liter water   |
| 2
| 2nd booster | 15 ml sodium phosphate and 0.5 liter water   |
| Suppository | 10 mg bisacodyl                            |

Table 7. Typical preparation protocol

Similar protocols have been described in various studies (Table 8). Attempts to replace the booster of sodium phosphate with PEG yielded inferior results (Pilz, 2010).

| Reference         | PEG | NaP booster | Prokinetic | Bisacodyl suppository | Low Fiber diet | Clear liquid diet |
|-------------------|-----|-------------|------------|-----------------------|----------------|------------------|
| Eliakim et al.    | 3   | 1-2         | Tegaserod  | Yes                   | Yes            | Yes              |
| Schoofs et al     | 4   | 2           | Domperidone| Yes                   | No             | Yes              |
| Van Gossum et al  | 4   | 2           | Domperidone| Yes                   | No             | Yes              |
| Eliakim et al.(2009) | 4  | 2          | Metoclopramide | Yes       | Yes            | Yes              |

PEG, polyethylene glycol; NaP, sodium phosphate

Table 8. Colonic preparation

**4.1 Preparation quality**

Various studies have addressed the issue of grading the quality of bowel preparation. Colon cleanliness is usually categorized into excellent, good, fair, or poor. For ease of reporting and
for statistical analyses, most studies use the combinations of good-excellent and poor-fair (Table 9). Other studies have reported the quality of preparation as clean, moderate, or poor (Eliakim, 2009). In addition to cleansing, bowel preparation for CCE also aims to facilitate the progress of the capsule through the digestive system as well as to keep certain amounts of clear liquids within the colonic lumen in order to allow visualization of the colonic mucosa. The latter is also known as the "submarine view", which substitutes for the insufflation and flushing used in OC.

| Reference                  | Good-Excellent (%) | Fair-Poor (%) |
|---------------------------|--------------------|---------------|
| Sacher-Huvelin et al.     | 52                 | 48            |
| Schoofs et al             | 88                 | 12            |
| Eliakim et al (2006)      | 84.4               | 15.6          |
| Van Gossum et al          | 72                 | 28            |
| Spada et al (2010)        | 70                 | 30            |
| Spada et al (2011)        | 42.5               | 57.5          |
| Eliakim et al (2009)      | 78                 | 22            |

*Meta-analysis*

Table 9. Colon cleanliness

As with all other imaging methods of exploring the colon, the quality of bowel preparation significantly affects the quality of a CCE study's interpretation and results. Unlike OC, the capsule requires a clean colon for a relatively long period of time and, as noted earlier, there is no means of remove content. Several studies have addressed the influence of bowel preparation on the CCE sensitivity. One large European multicenter study (Van Gossum, 2009), which recruited about 328 subjects, found a significant effect of bowel preparation on the CCE sensitivity, with a negligible impact on its specificity. Those authors noted that the sensitivity and specificity for polyps ≥6 mm in patients with excellent or good bowel preparation were 75% and 84%, respectively, compared with 42% and 84% fair or poor preparation. For lesions consistent with advanced adenoma, excellent or good bowel preparation yielded a sensitivity and specificity of 88% and 78% respectively, while fair to poor bowel preparation had a sensitivity and specificity of 44% and 81%, respectively. Therefore, it emerges that one of the limitations of CCE is the need for aggressive preparation protocol, which has a negative effect on patients' compliance (Van Gossum, 2009).

5. Capsule egestion

Capsule egestion while the battery is still operating is an important issue in terms of achieving a complete study of the bowel (Table 10). The location of the CCE within the colon upon "wake up" was also an important factor for the first generation of the Pillcam colon capsule.
At 10 hours (\%)
At 8 hours (\%)
At 6 hours (\%)
Reference
91   Sacher-Huvelin et al.
92.8  Van Gossum et al
64   Pilz et al
81   Eliakim et al.(2009)

Table 10. Capsule egestion

The absence of information from any location of the CCE distal to the cecum has been associated with loss of crucial information and considered as being an incomplete result. Although this phenomenon has been reported in only a minority of subjects, it still constituted a major pitfall of the procedure. In this context, Van Gossum et al (Van Gossum,2009). reported that after one hour and 45 minutes (consistent with the CCE "sleeping mode" phase), the capsule was found at or distal to the cecum in 312 of 320 patients (97.5\%), within the cecum in five (1.5\%), in the ascending colon in two (0.6 \%), and the sigmoid colon in one (0.3\%). The Pillcam Colon 2 technology has overcome this obstacle by its unique AFR feature.

6. Adverse events

Minimal side effects were reported in various studies on CCE. Most of them were mild to moderate in severity (e.g., nausea, abdominal pain, etc.), and they were mainly related to the bowel preparation. In their meta-analysis on CCE, Spada et al.(Spada 2011) reported that the rate of these side effects was ranged between 2.6 to 5.6\%.

6.1 Patient satisfaction

Only limited information is available on patient satisfaction with CCE. When tested on a visual analogue scale, the results were only slightly better for CCE compared to OC (Sacher-Huvelin,2010). Of 53 subjects who underwent colonoscopy in a CCE study published by Pilz et al. (Pilz, 2010), 40\% preferred the CCE, 38\% preferred OC, and 23\% had no preference.

6.2 CCE advantages and drawbacks

Advantages of this method are not needing sedation, intubation or air insufflation, thus obviating the risks of complications associated with an invasive test, especially in cases where the capsule yields negative results and colonoscopy is not required. The examination itself is free of pain and the examinee can carry on with regular activities. When CCE locates abnormal findings and the patient is referred to OC, the endoscopist knows in advance the size and location of the lesion. There is certain logistical limitation: in the case of abnormal findings on CCE, the patient can be spared undergoing a second cleansing preparation only if the CCE video is reviewed promptly and OC can be scheduled at short notice.
In terms of disadvantages, OC permits lens clearing by applying water jet, suctioning of colonic contents and irrigation capability, thus allowing visualization of the colonic mucosa and the interpretation of images obtained during colonoscopy at a lower level of cleanliness than that required by CCE. Because CCE lacks these features, a more intensive bowel preparation is required. Another reason for a more stringent bowel preparation is the need to facilitate capsule passage and allow a certain amount of clear liquids within the colonic lumen in order to enable visualization of the mucosa (made possible with the aid of air insufflation in OC). This aggressive bowel preparation might well be responsible for low compliance rates for undergoing CCE.

Another disadvantage of the CCE is the lack of therapeutic capabilities, even though several studies have shown that polyps <6 mm in size do not need to be removed due to the relatively low risk of malignancy (Johnson, 2008; Pickhardt, 2003). Furthermore, virtual colonoscopy does not capture images of polyps <6 mm. Limited battery power which sometimes precludes the ability to complete a full study is another drawback. Although the second generation CCE can save battery power through its AFR feature and do so without losing information (compared with the "sleeping mode" of the first generation CCE), this still poses a limitation, especially in cases where the capsule has been delayed in the stomach or small intestine.

The last issue in this respect is the high cost of the CCE system, which is a major factor in currently limiting its extensive clinical use.

6.3 Limitations of the research methodology

The element of reviewers' experience in interpreting CCE images is a significant factor. Gastroenterologists have accumulated considerable experience in OC, while experience with CCE is far more limited. Eliakim et al (Eliakim, 2006) reported that the specificity values of CCE ranged from 83% to 100%, depending on the reviewers' experience. Notably, most studies on CCE recruited subjects who were not representative of a typical screening population, so that their data could not be used to draw conclusions about the use of CCE in the setting of routine screening.

7. Conclusions

Based on currently available data, CCE can not be recommended as a substitute for OC, but it can serve as a supplementary test in cases of incomplete colonoscopy, when there are contraindications to colonoscopy, or for patients who are unwilling to undergo colonoscopy. The improvements afforded by the second-generation capsule are promising and encouraging, and such enhanced technology will lead to more widespread use that will reduce the cost of testing. Expectations in the future of CCE include self-propelled capsules, a more efficient/external energy source, a side imager for extending the field of view and minimizing blind areas, and a mouth to anus capsule with the ability for complete evaluation of all parts of the digestive system (e.g., in cases of obscure GI bleeding). Shortening the period of capsule reading and initial analysis of the images by a computerized "reviewer", and expanding the capsule to other fields, such as motility assessment, will add to the attractiveness of CCE in the clinical setting.

8. Acknowledgment

We thank Ms. Esther Eshkol for editorial assistance.
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As result of progress, endoscopy has became more complex, using more sophisticated devices and has claimed a special form. In this moment, the gastroenterologist performing endoscopy has to be an expert in macroscopic view of the lesions in the gut, with good skills for using standard endoscopes, with good experience in ultrasound (for performing endoscopic ultrasound), with pathology experience for confocal examination. It is compulsory to get experience and to have patience and attention for the follow-up of thousands of images transmitted during capsule endoscopy or to have knowledge in physics necessary for autofluorescence imaging endoscopy. Therefore, the idea of an endoscopist has changed. Examinations mentioned need a special formation, a superior level of instruction, accessible to those who have already gained enough experience in basic diagnostic endoscopy. This is the reason for what these new issues of endoscopy are presented in this book of New techniques in Gastrointestinal Endoscopy.

How to reference
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Zvi Fireman and Oren Atia (2011). Capsule Endoscopy - 2011, New Techniques in Gastrointestinal Endoscopy, Prof. Oliviu Pascu (Ed.), ISBN: 978-953-307-777-2, InTech, Available from: http://www.intechopen.com/books/new-techniques-in-gastrointestinal-endoscopy/capsule-endoscopy-2011
