Recent data and emerging indications for capsule endoscopy in the exploration of the small bowel

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“Video capsule endoscopy (VCE) devices have been refined and diversified: better resolution and adaptive image capture for Pillcam SB3 ® (Given-Covidien), lateral panoramic view for Capsocam ® (Capsovision), and new transmission modalities for Mirocam ® (Intromedic). These latter two devices are being subject to diagnostic performance comparisons with Pillcam SB2 ®, although not yet with SB3 ®. Some contraindications of VCE are being adressed (SB2 and implantable cardiac equipment in particular). Validated indications (obscure gastrointestinal bleeding, suspected Crohn’s disease) have now been integrated into international guidelines. Positive predictive factors for digestive bleeding have been identified: in particular, an early examination by VCE (acute hospitalization, or within seven days of bleeding) offers significant diagnostic gains. The application of small bowel VCE is being refined for other indications, such as resistance to a gluten-free diet in celiac disease (investigation of patchy, or distal, lesions) and in certain polyposes (Peutz-Jeghers and Lynch Syndrome). The capability of VCE to detect tumors of the small bowel other than polyposes remains less than perfect.”
Video capsule endoscopy (VCE) has become, within a decade, a key examination in the exploration of the small intestine. The devices that are commercially available are being perfected and diversified and their indications are progressively expanding, while some of the contraindications are increasingly being addressed (stenoses, implantable electronic equipment).

**Device**

The original manufacturer, and still the market leader, Given Imaging, has joined the multinational company, Covidien. Given Imaging – Covidien have recently marketed a new generation of capsule dedicated to the small intestine (Pillcam SB3 ®), associated with a more intuitive and user-friendly reading software (Rapid Reader 8 ®). The single optical dome is in the axis of the capsule. The images of the Pillcam system are transmitted by radio frequency to the recorder. The technical performance of SB3 has been improved, with, in particular, better resolution, better illumination, adaptive image capture, and two-way communication with the DR3 recorder1. Despite these substantial technological improvements, there is currently no study available that demonstrates an improvement in actual clinical benefit of SB3 in comparison with SB2 (evaluation in progress). The Pillcam ® capsule remains the most widely distributed and most widely evaluated clinically. A few studies are currently assessing the competing devices.

The Capsocam ® capsule (Capsovision) incorporates four optical heads with lateral vision, and with a fixed depth of view, facing the bowel wall and allowing a panoramic 360 ° view. Each camera captures five images per second for the first 2 ½ hours, then three images per second. A motion sensor activates the image capture (both saving battery life and potentially decreasing the duration of the reading). The proposed system does not send images directly: the patient must retrieve the device and return it to the operator. In a prospective, multicenter French study, Pioche et al. compared the Pillcam SB2 ® and Capsocam SV-1 ® capsules [1]. Seventy-three patients ingested the two capsules, in a random order, one hour apart, in an investigation of occult gastrointestinal bleeding. Technical problems occurred in 11 cases (15.1%) with Capsocam ® (ingestion failure in 1 patient; cap-

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sule not recovered by 5 patients; recording error in 5 patients) and in 2 cases (2.7%) with SB2 (ingestion failure in 1 patient, recording error in 1 patient). Analysis of the diagnostic performance was conducted in the remaining 60 patients. The examinations were concordant in 49 patients (positive result with both devices in 23 patients, or 38.3%; negative result with both devices in 26 patients, or 43.3%) and discordant in 11 patients (18.3%).

The analysis by intention to treat per patient (including technical failures) showed a similar rate of positive diagnoses (Pillcam ® SB2: 43.8% versus Capsocam SV-1 ®: 38.4%; P = 0.79) with an acceptable coefficient of concordance, $\kappa$ (0.60). The analysis by intention to treat (including technical failures) per lesion (122 relevant lesions, P1 or P2) showed a higher detection rate with Capsocam SV-1 ® (108 lesions; 88.5%) compared with Pillcam SB2 ® (85 lesions, 69.7%; P = 0.001). Average reading times were significantly shorter with Pillcam SB2 ® (26 minutes) than with SV-Capsocam ® 1 (32 minutes) [1].

The Mirocam ® capsule uses a system of image transmission by electromagnetic field, with the patient’s body serving as a transmission medium (low-voltage signals, with energy savings and extended examination time). A randomized, prospective, multicenter US study compared Pillcam SB2 ® with Mirocam ® [2]. One-hundred-and-five patients with occult gastrointestinal bleeding ingested each of the capsules consecutively, in a random order, with results evaluable for 89 patients. The results were concordant for 80 patients (normal for 46 patients, abnormal with both systems for the other 24 patients), with a $\kappa$ coefficient of 0.55. The remaining 19 patients had discordant results (7 cases positive with Pillcam SB2 ® only, 12 cases positive with Mirocam ® only). The detection capabilities of both systems were deemed to be not statistically different, but the proportion of complete examinations of the small intestine was higher with the Mirocam ® capsule, although this was not statistically significant (93.3% versus 84.3%; P = 0.10) [2].

**Tolerability**

Among recent studies concerned with the contraindications or complications of VCE, several studies have been dedicated to the potential interference between the transmission systems of the endoscopic capsule and other electronic devices (pacemakers, defibrillators, left ventricle
assist devices). A review highlighted the lack of interference in vivo in 99 cases out of 100 [3]. A distance of 10 cm between the generator and the electrodes appears to be sufficient to prevent all interference. These risks should be considered to differ between the different types of image transmission systems used. Although the product sheets emphasize that these interference risks represent contraindications, the risks can now be considered to be reduced. Interactions with MRI remain a contraindication – an abdominal X-ray without preparation is still required after VCE and before performing an MRI.

**Validated indications**

Obscure gastrointestinal bleeding (without obvious cause after upper endoscopy and colonoscopy), overt or occult, remains the main indication for VCE of the small bowel [4]. Three meta-analyses (the most recent in 2011) have confirmed that VCE (in the absence of modified anatomy) has an equivalent diagnostic performance to double-balloon enteroscopy, and should therefore be the preferred method of diagnosis, given its minimally invasive nature. In the indication of anemia or obscure bleeding, VCE maintains its place as a first-line examination procedure: a prospective, single-center study including 189 patients with occult and obscure anemia showed a lesion detection rate of 79% for VCE, significantly higher than by small bowel enterography with enteroclysis (22%), noticeably for flat lesions. The rate for detection during a VCE of lesions to which the anemia or bleeding can be attributed varies in different studies between 35% and 77%, with a therapeutic impact between 35% and 50%. Conversely, where the VCE outcome is normal, the likelihood of recurrent bleeding within six months is around 4%. Some independent predictive factors of VCE positivity have been defined in recent years: the early examination (within seven days or during hospitalization following an overt bleeding). The use in emergency of the VCE in cases of overt bleeding is becoming widespread. For example, studies suggest the use of VCE [5], by the emergency physicians themselves. Other predictive factors for a VCE are overt bleeding, the use of oral anticoagulants, chronic liver disease, male gender, and advanced age.

The suspicion of Crohn’s disease after a normal colonoscopy is the second validated indication for VCE. The diagnostic performance is considered to be superior to that of cross-sectional examinations, in
particular MRI enterography (sensitivity, 100% versus 81%, specificity, 91% versus 86%). In a large proportion of cases these examinations are not necessarily in competition but rather are often complementary in the suspicion and evaluation of Crohn’s disease in the small bowel. The practice of VCE is now included in the recommendations of the American and European expert societies (ECCO [European Crohn’s and Colitis Organisation]). The risk of retention of the capsule in this indication is equivalent to that encountered in the exploration of anemia/occult bleeding (in the order of 1%). Recent advances [6] in the diagnostic performance of VCE and severity scores in IBD are detailed in another chapter and will not be discussed here².

**Potential indications**

**Celiac disease**

VCE has the potential to highlight patchy and/or distal small bowel lesions in a significant proportion of cases, especially in refractory situations, even after conventional radiologic and endoscopic evaluations (figure 1). A recent meta-analysis [7] involving six studies including 166 patients determined the performance of VCE in the evaluation of celiac disease, with a sensitivity of 89% and a specificity of 95%.

**Tumors and polyposes**

The capability of VCE to detect small bowel tumors is not perfect. A pooled analysis of 24 prospective studies emphasized that the detection capacities of VCE are superior to those of small bowel transit time and CT scan, but the proportion of lesions that are not noticed by VCE is estimated to be around 20% [8]. Two recent studies suggested a superiority of enterography with enteroclysis for this indication. In a retrospective, single-center study including 17 patients, enterography with enteroclysis detected a lesion in 94% of cases and VCE in 35% of cases (P = 0.004). In a retrospective review considering 183 patients with occult bleeding, 18 had tumors identified by double-balloon enteroscopy, 15 of whom had also undergone VCE. The VCE had only identified a tumor in 5 cases [9]. When the hypothesis of a small bowel

tumor in the presence of occult bleeding is considered, a negative exploration by video capsule endoscopy does not therefore necessarily imply that digestive explorations should be discontinued.

**Figure 1.** Typical appearance of celiac disease in video capsule endoscopy of the small bowel, showing the surface relief of the squamous mucosa in front view and jagged edges of the folds in profile, reflecting villous atrophy.

VCE and MRI are emerging as the best tools for the assessment of Peutz-Jeghers syndrome (PJS) (*figure 2*).

A recent prospective study [10] conducted among 19 patients with PJS polyps demonstrated comparable detection rates of VCE and MRI for polyps > 15 mm, with better tolerance of the VCE, but better localization and estimation of polyp size by MRI. A study from St. Mark's Hospital ³ presented at the UEGW (United European Gastroenterology Week) in 2013, performed on a larger scale (83 patients, 76 VCE, 54 MRI), nevertheless suggested equivalent performance of VCE and MRI with respect to the detection of polyps larger than 10 mm, localization, and size estimation. In this work, however, 6 polyps larger than 15 mm were missed by VCE. These two techniques are still

considered as complementary, and not in competition in the evaluation of these patients.

![Image of video capsule endoscopy]

**Figure 2.** Hamartomatous jejunal polyp, typically pedunculated, observed using video capsule endoscopy in Peutz-Jeghers polyposis.

The use of VCE in the detection of small bowel adenocarcinomas in Lynch syndrome was evaluated in a study from the French Society of Digestive Endoscopy [11]. Among 35 asymptomatic patients, 3 patients (8.6%) had a significant lesion detected by VCE (1 adenocarcinoma, 2 adenomas with low-grade dysplasia), while two of these lesions were missed by enterography with enteroclysis. Similarly, according to Samaha et al. 4, VCE appears to be superior to cross-sectional imaging (MRI or CT) for the detection of tumors or polyps (8.4% versus 4.9%) but not for the diagnosis of cancer (3.6% versus 3.2%) in this condition.

The role of VCE in familial adenomatous polyposis remains marginal. According to two prospective studies [12], VCE can detect jejunal or ileal polyps in 24–57% of patients but the clinical value of this screening is modest and, conversely, evaluation of the duodenum by VCE is insufficient (the papilla is visible in only 20–25% of examinations).

Conclusion and perspectives for clinical development

In recent years, the role of VCE in the exploration of unexplained gastrointestinal bleeding and in Crohn’s disease has been consolidated. For other indications (tumors, polyposes, celiac disease) the level of evidence for the use of VCE is still modest but VCE is nevertheless providing new opportunities, for which the diagnostic capabilities are becoming clearer. It can be noted that use of VCE is expanding beyond the gastroenterological community – noticeably among emergency physicians, pediatricians, and geriatricians – and that it is now better accepted by cardiologists when electronic devices for conduction disorders or heart failure are in place. Moreover, VCE is now being used as an evaluation tool in research: for example, to assess drugs capable of protecting the gut upon intake of non-steroidal anti-inflammatory drugs [13].

Conflicts of interest

Xavier Dray is a consultant for Covidien, Given Imaging, and Life Partners Europe.

References

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