Capsule endoscopy: 10 years on and in the frontline

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Accepted 25 January 2010
Published Online First
14 May 2010

Capsule endoscopy is a safe, simple, remote method of visualising the gastrointestinal tract without resorting to conventional endoscopic intubation or radiation exposure. In addition, the ability to visualise the small bowel mucosa directly means that it is considerably more sensitive than existing small bowel imaging modalities in detecting subtle abnormalities. It is a firstline investigative modality for suspected small bowel bleeding and is being increasingly used for detecting evidence of other small bowel diseases. In Crohn's disease, it can confirm evidence of activity without recourse to repeated endoscopic intubation or radiation but does not replace MRI and CT which are better suited to defining stricturing disease and transmural complications. The production of different capsule endoscopes to examine the oesophagus, small bowel and colon now means that almost all of the gut can be examined using this technology.

Capsule endoscopy is the most exciting development in endoscopy since the flexible fiberoptic endoscope was introduced.¹ It is the first remote imaging tool of the gastrointestinal tract that obviates the need for intubation, sedation and radiation with all their inherent risks. The technique was first described a decade ago by Iddan, Meron, Glukhovsky and Swain who designed a swallowable pill camera which took two images per second using microtransistor technology as it passed through the gut under the action of peristalsis.² The first capsule licensed by Given Imaging (Yoqneam, Israel) to examine the small bowel was rapidly followed by an oesophageal capsule and later by a colon capsule (during which time Olympus (Tokyo, Japan) developed the EndoCapsule; IntroMedic (Seoul, Korea) the MiroCam; and JinShan Science and Technology Co Ltd (Chongqing, China) the OMOM small bowel capsules), raising the future prospect of remote whole gut visualisation.

Small bowel capsule endoscopy

The PillCam SB (Given Imaging) small bowel capsule contains a battery powered complementary metal oxide semiconductor imager, a transmitter, antenna and light emitting diodes. It is activated when extracted from its magnetic holder, swallowed with water and deactivates after approximately 8 h and 45 min, by which time 80–90% of capsules have reached the caecum.^{3–5} Completion rate is further improved by technology which extends battery life and prolongs image acquisition time (currently 10 h for the EndoCapsule and 11 h for the MiroCam).^{6–7} Bowel preparation may benefit patients undergoing capsule endoscopy: meta-analyses suggest improved mucosal visualisation^{3–4} and a better diagnostic yield.⁴

The most common indication for small bowel capsule endoscopy is 'obscure' gastrointestinal bleeding (presenting as overt bleeding or recurrent iron deficiency anaemia) not diagnosed at gastroscopy or colonoscopy.⁸ Historically, the implication has been that these patients (about 5% of all with bleeding)⁹ have a small bowel source although it is widely accepted that small bowel radiology identifies a cause in only 5–10%.^{8–9} This may partly be due to missed pathology: repeat gastroscopy detects relevant pathology in up to 50% and colonoscopy in 6% of cases.⁸ But it also reflects the fact that most bleeding arises from subtle mucosal lesions which do not have a mass effect or cause small bowel deformity. Capsule endoscopy studies now show that angioectasia is the commonest diagnosis (22–29%), followed by ulcers (due to Crohn's disease, non-steroidal anti-inflammatory drugs or of uncertain origin; 6–13%).^{5–10} Tumours are responsible for bleeding in 3–5% of cases,^{5–10–11} although with angioectasia tending to affect older patients, tumours are a relatively common cause in those under 50 years of age.¹² Studies comparing

diagnostic yield by capsule endoscopy and small bowel radiology reflect the advantage of direct mucosal visualisation, meta-analyses suggesting a yield of 42% and 6%, respectively. Push enteroscopy, although not designed to visualise the whole small bowel, also fairs poorly in comparison with capsule endoscopy, with yields of 26% and 56%, respectively.^{13 14} It is interesting to reflect on the yield of capsule endoscopy of about 50% or more in routine clinical practice (as opposed to clinical trials which may contain select groups of patients).^{5 10 15} The figure quoted of 5–10% of bleeding arising from the small bowel is derived from studies which predate the capsule endoscopy era when bleeding may have been attributed to insignificant upper gastrointestinal or colonic lesions simply because available small bowel investigative modalities were too insensitive to make the correct diagnosis. Arguably, the term ‘obscure’ should be replaced by ‘incompletely investigated’ gastrointestinal bleeding.

The other main cohort of patients investigated by small bowel capsule endoscopy are those with suspected Crohn’s disease—that is, symptoms consistent with Crohn’s in whom ileocolonoscopy and small bowel imaging are negative or equivocal.^{5 16} Many of these patients have features (weight loss, anaemia, an acute phase response, non-specific radiological, endoscopic or histological abnormalities) which are not consistent with a diagnosis of a functional bowel disorder. Other factors which have been suggested as indicators for small bowel capsule endoscopy in this setting include hypoalbuminaemia, extraintestinal manifestations or a family history of inflammatory bowel disease.¹⁷ Whether or not all findings of erosions and ulcers represents Crohn’s disease, however, is unclear. Depending on how mucosal breaks are defined, lesions can be found in as many as 13–40% of healthy volunteers.^{18 19}

Capsule endoscopy has greater diagnostic sensitivity for Crohn’s disease than double contrast barium radiology and CT enteroclysis.^{14 20 21} Furthermore, it is easy to perform and does not require nasojejunal intubation or irradiation. The difficulty arises when symptoms raise the possibility of stricturing disease, as capsule retention is more common in patients with suspected Crohn’s disease (1.5%) and known Crohn’s disease (as high as 13%) than in obscure gastrointestinal bleeding (1%).^{20 22} In this situation, the aim should be to acquire as much diagnostic information as possible while minimising discomfort, risks and number of tests in a cohort of patients who may need repeated investigation over the course of their disease.

One method that reliably predicts safe capsule endoscopy is the use of the Agile patency capsule (Given Imaging). The original version of this pill contained lactose and barium in an impermeable membrane with a plug at one end, which dissolved over 40–90 h, and a radiofrequency tag, in the size and shape of the real capsule. Several small studies (total n=166) showed

that passage of the intact capsule through the gut, reported by the patient, demonstrated by the absence of a radiofrequency signal detected by a handheld scanner or absence of the device on an abdominal radiograph, predicted safe subsequent real capsule endoscopy. However, the device was modified to incorporate timer plugs at both ends as several incidences of occlusion by the original patency device were reported, perhaps due to impaction of the timer plug end in a stricture where dissolution was impeded.²³ A multi-centre trial using the Agile device in 106 patients with strictures showed that passage of the device intact, or within 30 h of ingestion, predicted safe real capsule endoscopy with no cases of obstruction by the Agile device or capsule.²⁴

MR imaging of the small bowel appears to be as sensitive as double contrast barium radiography in detecting stenoses²⁵ although false negative studies occur.^{26 27} It compares favourably in terms of diagnostic yield in Crohn’s disease, partly because of the excellent mural and extraintestinal detail obtained although it appears to be inferior to conventional enteroclysis in detecting early mucosal lesions.^{25 28} Meta-analysis suggests no difference between capsule endoscopy and MR in diagnostic yield although only three studies were included.²¹ The advantage of this technique is the absence of irradiation. The majority of studies, however, involve enteroclysis in which contrast is administered via a nasojejunal tube, a procedure which is very unpopular with patients. Unfortunately, MR enterography, in which large volumes of contrast are swallowed by the patient (such that intubation is not needed), is associated with a reduced diagnostic sensitivity in comparative trials (83.7% compared with 95.9%).²⁸

As with MR, small bowel CT performs less well than barium contrast radiography in identifying mucosal abnormalities in Crohn’s disease. Extramural complications are well visualised and while diagnostic sensitivities are comparable to MR, the radiation dose is considerable, there may be small additional risks administering intravenous contrast and much of the data are derived following intubation for enteroclysis.^{25 28}

In summary, capsule endoscopy provides the best mucosal detail, avoids irradiation and is well tolerated, but incurs the risk of retention. The Agile patency device predicts safe capsule endoscopy but further data are required before patients can be reassured that a partially, or indeed completely, collapsed device never causes obstruction in a stricture. MR is a sensitive diagnostic test for Crohn’s disease and strictures without irradiating the patient but a normal study excludes neither, and enterography to avoid nasojejunal intubation may be associated with a reduced sensitivity. MR enteroclysis approaches barium radiography in sensitivity in detecting fistulae²⁵ and both CT and MR provide important extramural imaging which is not provided by a luminal study. Investigation of Crohn’s disease,

therefore, will be influenced by the clinical scenario, local availability of technology, expertise and patient preference.

There are several other patient groups in whom small bowel capsule endoscopy may be helpful. Capsule endoscopy is commonly used in coeliac disease. Macroscopically, mucosa affected by villous atrophy has a mosaic pattern, folds have a scalloped edge and resemble octopus tentacles. Small superficial ulcers occur in 5–10% of patients with new diagnoses. A diagnostic sensitivity of about 85% suggests that duodenal biopsy should remain the gold standard although typical findings in antibody positive patients appear to be diagnostic in patients who decline conventional endoscopy.^{29–30} The main role for capsule endoscopy in coeliac disease is not in diagnosis, however, but in distinguishing type I from type II refractory disease³¹; ulcerative jejunitis and malignant disease are usually easily recognised and their absence provides greater confidence to pursue dietary and immunosuppressive treatment.

Capsule endoscopy may find a limited role in familial polyposis syndromes. Typical whitish, often confluent sessile duodenal polyps are commonly seen in familial adenomatous polyposis. Capsule endoscopy probably represents an improvement in polyp detection over both small bowel barium and MRI.^{33–34} However, the fact that the ampulla may be seen in as few as 10% of cases³⁵ suggests that it should not replace duodenoscopy in the surveillance process. Larger polyps may occasionally be seen more distally, but while large series show that about 5% of patients die of peri-ampullary carcinoma,³⁶ distal small bowel malignancies are extremely rare, so it seems unlikely that these patients benefit from capsule endoscopy unless unexplained pain or anaemia develops. In Peutz–Jegher syndrome, it is generally accepted that larger polyps (2 cm or more) should be removed, especially in patients with abdominal pain, in order to prevent intussusception. Capsule endoscopy may identify polyps more reliably than small bowel barium and MR studies,^{33–37} but assessment of size is difficult and double balloon enteroscopy (during which polypectomy can be performed) might be considered a firstline investigation in patients with symptoms.

The cohort in which capsule endoscopy seems to have a limited diagnostic yield is those with abdominal pain alone.³⁸ The yield may be increased in patients who also have weight loss or evidence of an acute phase response.^{39–40} Furthermore, in a series of patients suspected of having recurrent small bowel obstruction, capsule endoscopy revealed a diagnosis in five of 19 patients, four of whom had capsule retention, but all of whom required surgical treatment of their strictures.⁴¹

Double balloon enteroscopy

Double balloon enteroscopy is the therapeutic counterpart to small bowel capsule endoscopy. Described

by Yamamoto in 2001,⁴² it allows much deeper intubation of the small bowel, complete examination being achieved in 42–86% of cases,^{43–45} usually by successive oral and anal intubations—that is, two examinations, nearly always performed on different days. The variability is likely to reflect experience and sedation practices which include benzodiazepine sedation, the use of opiate analgesia and, in some centres, general anaesthesia. Each approach (oral and anal) may take up to an hour,^{43–44} although both may not be necessary if the relevant pathology can be reached during the first examination. A 1% complication rate for a diagnostic procedure (up to 4% following a therapeutic procedure)⁴⁶ is higher than for other endoscopies, but reflects the degree of difficulty, the duration of the procedure and the amount of sedation required. Meta-analyses comparing the two modalities suggest an equivalent diagnostic yield.^{47–48} For obscure bleeding, two studies suggest that double balloon enteroscopy might be a more cost effective initial investigation than capsule endoscopy unless the diagnostic sensitivity falls below a given level.^{49–50} Both concede that initial capsule endoscopy might be associated with a better long term outcome, however, because of a reduction in complication rate and use of endoscopic resources. Furthermore, diagnostic sensitivity of double balloon enteroscopy will be less in centres with less expertise. So most centres use capsule endoscopy to make diagnoses and target the use of double balloon enteroscopy to those requiring biopsy or therapy, a policy which seems likely to avoid unnecessary intervention. Finally, using the oral approach for lesions in the upper two thirds of the small bowel (determined on the basis of the time taken for the capsule to pass from the pylorus to the caecum) and anal approach for distal lesions appears to avoid unnecessary bidirectional procedures.^{51–52}

Oesophageal capsule endoscopy

Shortly after introducing the small bowel capsule endoscope, Given Imaging introduced an oesophageal capsule (the latest model being PillCam ESO2). This differs from the small bowel capsule in having viewing heads at both ends of the capsule obtaining a total of 18 frames per second. The battery is programmed to drive image acquisition for 30 min. To slow oesophageal transit and maximise image capture time, the protocol generally involves swallowing the capsule recumbent in the right lateral position aided by taking sips of water through a straw. Oesophageal capsule might offer an alternative to oesophagoscopy in the diagnosis of Barrett's oesophagus (sensitivity and specificity of 67–100% and 74–87%, respectively), erosive oesophagitis (50–80% and 87–90%)^{53–54} and oesophageal varices (86% and 88%).⁵⁵ However, screening for Barrett's oesophagus is not currently supported⁵⁶ and the potential for avoiding conventional endoscopy for varices screening or surveillance by

using oesophageal capsule endoscopy does not seem to have been taken up by many centres. This may be partly due to varices assessment forming a relatively small proportion of endoscopic workload, and the lack of a therapeutic facility which would allow varices ligation during conventional endoscopy. As complete oesophagogastrroduodenoscopy is generally performed for these patients, it may be that there is a perception that an oesophageal capsule examination seems rather too limited in extent. Perhaps further development of upper gastrointestinal tract capsule endoscopy will only occur with the advent of a capsule designed to visualise the whole upper gastrointestinal tract.

Colon capsule endoscopy

Colon capsule endoscopy, however, may establish a role in colonic imaging. The technological aspects of the PillCam Colon (Given Imaging Ltd) are similar to those of the PillCam SB, except that it deactivates after 3 min and reactivates 2 h later providing another 8 h of image acquisition time. Two viewing heads capture a total of four frames per second. Bowel preparation is obviously critical using this remote technology and relies on quite a complex protocol of preprocedural dietary restrictions, laxatives and prokinetic agents. The capsule reactivates prior to reaching the caecum in 97% of cases and while early data were less promising, complete colonic examination was as high as 93% in a recent large multicentre study.^{57–60} Compared with conventional colonoscopy, studies demonstrate a sensitivity and specificity in detecting significant polyps (three or more lesions or a single lesion of greater than 5mm) of 50–74% and 68–100%.^{57–60} One of the preliminary studies showed that detection rate improved following readings by all three members of a reading panel, reinforcing the importance of vigilance and experience in colon capsule video reading. Van Gossum *et al* also found a higher sensitivity for lesion detection in patients with cleaner colons,⁶⁰ findings that have been replicated in preliminary data from a multicentre Italian study,⁶¹ emphasising the crucial role of bowel preparation when using this modality. At the present time, therefore, conventional colonoscopy should remain the gold standard to diagnose lesions in patients with symptoms. There is, however, current interest in the potential value of colon capsule endoscopy in colorectal cancer screening, the non-invasive nature of the procedure and absence of radiation readily lending itself to repeated procedures. In a Markov computer model comparison by Hassan *et al*, colon capsule endoscopy required only a 30% better initial compliance than conventional colonoscopy in screening uptake to become more cost effective,⁶² something that may be possible in many programmes in which compliance is generally poor. Finally, there are emerging reports suggesting that colon capsule endoscopy may find a role in assessing inflammatory bowel disease activity,^{63 64} in which the diffuse nature

of the disease means that a loss of sensitivity in identifying single or few lesions compared with conventional colonoscopy is less important.

Summary

Capsule endoscopy offers a whole new approach to the diagnosis of gut disorders: non-invasive, easy to perform and patient friendly. It is firmly established as a firstline small bowel examination and for most scenarios is the investigation of choice,^{65–69} valuable in directing the use of double balloon enteroscopy to obtain biopsy or deliver therapy. As Crohn's disease is a transmural disease, its role will complement rather than replace cross sectional imaging, particularly as the reported accuracy of magnetic resonance, which does not involve radiation, translates to routine clinical practice. The oesophageal capsule seems likely to have a limited role until it is replaced by an extended upper gastrointestinal tract capsule, but this does not seem to be beyond the reach of the current technology. The colon capsule may establish a role in colonic imaging: although the first model is not as sensitive as conventional colonoscopy in diagnosis, the technology is being improved, it does not require intubation, sedation or radiation exposure and may find a role as an alternative choice for patients or in colon cancer screening. Whether or not a whole gut capsule endoscope is developed, we have reached an era in which completely remote endoscopic examination of the whole of the gastrointestinal tract is possible!

Competing interests MEMcA was sponsored by Given Imaging to attend the 3rd International Conference on Capsule Endoscopy in 2004 and the United European Gastroenterology Week in 2006. He is a co-director of the European Castle Capsule Course which is supported by Diamed Healthcare Ltd. He has received an honorarium from IntroMedic to provide capsule endoscopy training at the World Congress of Gastroenterology in 2009.

Provenance and peer review Commissioned; externally peer reviewed.

MEMcA wrote the first draft of the article which was modified by DSS and RS. MEMcA addressed the reviewers comments.

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