Endoscopy and esophageal pathology: what should we expect?

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" Endoscopic esophageal exploration is usually performed by esophagogastroduodenal endoscopy (EGD), whereby the stomach and the first segments of the duodenum can be explored during the same examination. In certain circumstances, such as the exploration of gastroesophageal reflux disease (GERD) in search of esophagitis, or of patients with cirrhosis and suspected esophageal varices (EV), exploration alone of the esophagus is sufficient, without the intention to take a biopsy. The development and commercialization of an endoscopic capsule specific for the esophagus offers the opportunity for precise exploration of the esophagus via a minimally invasive examination. Since 2004, numerous clinical trials have studied PillCam ® ESO for these principal indications, considering EGD as the "gold standard". Although an exact equivalence in performance has never been demonstrated for any of these indications, the performance of PillCam ® ESO is nevertheless interesting from a technical point of view (ease of ingestion of the capsule, visibility of the esophageal mucosa and anomalies without the requirement for air insufflation) and also from the point of view of acceptability to patients, who systematically prefer PillCam ® ESO to EGD. Taking into account these interesting properties and the patient acceptability, a better management of certain patient populations can be envisaged, in particular patients with liver cirrhosis, for whom the presence of EV has an immediate therapeutic impact. "

Upper gastrointestinal endoscopy (EGD) has long been considered as the "gold standard" for exploration of the esophagus. It is a quick examination (less than 15 minutes), with both diagnostic and therapeutic capabilities. However, endoscopy as it is currently practiced has many drawbacks, the most important being its tolerability and its actual impact on patient care. Indeed, despite the technological progress, and even the possibility of performing nasogastric endoscopy, the tolerance of this examination is generally poor when it is not carried out under general anesthesia. The perception of this examination by the public and by patients is often very poor, leading clinicians to perform endoscopies more and more frequently under general anesthesia (50% of EGD in France). Performing EGD under general anesthesia, nevertheless, has serious drawbacks, including both the cost of the procedure and the availability of anesthetists [1, 2]. It is in this context that an esophageal capsule allowing direct visualization of the esophagus using a minimally invasive technique, without the need for sedation and with very good patient tolerability, was developed and commercialized in 2004.

Figure 1. PillCam ® ESO. Note the existence of an optical dome at each end. Dimensions: 11 x 26 mm.

Device

The PillCam ® ESO 2 (Given Imaging Ltd) (*figure 1*) that is currently marketed is a capsule measuring 11 mm by 26 mm (the same size as the small bowel capsule), which acquires video images from two cameras located at the proximal and distal poles of the capsule, at the rate of 14 images per second (7 images at each pole) during its natural progression through the esophagus. The PillCam ® ESO 2 battery has 30 minutes of autonomy, allowing the recording of more than 15,000 images during an examination. Once the examination is completed, the recording is transferred in a few minutes to a workstation equipped with the RAPID ® software, which allows a rapid interpretation, the reading time being only a few minutes. PillCam ® ESO is a single-use device.

Procedure

As for EGD, patients are required to fast for 6 hours before the examination is performed. Before ingestion of the capsule, the patient drinks a small amount of water (100 mL), in an upright position, in order to clean any deposits that may be present on the walls of the esophagus. The procedure for ingestion and progression of the capsule that permits optimal exploration of the esophagus has evolved since 2004. Initially, the capsule was swallowed by the patient while lying on his/her back, and then progressed along the esophagus by changes in their inclination, to 30 ° and then to 60 °. This first ingestion method did not allow the acquisition of a sufficiently satisfactory recording, particularly in terms of visualization of the lower esophagus. Hence, in 2006 Gralnek *et al.* [3] developed a simplified, better quality esophageal exploration procedure, which remains the recommended procedure. This comprises swallowing the PillCam ® ESO in the right lateral decubitus position, and then swallowing a sip of water every 30 seconds for 7 minutes. The patient can then get up and walk around until the battery is drained.

Indications

Patients with symptoms of GERD

Symptoms of gastroesophageal reflux disease (GERD) and dyspeptic disorders are very common in the general population [4]. They are a reason for healthcare consultations and are the main indication for upper gastrointestinal tract endoscopy in current practice [5, 6]. EGD is a powerful examination permitting the detection and/or exclusion of esophagitis (20–40% prevalence of erosive esophagitis in this population) [7, 8], detection of the presence and evaluation of the severity of Barrett's esophagus (a prevalence of about 10% in this population) and of ulcerative gastroduodenal lesions (9.5%) [10], and, much more rarely, of neoplastic digestive tract lesions (0.3%) [10]. Considering the poor tolerability of EGD and the noninvasive nature of PillCam ® ESO, clinical trials have been implemented very rapidly in patients with chronic GERD symptoms, with a diagnostic aim, to investigate the presence of esophagitis and a possible suspicion of Barrett's esophagus.

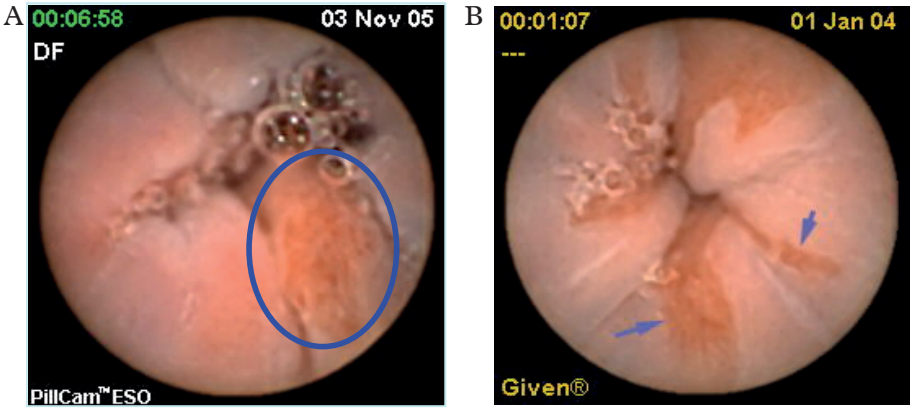

Figure 2. Endoscopic features seen using PillCam ® ESO.
A) esophagitis; B) suspicion of Barrett's esophagus.

The principal studies carried out in large cohorts of patients with GERD have compared PillCam ® ESO with EGD [11-13]. They have confirmed the feasibility (f*igure 2*) and safety of the technique for this indication, as well as its good level of acceptability by patients. The results of these studies demonstrated a high specificity (78–100%) and

negative predictive value (88–95%) of the capsule for screening for Barrett's esophagus and esophagitis, but a lower sensitivity (50–79%). A subsequent meta-analysis including more than 600 GERD patients confirmed these data, with a sensitivity of 78% and specificity of 90% (*figure 3*) [14]..

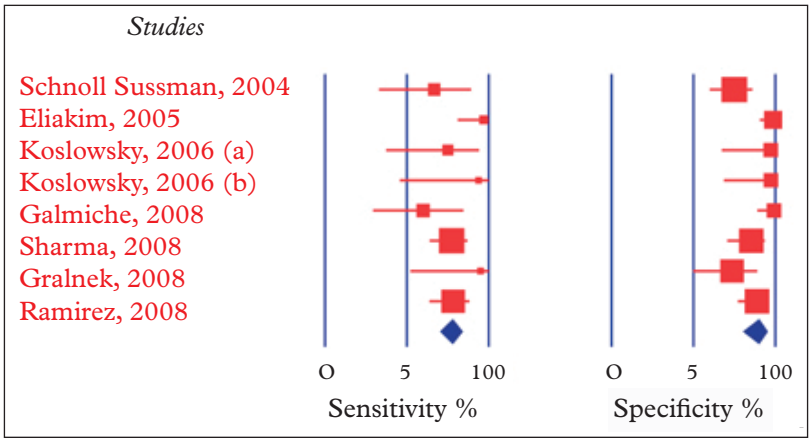

Figure 3. Results in terms of sensitivity and specificity of the meta-analysis of Bhardwaj *et al.*[14] (blue diamonds). References cited in [14].

Thus, although patient preference is in favor of PillCam ® ESO in terms of tolerability, the esophageal capsule is still not commonly used in clinical practice, principally because of its limitations: the impossibility to take biopsies when there is a suspicion of Barrett's esophagus, and the absence of complete and reliable exploration of the stomach, contrary to EGD. The first indication for esophageal exploration using PillCam® ESO could, therefore, only result from future health economic studies, which would take into account not only the performance of the technique but also the cost and the acceptability by the patient – guaranteeing better adherence to a screening or monitoring program.

Patients with suspected portal hypertension

Portal hypertension (PHT) is a frequent and severe complication of cirrhosis, in particular due to the development of esophageal varices (EV) and their risk of rupture and gastrointestinal hemorrhage [15-17]. EGD is the key examination for exploration and therapeutic deci-

sion making in cirrhotic patients suspected of PHT, through the search for EV. The presence of large EV is associated with a significant risk of gastrointestinal hemorrhage, which justifies the initiation of a prophylactic treatment with β-blockers or by ligature, for which the effectiveness is well proven [18-20]. Nevertheless, for the endoscopic surveillance of these patients with known cirrhosis (an EGD every 2 years), compliance remains insufficient due to poor tolerance of EGD [21, 22]. In addition, the use of general anesthesia constitutes an increased risk of complications, in particular of cardiopulmonary complications, in these fragile patients with liver failure [1, 2].

In this context, the PillCam ® ESO has been studied and compared with EGD. The first, pilot studies have shown encouraging results in terms of the detection and classification of EV (small *versus* large varices) [23-26] (*figure 4*). Larger, multicenter cohort studies [27-29] have confirmed the feasibility and effectiveness of the technique for the diagnosis of EV (sensitivity and specificity of 76–88% and 84–91%, respectively), and for discrimination between small and large EV (sensitivity and specificity of 76–78% and 88–96%, respectively) with a diagnostic accuracy of 81–92% for the indication of prophylactic treatment. The statistical equivalence between the two endoscopic techniques was, however, not established, considering EGD as the gold standard.

A meta-analysis published prior to the completion of the studies of Lapalus and Sacher-Huvelin *et al.* confirmed these performance data by distinguishing the performances in the context of a diagnosis in patients with suspected portal hypertension (sensitivity 83% and specificity 55%) from the performances in the context of the surveillance of patients known to have EV (sensitivity 87% and specificity 85%) [30]. More recently, a French study focused more specifically on this latter group of patients [31]. This study included 80 patients with cirrhosis and EV eradicated by ligature. PillCam ® ESO evaluation and EGD were carried out after an average of 16 months of follow-up. PillCam ® ESO showed a performance of 80% sensitivity and 87% specificity for the diagnosis of EV.

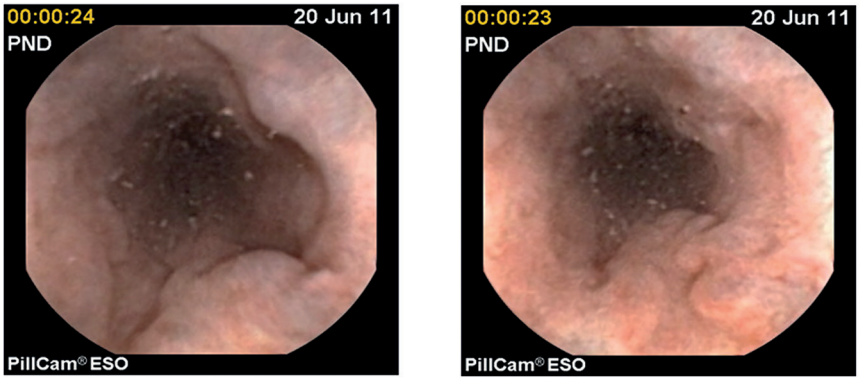

Figure 4. The presence of esophageal varices seen with PillCam ® ESO.

Cost-effectiveness studies have been published as part of a program of screening and prophylactic treatment decision-making for EV. In 2007, Spiegel *et al.* compared several strategies for the management of cirrhotic patients at risk of gastrointestinal hemorrhage [32]. Conventional endoscopic screening strategies based on EGD or PillCam ® ESO were compared with empirical treatment with β-blocker. The most efficient strategy was that of empirical treatment, with no significant difference in efficiency between the two endoscopic techniques. In 2009, White and Kilgore [33] used a Markov model to compare the screening strategy by PillCam ® ESO with that by EGD. Using this model, again no difference in efficiency was observed between the two techniques.

Much better accepted by patients with cirrhosis [29,31], and with a satisfactory efficacy for the diagnosis of EV in the context of screening or follow-up, PillCam ® ESO seems to have found its main indication for use in esophageal exploration in PHT. It could, in particular, be proposed to patients who refuse EGD or who are too frail to undergo this examination.

Other indications

A French study compared PillCam ® ESO with EGD for routine screening for neoplastic esophageal lesions in patients with a history of ENT cancer. For this indication, the performance of PillCam ® ESO

was insufficient in comparison with EGD, alone or in association with iodine staining (sensitivity 46% and 54%, respectively) [34].
Furthermore, PillCam ® ESO was tested as an examination to select patients with upper gastrointestinal bleeding, to facilitate diagnosis (a minimally invasive examination, well tolerated by the patient). However, when the PillCam ® ESO could not reach the duodenum (in 75% of cases in this study), there were too many discordances with EGD (45%) to recommend PillCam ® ESO as first-line examination for this indication [35].

Conclusion

In conclusion, the technique of esophageal exploration using PillCam ® ESO is reliable, well tolerated, and appreciated by patients, both for the exploration of GERD and for the screening and follow-up of patients with cirrhosis. However, in terms of service to the patient, the primary indication remains the exploration of portal hypertension. In this field, the development of noninvasive methods to predict the presence of EV (FibroMeter, FibroTest, Fibroscan ...) would require study of the role of PillCam ® ESO in an algorithm of the management of cirrhotic patients in complement or synergy with one or the other methods.

Conflicts of interest

Sylvie Sacher-Huvelin is a consultant for Given Imaging (Covidien GI Solutions).

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