From technological innovation to Medical Practice

Towards new algorithms

Symposium Given Imaging Covidien
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LGM *Sciences*

From technological innovation To Medical Practice

Towards new algorithms

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The Old and the New

"*Das Neue wächst nicht einfach aus dem Alten heraus, sondern tritt an seine Seite und eliminiert es im Wettbewerb.*" Joseph Schumpeter (1883-1950), economist and inventor of Creative Destruction.

Innovation is, in medicine, as indeed in many areas of science, industry, and even art, a key issue. It shapes medical progress to a great extent, and this can be assessed using different indicators such as life expectancy, morbidity, resulting costs (direct and indirect), quality of life, and patient satisfaction. From this point of view, it is not incorrect to measure the dynamism of a discipline by the number and quality of associated innovations that may be developed and implemented – in practice, to the stage of commercialization and funding by social security systems. This approach is, in France, as in most developed countries, tightly controlled by a set of methodological, legal, and administrative procedures whose onerous nature does not need further emphasis, but which seem to be a necessary prerequisite to ensure, on behalf of the sacrosanct principle of precaution, the safety of the "consumer" – in this instance the patient (this term being used in the broad sense, including, for example, individuals undergoing screening). Apart from the agencies responsible for this evaluation, which aims, a priori, to be objective, it is increasingly clear that many players have a stake in the process of recognizing innovation, for example, patients' associations and political or economic pressure groups ("lobbies"). To these players must finally be added the growing influence of the media, always on the lookout for the latest moral or public-health "scandal", leading to repeated calls for transparency and the denunciation of conflicts of interest. The result of this is a general climate of suspicion towards the medical profession, and especially its relations with the biomedical industry.

What is the situation in gastroenterology? The second half of the twentieth century has witnessed major advances, which have resulted in a hitherto unprecedented increase in life expectancy, the disappearance

of certain diseases (such as peptic ulcer disease), and the use of imaging techniques that are increasingly performant and decreasingly invasive: ultrasound, CT, MRI... It is only fair to recognize the important contribution of industry in this progress, even though academic research, notably in the biological field, has also played a crucial role. In reality, it would be pointless and even foolish to oppose academic research and industrial research and development, as it is clear that we, doctors and patients, need their cooperation and their partnership if we are to address with any chance of success the many challenges that we face in this new century. We must, therefore, with due respect to the naysayers, develop, and even stake a claim to, the collaborations of our discipline with industry, even beyond the usual boundaries of the biomedical industry.

Endoscopy, both diagnostic and interventional, represents one of the most exemplary aspects of what medicine, and in particular hepatogastroenterology, can expect from technological advances. The advent of capsule endoscopy in the 2000s was a major technological leap rendering the small bowel (finally!) accessible to reliable exploration. It is clear that the adventure continues with promising new fields of investigation, in particular for the colon. In the therapeutic domain, the treatment of high-grade dysplasia in Barrett's esophagus has benefited in the past decade from modern endoscopic treatments, notably radiofrequency ablation (unfortunately not currently available in France), relegating invasive and mutilating surgical resection almost to the history of medicine. Finally, the functional exploration of the digestive system is too often equated with a set of costly and unnecessary gadgets; however, this point of view would not withstand a serious and objective examination of the facts when considering, for example, the cost of the treatment of gastroesophageal reflux (PPI prescriptions – justified or not, absenteeism from work, sleep disorders) or the impact of chest pain of extracardiac origin on quality of life ...

It is, thus, with these reflections in mind that we have assembled with our colleagues from Given Imaging Covidien (GI Solutions) the program of this symposium and the content of this book.

This is intended to be a convincing illustration of the present and future impact of technological innovations in medical practice, as de-

monstrated in several algorithms of the book. We hope that this book will meet your expectations, from a scientific as well as a didactic and editorial point of view. We extend our sincere gratitude to the authors, who agreed to provide us, with timeliness, with high quality texts, and also to the moderators and reviewers of the book. Finally, our thanks go to Given Imaging Covidien, and more particularly to Luis Miguel Deretz and Philippe Pommier, without whom this symposium and book would not have been possible.

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Scientific Coordinator

Chairman

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President of the French
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Chairman

High-resolution manometry and the Bravo ® capsule®

Are there real improvements compared with conventional techniques?

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" High-resolution esophageal manometry represents undeniable progress in the exploration of esophageal motility. Studies indicate a diagnostic gain of between 5% and 20% compared with conventional manometry. Above all, high-resolution manometry improves the characterization of the different subtypes of achalasia, with implications for the therapeutic management of patients. The ease of implementation and training allows for skill transfer and easy retrospective review. Wireless pH measurement by Bravo Capsule® for the diagnosis of gastroesophageal reflux is a significant improvement on classical "wired" pH measurement, both in terms of safety and diagnostic yield. The diagnostic gain associated with this technique is due both to a reduced limitation of patient activity and also an extension of the recording period (up to 48 to 96 hours). This is a technique that can easily be proposed in the immediate aftermath of an upper endoscopy. The dissemination of these two techniques beyond expert centers is unfortunately limited due to their higher cost, which is poorly adapted to the modalities of healthcare reimbursement currently in operation."

High-resolution esophageal manometry

Esophageal motility disorders (EMD) can cause dysphagia and even chest pain. Although EMD may be secondary to systemic diseases, they are most often primary motility disorders that can be diagnosed and characterized by esophageal manometry.

High-resolution manometry

"Conventional" esophageal manometry is performed using perfused catheters that usually consist of four sensors, allowing assessment of the body of the esophagus and the lower esophageal sphincter (LES). In recent years, conventional manometry has gradually been replaced – at least in expert centers – by "high-resolution" manometry (HRM), which has two distinct innovations:

- the development of solid electronic pressure sensors, allowing the manufacture of catheters containing 36 pressure sensors spaced 1 cm apart (*figure 1*) ;

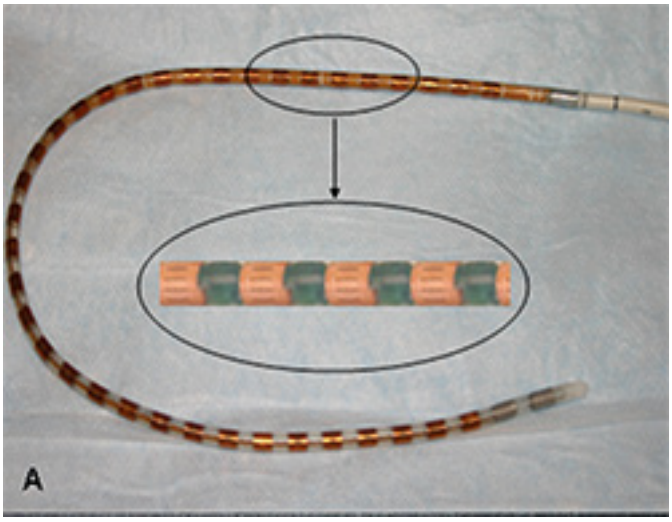

Figure 1. High-resolution manometry catheter with electronic sensors.

- computer processing of the data, which are presented as a function of time in three dimensions, rather than as traditional pressure curves: the pressure variations (represented by a color code) are

given according to the anatomical position of the sensors (*figure 2*).

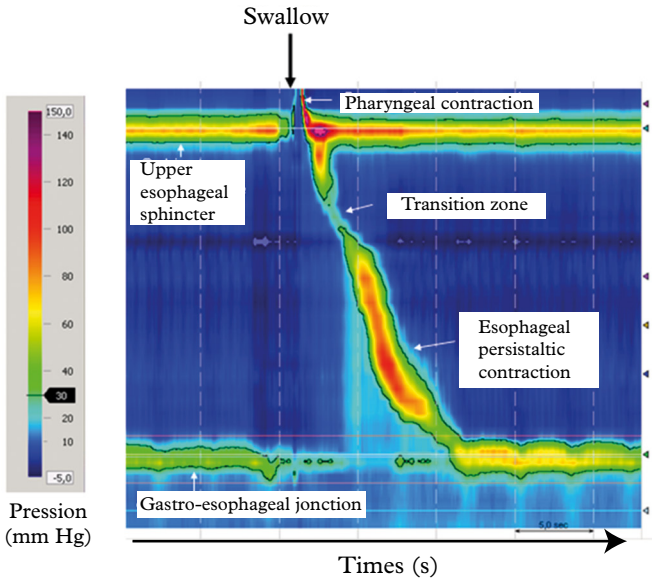

Figure 2. Representation of a high-resolution esophageal manometry. Normal peristaltic sequence.

Compared to conventional manometry, HRM is faster and better tolerated [1] because the two areas of high pressure corresponding to the upper sphincter and gastroesophageal junction can be easily located, allowing verification of the correct positioning of the catheter. Measurements are made simultaneously from the pharynx to the stomach, without the requirement to gradually withdraw the catheter, which significantly shortens the duration of the examination. In addition, the color-coded graphical representation of the pressure variations facilitates learning of the technique and improves interobserver reproducibility, even for nonexperts [2]. The major drawback of HRM remains the high cost of the catheters, which explains why it is mostly only expert centers that are currently equipped for this procedure. The dissemination of this technique is, nevertheless, in progress in France. The gain in diagnostic performance of HRM compared with conventional manometry is estimated to be between 10% and 20% for the exploration of unexplained dysphagia [3]. A recent, multicenter French study, for which the results are currently in press, showed a diagnostic

gain of a little less than 5% in expert centers. The main advantage of high-resolution manometry is probably a better distinction between esophageal achalasia and esophageal spasms, according to the Chicago classification criteria. This distinction is important because the prognoses and treatments of these two diseases are different

The Chicago classification

This classification [4] allows for a "step by step" analysis, based on the parameters obtained by HMR (*figure 3*).
The key parameter is the four-second integrated relaxation pressure (4s-IRP), which corresponds to the lowest pressure recorded at the esophagogastric junction during four (consecutive or nonconsecutive) seconds, in response to swallowing. The threshold of 15 mm Hg allows for good discrimination between patients with achalasia and control subjects. Analysis of the body of the esophagus allows for the distinction of three types of achalasia, plus possible variants. In the event of a normal IRP, significant abnormalities in the motility of the esophageal body may be responsible for dysphagia (esophageal spasm, "jackhammer esophagus"). Other anomalies (esophageal hypoperistalsis, nutcracker esophagus, etc.) are found more frequently than in controls, but their roles in the occurrence of dysphagia are debated. It is important to note that the Chicago classification does not address postoperative problems, motility disorders related to gastroesophageal reflux disease (GERD), or pharyngolaryngeal dysphagias. High-resolution manometry has facilitated the identification of three different profiles of esophageal achalasia (*figure 4*).

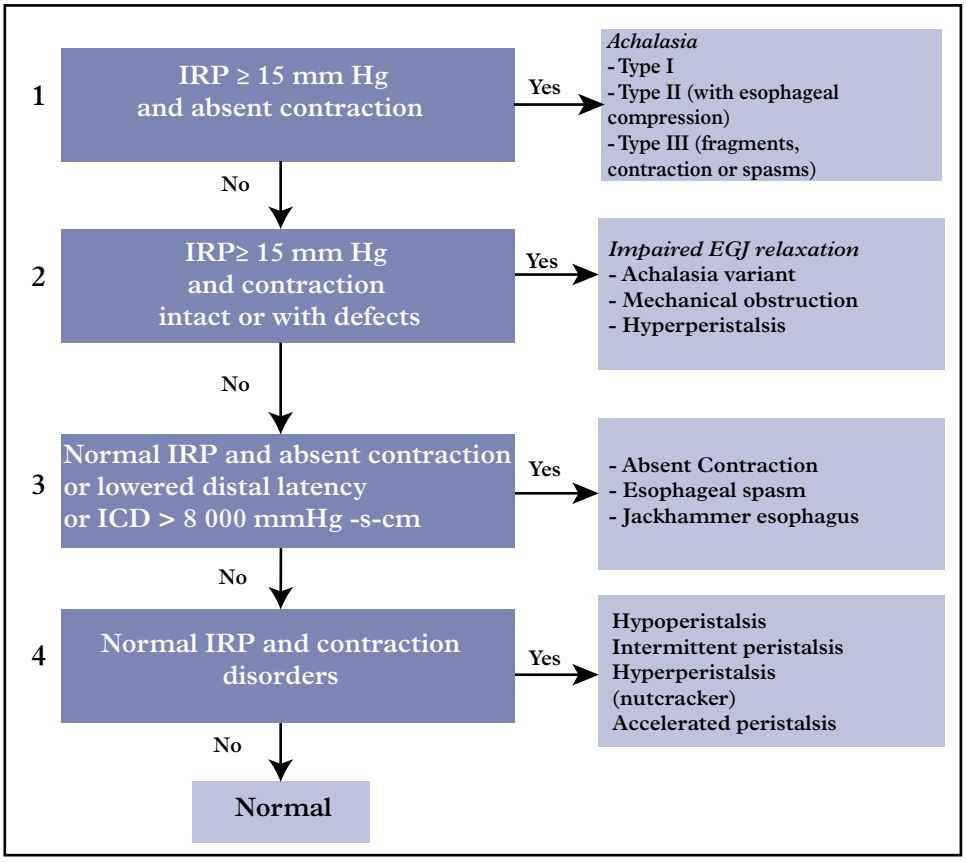

Figure 3. Diagnostic algorithm for the Chicago classification. EGJ: esophagogastric junction; IRP: integrated relaxation pressure; ICD: distal contractile integral.

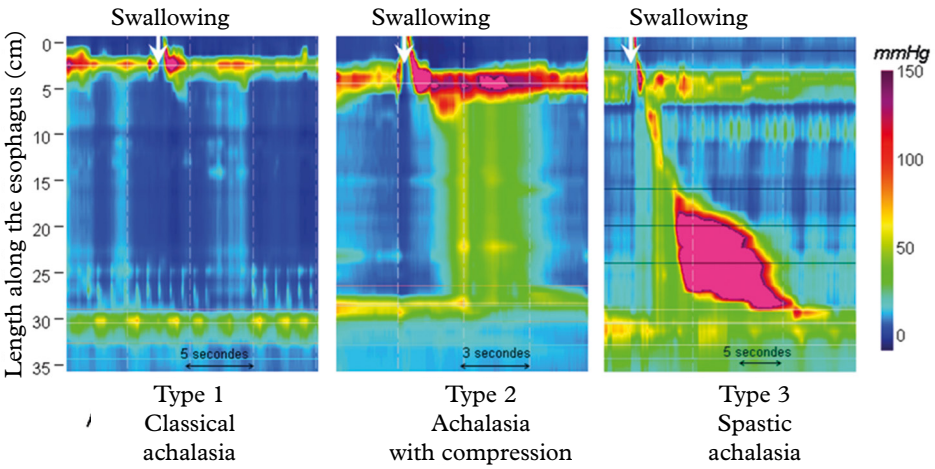

Figure 4. The three types of esophageal achalasia. In all cases there is a impaired relaxation of the gastroesophageal junction and a lack of peristaltic sequence. Type I: lack of pressurization; type II: pan-esophageal pressurization; type III: esophageal contractions.

In type I ("classical") achalasia, there is no increase in pressure in the esophagus in response to swallowing, and a relaxation defect of the gastroesophageal junction. In type II, there is pressurization of the esophagus associated with a compression of the ingested bolus between the UES and the distal functional obstruction. In type III ("spastic") achalasia, there are nonpropagated esophageal waves of large amplitude. It now appears to be well established that the response to treatment (dilatation, botox injection, or surgery) is better for type II achalasia [5]. Type III appears to fall within the scope of surgery rather than balloon dilatation, as shown by a recent randomized study [6]. HRM would allow a better differentiation between achalasia and diffuse esophageal spasm disease via the identification of pseudo relaxations of the LES associated with the ascent of the lower esophageal sphincter during swallowing. It is also easier to distinguish between an increase in intraesophageal pressure (pressurization of the esophagus) and an authentic esophageal contraction [7].

The exploration of oropharyngeal dysphasias

Another advantage of HRM compared with conventional manometry is that HRM allows the evaluation of dysphagia of pharyngeal origin. The study of pharyngeal contraction waves, of the pressurization of the UES, and of the waves in the proximal third of the esophagus may reveal abnormalities affecting the striated muscles (e.g. absence of pharyngeal contraction wave or relaxation defect of the UES during swallowing). Although a cricopharyngeal bar can be suspected in the case of a pharyngoesophageal pressure gradient, swallowing analysis using fluoroscopy remains the gold standard for pharyngolaryngeal dysphagias.

Conclusion

HRM of the esophagus represents undeniable progress in the exploration of esophageal motility. Characterization of the different subtypes of achalasia has consequences for therapeutic management. The ease of implementation and training allows for skill transfer and easy post-event review, however the cost of the equipment currently limits its diffusion.

The wireless pH-monitoring Bravo ® capsule

Esophageal pH monitoring is essential in the diagnosis of GERD. If endoscopy is normal, esophageal pH monitoring is most frequently indicated to establish a diagnosis of GERD when atypical symptoms (digestive, respiratory, ENT) are present. Conventional pH monitoring is carried out by placing an electrode in the esophagus, inserted through the nose. Despite miniaturization of the equipment and the widespread use of antimony electrodes, which are much better tolerated than glass electrodes, tolerance of the examination is often poor. In fact, the “wired” (nasoesophageal) catheter per se is the cause of the nasal, oral, and sometimes pharyngeal, discomfort. Patients, thus, have a tendency to alter their activities (social, professional, leisure) and diet during the recording, which may decrease the sensitivity of the test for the diagnosis of GERD. In wireless pH monitoring, the antimony electrode is incorporated into a capsule that is attached to the wall of the esophagus, and pH changes are transmitted from the

capsule to an external receiver by telemetry. This technique allows the discomfort associated with the presence of the catheter to be limited. In addition, it allows for an extension of the recording time up to 48 to 96 hours, and hence an additional increase in the sensitivity of the pH measurement [8].

Technical aspects

The Bravo ® capsule measures 25 x 6 x 5.5 millimeters and contains a battery, a radio transmitter, and an antimony pH electrode at its distal end (*figure 5*)

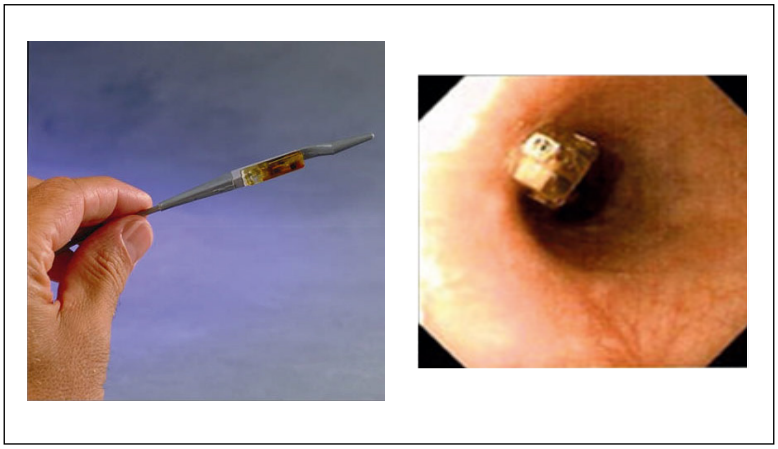

Figure 5. Bravo ® capsule on its delivery catheter, and attached to the wall of the esophagus.

As for "wired" pH monitoring, the pH electrode of the capsule is calibrated with buffer solutions before use. The insertion and fixation device allows the aspiration of a mucosal fold of the esophagus onto which the Bravo ® capsule is "stapled". The device can be inserted into the esophagus either through a nostril or, more easily, through the mouth. Once in place and activated, the electrode samples the esophageal pH once every six seconds and the data are transmitted every twelve seconds to a receiver box attached to the patient's belt. It is currently recommended that the capsule be positioned 6 cm above the squamous junction identified by endoscopy (assuming that the proximal edge of the LES is about 1 cm above this junction) [9]. The

alternative is to locate the superior edge of the LES by manometry, applying a correction of 4 cm for introduction via the mouth [10]. The various possibilities for installation of the capsule are represented in *figure 6*.

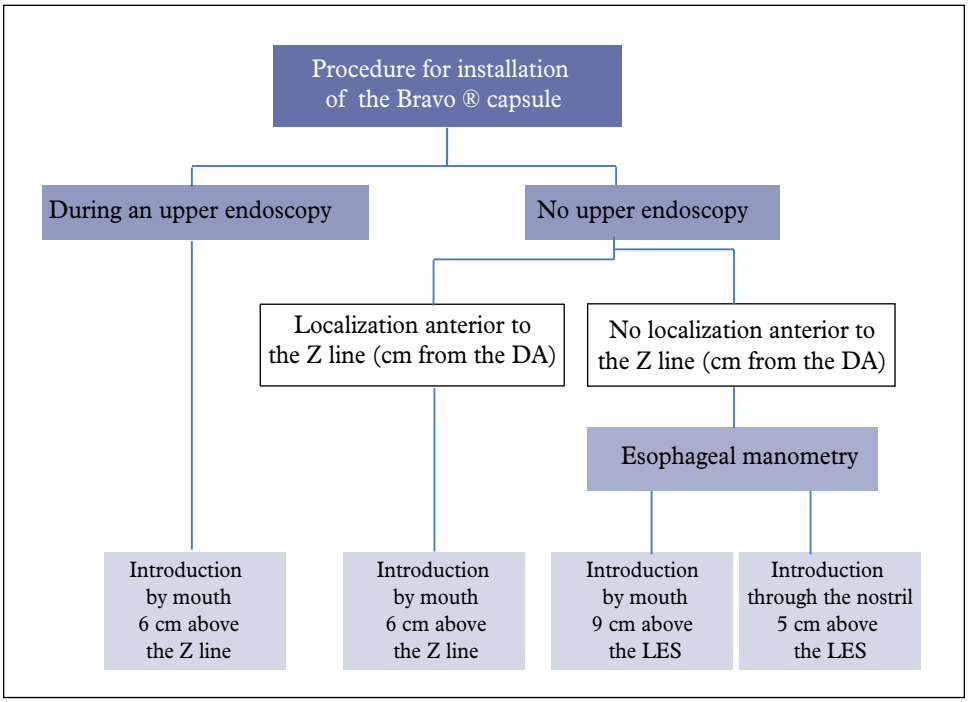

Figure 6. Installation procedures for the Bravo ® capsule.
DA: dental arches; LES: lower esophageal sphincter.

This is a simple installation technique, with a 90–95% success rate [11, 12]. Early detachment of the capsule may be observed in about 10% of cases, with premature passage of the capsule into the stomach and a misinterpretation of the acid exposure [12, 13]. pH profiles in the case of capsule detachment are, however, quite easy to recognize and interpretation errors are extremely unusual. Loss of the pH capsule signal can occur if the patient is too far from the receiver, however the missing data are generally of minimal importance and do not impact on the overall result of the recording [11].

Comparison of wired- and wireless pH monitoring

As classical pH monitoring has a higher sampling frequency than wireless pH monitoring, significantly more reflux episodes are observed with the former type of measurement, principally short reflux episodes that have a limited impact on esophageal acid exposure [14]. This is the reason why there is a good correlation between the two devices for the evaluation of esophageal acid exposure and the diagnosis of GERD [11]. Nevertheless, it must be borne in mind that these differences can have an impact on the calculation of reflux-symptom indexes, which themselves take into account each detected reflux episode. Finally, to date there has been no validation study of symptomatic indexes for wireless pH monitoring.

Tolerability and complications

The most common symptoms associated with the attachment of the capsule are chest pain, dysphagia, and the sensation of a foreign body, which are usually mild. Exceptionally, this may lead to the endoscopic removal of the capsule [11, 12,15], which proves to be necessary in less than 2% of cases. To date, only one case of esophageal perforation has been reported in the literature [16]. A failure of capsule detachment with prolonged retention requiring endoscopic resection is rare. Two randomized studies [13, 17] showed a better tolerance of wireless pH monitoring than of pH monitoring with a catheter; this better tolerance was related to the level of nasal, oral, and pharyngeal discomfort experienced, the maintenance of normal daytime activity, and the preservation of quality of sleep and of the diet

Potential advantages of prolonged recording

For wireless pH monitoring, numerous studies have shown that extension of the recording time to 48 hours increases the likelihood of diagnosing GERD. This analysis can take into account the total acid exposure over the entire recording time and/or day during which the acid exposure is abnormal (*figure 7*) [8].

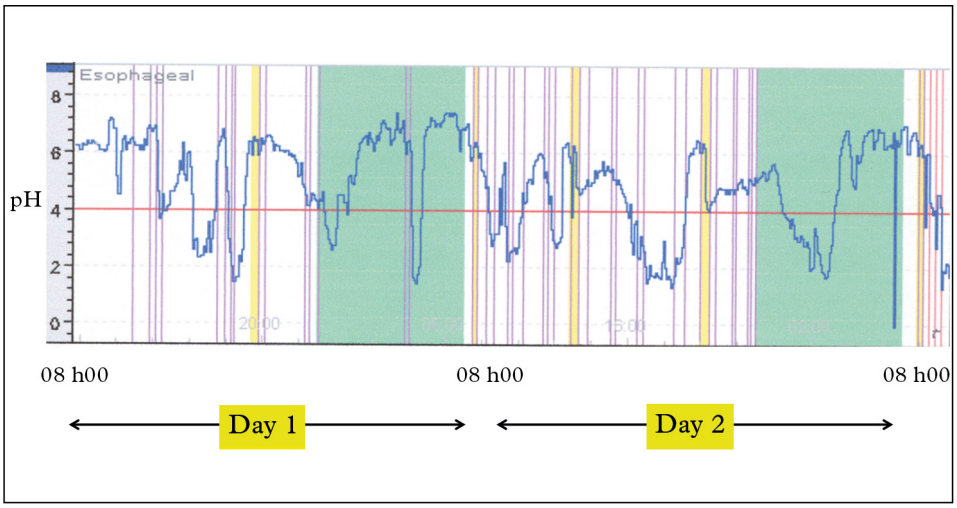

Figure 7. Example of a 48-hour Bravo ® pH monitoring plot. Nighttime periods are in green, meals are in yellow. The vertical bars correspond to activation of the event marker.

For example, a study in patients who had negative results from 24-hour wired pH monitoring showed that pathological acid exposure was found in 37% (average) and 47% (day of worst registration) of cases when prolonged Bravo pH monitoring (mean 72 hours) was performed. When the probability of symptom association was taken into account, these percentages were 34% and 63%, respectively [18]. Wireless pH monitoring prolonged to 96 hours also gives the opportunity to evaluate GERD without, and then with, treatment with proton pump inhibitors (PPI). Using two different receivers calibrated to the same Bravo ® capsule, Garrean et al. performed esophageal pH monitoring for four days in 60 patients with refractory symptoms, permitting an analysis "without" and then "with" double-dose PPI [19]. Of the patients presenting an abnormal acid exposure on day 1, only 2% had not normalized their exposure by the fourth day. This study demonstrated the feasibility that measuring pH for four days can facilitate, in a single procedure, documentation of the presence of symptoms associated with acid reflux, both without and with treatment.

Role of the Bravo ® capsule in the diagnosis of GERD

Schematically, the indications for Bravo ® pH monitoring are the same as those for conventional pH monitoring, namely to document GERD in the case of atypical symptoms and/or resistance to empirical medical treatment *(figure 8)*. The capsule seems to be particularly useful in cases where symptoms are intermittent and infrequent. It is also very easy to pose the capsule in the immediate aftermath of a normal upper endoscopy (in the absence of esophagitis) performed to investigate GERD, especially if this procedure is performed under sedation. This approach allows for a comprehensive management of the patient within a single time frame..

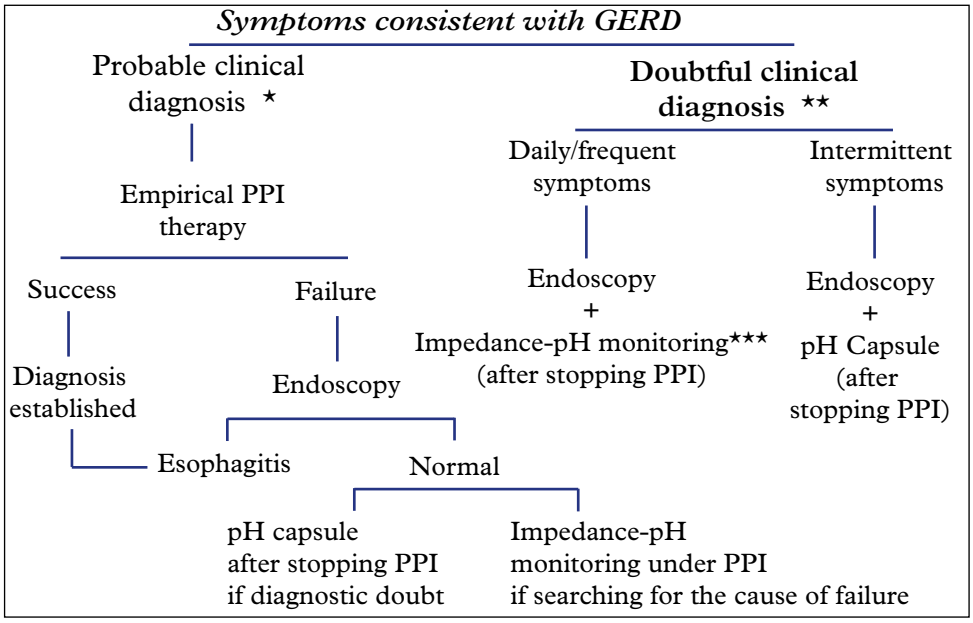

Figure 8. Algorithm for the diagnostic management of gastroesophageal reflux disease (GERD). PPI: proton pump inhibitors. *Typical symptoms and/or a known history of esophagitis; **atypical symptoms; ***replaced by "conventional" pH monitoring in non-equipped centers.

Conclusion

There is no doubt that wireless pH monitoring represents an improvement over the conventional "wired" pH monitoring technique, both in terms of patient tolerance and of diagnostic yield. It is a technique that can be easily proposed in the immediate aftermath of an upper endoscopy. In France, the distribution of wireless pH monitoring is currently limited by its cost and by lack of reimbursement by the healthcare system.

Conflicts of interest

Frank Zerbib is a speaker and consultant for Covidien GI Solutions, Shire-Movetis, and Reckitt Benckiser

References

1. Roman S, Bruley Des Varannes S, Cargill G, *et al.* Manométrie œsophagienne de haute résolution avec analyse topographique des pressions œsophagiennes : conseils pour la pratique et adaptation française de la classification de Chicago. *Hépato-Gastro et Oncologie Digestive* 2012 ; 19 : 316-28.
2. Soudagar AS, Sayuk GS, Gyawali CP. Learners favour high resolution oesophageal manometry with better diagnostic accuracy over conventional line tracings. *Gut* 2012 ; 61 : 798-803 (Epub 2011/10/15). doi: 10.1136/gutjnl-2011-301145
3. Pandolfino JE, Fox MR, Bredenoord AJ, Kahrilas PJ. High-resolution manometry in clinical practice: utilizing pressure topography to classify oesophageal motility abnormalities. *Neurogastroenterol Motil* 2009 ; 21 : 796-806 (Epub 2009/05/06). doi: 10.1111/j.1365-2982.2009.01311.x
4. Bredenoord AJ, Fox M, Kahrilas PJ, *et al.* Chicago classification criteria of esophageal motility disorders defined in high resolution esophageal pressure topography. *Neurogastroenterol Motil* 2012; 24 Suppl 1 : 57-65 (Epub 2012/02/22). doi: 10.1111/j.1365-2982.2011.01834.x.
5. Pandolfino JE, Kwiatek MA, Nealis T, Bulsiewicz W, Post J, Kahrilas PJ. Achalasia: a new clinically relevant classification by high-resolution manometry. *Gastroenterology* 2008 ; 135 : 1526-33. doi: 10.1053/j.gastro.2008.07.022.
6. Rohof WO, Salvador R, Annese V, *et al.* Outcomes of treatment for achalasia depend on manometric subtype. *Gastroenterology* 2013 ; 144 : 718-25; quiz e13-4 (Epub 2013/01/02). doi: 10.1053/j.gastro.2012.12.027.
7. Roman S, Zerbib F, Queneherve L, Clermidy H, Varannes SB, Mion F. The Chicago classification for achalasia in a French multicentric cohort. *Dig Liver Dis* 2012 ; 44 : 976-80 (Epub 2012/09/04). doi: 10.1016/j.

dld.2012.07.019
8. Roman S, Mion F, Zerbib F, Benamouzig R, Letard JC, Bruley des Varannes S. Wireless pH capsule--yield in clinical practice. *Endoscopy* 2012 ; 44 : 270-6 (Epub 2012/01/26). doi: 10.1055/s-0031-1291541
9. Hirano I, Richter JE. ACG practice guidelines: esophageal reflux testing. *Am J Gastroenterol* 2007 ; 102 : 668-85.
10. Ayazi S, Lipham JC, Portale G, *et al.* Bravo catheter-free pH monitoring: normal values, concordance, optimal diagnostic thresholds, and accuracy. *Clin Gastroenterol Hepatol* 2009 ; 7 : 60-7. doi: 10.1016/j.cgh.2008.08.020
11. des Varannes SB, Mion F, Ducrotte P, *et al.* Simultaneous recordings of oesophageal acid exposure with conventional pH monitoring and a wireless system (Bravo). *Gut* 2005 ; 54 : 1682-6. doi: 10.1136/gut.2005.066274
12. Remes-Troche JM, Ibarra-Palomino J, Carmona-Sanchez RI, Valdovinos MA. Performance, tolerability, and symptoms related to prolonged pH monitoring using the Bravo system in Mexico. *Am J Gastroenterol* 2005 ; 100 : 2382-6.
13. Pandolfino JE, Richter JE, Ours T, Guardino JM, Chapman J, Kahrilas PJ. Ambulatory esophageal pH monitoring using a wireless system. *Am J Gastroenterol* 2003 ; 98 : 740-9.
14. Pandolfino JE, Zhang Q, Schreiner MA, Ghosh S, Roth MP, Kahrilas PJ. Acid reflux event detection using the Bravo wireless versus the Slimline catheter pH systems: why are the numbers so different? *Gut* 2005 ; 54 : 1687-92.
15. Prakash C, Jonnalagadda S, Azar R, Clouse RE. Endoscopic removal of the wireless pH monitoring capsule in patients with severe discomfort. *Gastrointest Endosc* 2006 ; 64 : 828-32.
16. Fajardo NR, Wise JL, Locke GR, 3rd, Murray JA, Talley NJ. Esophageal perforation after placement of wireless Bravo pH probe. *Gastrointest Endosc* 2006 ; 63 : 184-5.
17. Wong WM, Bautista J, Dekel R, *et al.* Feasibility and tolerability of transnasal/per-oral placement of the wireless pH capsule vs. traditional 24-h oesophageal pH monitoring--a randomized trial. *Aliment Pharmacol Ther* 2005 ; 21 : 155-63.
18. Sweis R, Fox M, Anggiansah A, Wong T. Prolonged, wireless pH-studies have a high diagnostic yield in patients with reflux symptoms and negative 24-h catheter-based pH-studies. *Neurogastroenterol Motil* 2011 ; 23 : 419-26. doi: 10.1111/j.1365-2982.2010.01663.x
19. Garrean CP, Zhang Q, Gonsalves N, Hirano I. Acid reflux detection and symptom-reflux association using 4-day wireless pH recording combining 48-hour periods off and on PPI therapy. *Am J Gastroenterol* 2008 ; 103 : 1631-7. doi: 10.1111/j.1572-0241.2008.01829.x

SmartPill ®: a new methodology for the study of digestive motility

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" SmartPill ® is a new, single-use capsule allowing the continuous recording of pH, temperature, and pressure in the gastrointestinal tract for up to five days. The data collected by this capsule are transmitted by telemetry to an external, portable recorder. The pH and temperature curves, and the profile of the digestive contractions, can be consulted on screen through the connection of this box to a computer. Tracking of the capsule can be performed by monitoring the variations in pH, with a very rapid transition from acidic pH to a pH greater than 4 when the capsule leaves the stomach, followed by the recording of a clear fall in pH when the capsule crosses the ileocecal valve. This video capsule allows, with a very good tolerance, an ambulatory study of total and segmental transit times (gastric emptying, small bowel transit time, colonic transit time), with results that correlate well with those of the reference methods. Analysis of the propagation of contractions cannot be obtained with the capsule, however it does allow the recognition of gastric hypomotility in gastroparesis patients (gastric emptying > 300 minutes), and the distinction of low colonic motility or, on the contrary, excessive colonic motility (irritable bowel) in constipated patients (colonic transit > 59 hours). This new tool thus offers an exciting new alternative for the direct or indirect (transit time) study of digestive motility."

SmartPill ® is a new, single-use capsule allowing the continuous recording of pH, temperature, and pressure in the gastrointestinal tract for up to five days. The data collected by this capsule are transmitted by telemetry to an external, portable recorder. The pH and temperature curves, and the profile of the digestive contractions, can be consulted on screen through the connection of this box to a computer. Tracking of the capsule can be performed by monitoring the variations in pH, with a very rapid transition from acidic pH to a pH greater than 4 when the capsule leaves the stomach, followed by the recording of a clear fall in pH when the capsule crosses the ileocecal valve. This video capsule allows, with a very good tolerance, an ambulatory study of total and segmental transit times (gastric emptying, small bowel transit time, colonic transit time), with results that correlate well with those of the reference methods. Analysis of the propagation of contractions cannot be obtained with the capsule, however it does allow the recognition of gastric hypomotility in gastroparesis patients (gastric emptying > 300 minutes), and the distinction of low colonic motility or, on the contrary, excessive colonic motility (irritable bowel) in constipated patients (colonic transit > 59 hours). This new tool thus offers an exciting new alternative for the direct or indirect (transit time) study of digestive motility.

Technical aspects

The single-use SmartPill ® capsule is 26.8 mm long, with a diameter of 11.7 mm. It is equipped with pH, pressure, and temperature sensors. The capsule can measure pH changes in the range of pH 0.05 to 9.0, with an accuracy of 0.5 pH units. The pressure sensor is accurate to 5 mm Hg for pressures not exceeding 100 mm Hg. Temperatures can be measured between 25 °C and 49 °C, with an accuracy of 2 °C [1,2].
Data are transmitted from the capsule by telemetry, and are received and stored by a recorder attached to the patient's belt (*figure 1*).

Figure 1. SmartPill ® device: Photographs of the capsule and the recorder.

At the end of the examination, data are downloaded from the recorder to a computer hard drive for reconstruction of pressure, pH, and temperature curves using the MotiliGI Software (SmartPill Corporation) [1, 2].

Examination procedure

In performance validation studies, the subjects fasted overnight and then ingested the capsule immediately after eating a 255-calorie meal containing 2.2% fat, with 50 ml water. No further food intake was permitted until the sixth hour after ingestion of the capsule. Patients were then free to walk and to eat as they wished [2]. A button on the recorder allows events (meals, periods of sleep, elimination of a stool, onset of a symptom, etc.) to be reported, which is useful in the analysis of the graphic representation. The examination, which is carried out as an ambulatory procedure, lasts for a maximum of five days.

The procedure is contraindicated in patients with a history of gastric bezoar and in those with swallowing disturbances, dysphagia, or symptoms suggestive of digestive stenosis. To avoid interference between the capsule and another device, the SmartPill ® cannot be used in patients fitted with electromechanical devices, such as cardiac pacemakers or implanted insulin pumps.

The procedure is not approved by the US-FDA (Food and Drug Administration) for use in children.

Analysis of graphic representation

Ingestion of the capsule results in a rise of the temperature curve. Its arrival in the stomach results in the recording of an acid pH. Subsequently, a substantial increase in pH (at least 2 pH units), above pH 4, marks the arrival of the capsule in the duodenum (*figure 2*) [1].

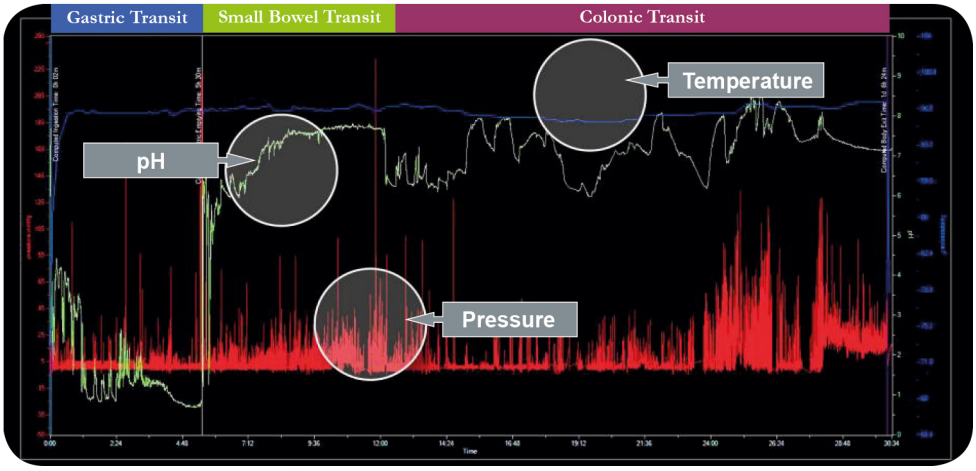

Figure 2. Example of a recording with pH, temperature, and pressure measurement curves. pH variations indicate arrival of the capsule in the stomach, passage through the pylorus and the ileocecal valve.

This increase in pH, although less pronounced, is observed in patients receiving antisecretory treatment with proton pump inhibitors [3]. Taking proton pump inhibitors before the examination is, however, advised against. Considering its size, the capsule only crosses the pylorus during the return of the first antral phase III, a substantial time after the meal [4], passage of the pylorus occurring when 97% of the volume of the meal has been evacuated from the stomach [4]. The sharp and prolonged fall in pH, of at least 1 unit for at least 10 minutes, reflects the passage of the ileocecal valve by the capsule, if this pH fall occurs at least 30 minutes after passage of the pylorus [1, 5]. Subsequently, a sudden drop in temperature (from 37 °C to ambient temperature) or loss of signal reflects the elimination of the capsule.

Analysis of the plot is firstly visual, to determine the times of the different steps in the progression of the capsule. A pressure analysis software program allows the calculation of the frequency of contractions

at various levels of the gastrointestinal tract, the area under the curve for endoluminal pressure, and a motility index, defined as:

Ln (sum of amplitudes x number of contractions + 1) [2].

Indications and results

The capsule provides information on both total and segmental transit times (*table 1*).

Table 1. Cut-off values for the interpretation of segmental transit times using the SmartPill ® capsule.

	Acceleration	Delay
Gastric emptying	< 2.5 hours rapid transit diarrhea)	> 5 hours (gastroparesis)
Small bowel transit time	< 2.5 hours (rapid transit diarrhea)	> 6 hours
Colonic transit time	< 5 hours (rapid transit diarrhea)	> 59 hours (constipation)

It also permits quantification of the amplitude and frequency of digestive contractions.

Studying different digestive transit times

Studying gastric emptying to investigate gastroparesis

One of the two main indications of this capsule is the diagnosis of gastroparesis, which is defined as an objective slowing of gastric emptying in the absence of any mechanical obstacle.
The reference method for studying gastric emptying is scintigraphy, which measures, with a gamma camera, the decrease in radioactivity in

the stomach area after ingestion of a doubly labeled meal (technetium 99 for the solid phase of the meal, indium 111 for the liquid phase). Measurement of emptying for at least four hours after the meal is recommended. The parameters calculated are the retention of isotopes at the second, and most importantly at the fourth hour. International standards base the diagnosis of gastroparesis on the demonstration of a gastric retention of the isotope greater than 60% at two hours and 10% at four hours after a meal of 255 calories containing only 2% fat and 2% fiber [6]. An alternative to scintigraphy is a breath test for octanoic acid labeled with a stable, nonradioactive isotope of carbon, 13C. This test, validated by several groups, allows the measurement of the T50 for gastric emptying of solids, with an accuracy comparable to scintigraphy [7]. These two tests both have shortcomings (*table 2*) and are available only in expert centers.

The validity of the capsule for the evaluation of gastric emptying has been the subject of several studies. Comparative studies showed that the parameter best correlated with the gastric emptying time measured with the capsule was the amount of isotope remaining in the stomach at four hours during a scintigraphic emptying study ($r = 0.73$). If this retention of isotope at four hours is taken as a reference, the sensitivity and specificity of the data provided by the capsule for the diagnosis of gastroparesis are 87% and 92%, respectively [8, 9]. A lower level of correlation is obtained for isotope retention at two hours ($r = 0.63$). The American and European Societies of Neurogastroenterology and Motility have concluded that an elimination time of the capsule from the stomach of less than five hours should be considered as normal [1], and that a gastric emptying time greater than 300 minutes supports a diagnosis of gastroparesis, with a sensitivity of 65% and a specificity of 87%. This value of 300 minutes has led to the overdiagnosis of gastroparesis in only 13% of controls. However, the diagnosis of gastroparesis is more common with the capsule than with scintigraphy (65% *versus* 44%). This is because scintigraphy measures only the evacuation of the isotopically labeled meal, whereas the capsule calculates the time between ingestion of the meal and its propulsion into the duodenum during the return of the first antral phase III. This return may be a little delayed compared to the complete evacuation of the two phases of the meal.

The capsule could also be used to demonstrate an acceleration of gastric emptying. However, the threshold value below which a diagno-

sis of accelerated gastric emptying can be made is not currently clearly established [1, 2].
A final point to highlight is that the capsule is able to detect accelerated emptying under the effect of drugs.

Table 2. Advantages and disadvantages of different gastric emptying study techniques according to the American and European Neurogastroenterology and Motility Societies [2].

	Scintigraphy	*Breathtest*	*SmartPill ®*
Validation	+++	+++	+++
Standardization	++	+++	+++
Stable quantitative results	+++	+++	+++
Availability	+	+	++
Ease of implementation	+	++	++
Patient discomfort	++	++	+
Tolerance	+++	+++	+++
Irradiation	+	-	-
Cost	++	+	++

Studying small intestinal transit time

An evaluation of small bowel transit time can be considered in patients suffering from unexplained and refractory nausea, vomiting, or bloating, or to investigate an endoluminal bacterial overgrowth.
The main method of analysis is the breath test, usually after the ingestion of 10 g lactulose. This test is based on the detection of a peak of hydrogen and/or methane of at least 5–10 ppm in the exhaled air after ingestion of the sugar. This peak is the manifestation of lactulose transformation by colonic bacteria. It thus reflects the arrival of sugar in the cecum after oral intake. This breath test has been criticized for three main reasons:

a) its result encompasses gastric emptying time and transit time in the small intestine;
b) the interpretation of the hydrogen peak can be awkward, as it can be an indication of sugar metabolism by small intestinal rather than colonic bacteria (endoluminal bacterial overgrowth), thus leading to an overdiagnosis of accelerated small bowel transit;
c) lactulose modifies transit time.

The other technique is scintigraphy, which is not widely implemented, and which encompasses gastric emptying and small bowel transit time. With the SmartPill ®, small bowel transit time is defined as the time interval between the arrival of the capsule in the duodenum (reflected by the sudden appearance of a pH close to neutral) and its entry into the cecum (extended fall in pH, of at least 1 pH unit, after a period of at least 30 minutes following the gastric exit of the capsule). The normal transit time is on average 4.6 hours, ranging from 4.0 to 5.9 hours in control subjects [1, 2, 10].

Studying colonic transit time

The benefit of measuring colonic transit in patients with diarrhea, and especially in those with constipation, is the interpretation of symptoms and possible adaptation of treatment. The two current main study methods are the measurement of radio-opaque marker colonic transit time (which can be performed by various methods) and colonic scintigraphy, which is only available in a few centers throughout the world, primarily for use in pharmacological research.
Using SmartPill ®, the colonic transit time is defined as the time between the arrival of the capsule in the cecum and its expulsion

through the anus.
Comparisons of capsule performance have mostly been carried out in relation to colonic transit times established with markers. The study by Rao et al. [11] showed that the capsule identified decelerations of transit and differentiated constipated subjects from a control population. There is a good correlation between the transit times determined by the number of radio-opaque markers eliminated and those calculated using the capsule. The correlation coefficients between the two calculation techniques at day 2 and day 5 were 0.74 and 0.69, respectively, in constipated subjects, and 0.70 and 0.40 in control subjects. At day 2, the sensitivity of the capsule as compared with transit time for the diagnosis of constipation was 0.73, with a specificity 0.95. At day 5, the sensitivity and specificity were 71% and 95%, respectively [11, 12]. In addition, the reproducibility of the results of the calculation of colonic transit times using the capsule may support its use in evaluation of the effectiveness of new treatments. However, this indication has not yet been validated.

Studying digestive contractions

This application of the capsule has been less well evaluated. As well as stationary recordings, the capsule also provides the possibility of recording in ambulatory conditions. However, in such conditions, motion artifacts may occur. In addition, the capsule has only one sensor. It cannot, therefore, provide any information regarding the propagated nature of the contractions registered. Explorations in gastroparetic patients have identified those in whom the slowdown in gastric emptying is associated with a significant decrease in the frequency and amplitude of antral contractions. In constipated patients with a transit time greater than 59 hours, exploration by capsule has led to the identification of two subgroups: constipated patients in whom colonic contractions are reduced, and those in whom these contractions were, on the contrary, increased in comparison with a control population, which directs the diagnosis towards that of irritable bowel syndrome with constipation. This potential diagnostic value of the capsule requires confirmation.

Technical failures and tolerance

Only 0.6% of patients were unable to swallow the capsule. Genuine technical failures (absence or interruption of recording before elimina-

tion of the capsule, impossibility to transfer capsule data to computer) were identified in only 36 of 495 cases [2]. The difficulties were mainly problems of interpretation: in approximately 5% of patients, this was due to the impossibility to determine with certainty the successive stages of capsule progression using the pH measurement data. The failure rate for the calculation of colonic transit time was calculated as 3%. Published findings all show agreement that the procedure is generally very well tolerated.

Conclusions

The SmartPill ® capsule is a new and interesting alternative for exploration, in ambulatory conditions, of the phenotype of patients with different functional digestive disorders. In particular, it represents a real alternative to the tests that are currently available to study the total transit time, and for the calculation of segmental transit times, particularly gastric and colonic transit times. It has been approved by the US FDA for these two latter indications

Conflicts of interest

Philippe Ducrotté is a member of the scientific advisory board of Given Imaging Covidien GI Solutions.

References

1. Rao SSC, Camilleri M, Hasler WL, *et al.* Evaluation of gastrointestinal transit in clinical practice : position paper of the American and European Neurogastro-enterology and Motility Societies. *Neurogastroenterol Motil* 2011 ; 23 : 8-23. doi : 10.1111/j.1365-2982.2010.01612.x
2. Saad R, Hasler WL. A technical review and clinical assessment of the wireless motility capsule. *Gastroenterol Hepatol* 2011 ; 7 : 795-804.
3. Michalek W, Semler JR, Kuo B. Impact of acid suppression on upper gastrointestinal pH and motility. *Dig Dis Sci* 2011 ; 56 : 1735-42. doi: 10.1007/s10620-010-1479-8
4. Cassilly D, Kantor S, Knight LC, *et al.* Gastric emptying of a non-digestible solid : assessment with simultaneous SmartPill pH and pressure capsule, antroduodenal manometry, gastric emptying scintigraphy. *Neurogastroenterol Motil* 2008 ; 230 : 311-9. doi: 10.1111/j.1365-2982.2007.01061.x
5. Zarate N, Mohammed SD, O'Shaughnessy E, *et al.* Accurate localization

of a fall in pH within the ileacecal region: validation using a dual-scintigraphic technique. *Am J Physiol Gastrointest Liver Physiol* 2010 ; 299 : G1276-86. doi: 10.1152/ajpgi.00127.2010
6. Tougas G, Eaker EY, Abell TL, *et al*. Assessment of gastric emptying using a low fat meal: establishment of international control values. *Am J Gastroenterol* 2000 ; 95 : 1456-62.
7. Ghoos YF, Maes BD, Geypens FD, Bellon M, Chatterton BE. Simultaneous 13C/14C dual isotope breath test measurement of gastric emptying of solid and liquid in normal subjects and patients: comparison with scintigraphy. *Nucl Med Rev Cent East Eur* 2003 ; 6 : 29-33.
8. Kloetzer L, Chey WD, McCallum RW. Motility of the antroduodenum in healthy and gastroparetics characterized by wireless motility capsule. *Neurogastroenterol Motil* 2010 ; 22 : 527-33. doi: 10.1111/j.1365-2982.2010.01468.x
9. Sarosiek I, Selover KH, Katz LA, *et al*. The assessment of regional gut transit times in healthy controls and patients with gastroparesis using wireless motility technology. *Aliment Pharmacol Ther* 2010; 31 : 313-2. doi : 10.1111/j.1365-2036.2009.04162.x
10. Maqbool S, Parkman HP, Friedenberg FK. Wireless capsule motility: comparison of the Smartpill GI monitoring system with scintigraphy for measuring whole gut transit. *Dig Dis Sci* 2009 ; 54 : 2167-74. doi: 10.007/s10620-009-0899-9
11. Rao SS, Kuo B, McCallum RW, *et al*. Investigation of colonic and whole-gut transit with wireless motility capsule and radiopaque markers in constipation. *Clin Gastroenterol Hepatol* 2009 ; 7 : 537-44.
12. Camilleri M, Thorne NK, Ringel Y, *et al*. Wireless pH-motility capsule for colonic transit: prospective comparison with radiopaque markers in chronic constipation. *Neurogastroenterol Motil* 2010 ; 22 : 874-82. doi : 10.1111/j.1365-2982.2010.01517.x

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.

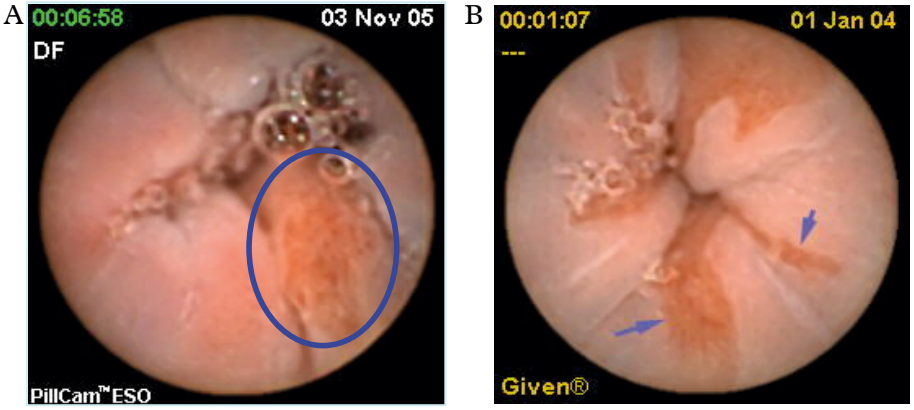

Figure 2. Endoscopic features seen using PillCam ® ESO.
A) esophagitis; B) suspicion of Barrett's esophagus.

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 (*figure 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]..

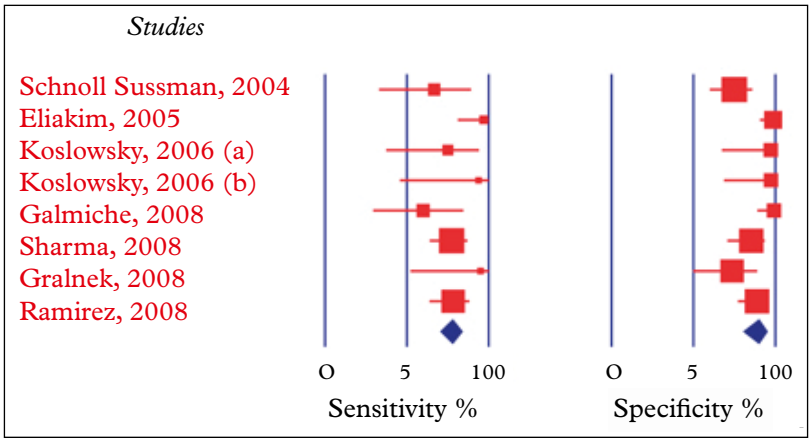

Figure 3. Results in terms of sensitivity and specificity of the meta-analysis of Bhardwaj *et al.*[14] (blue diamonds). References cited in [14].

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.

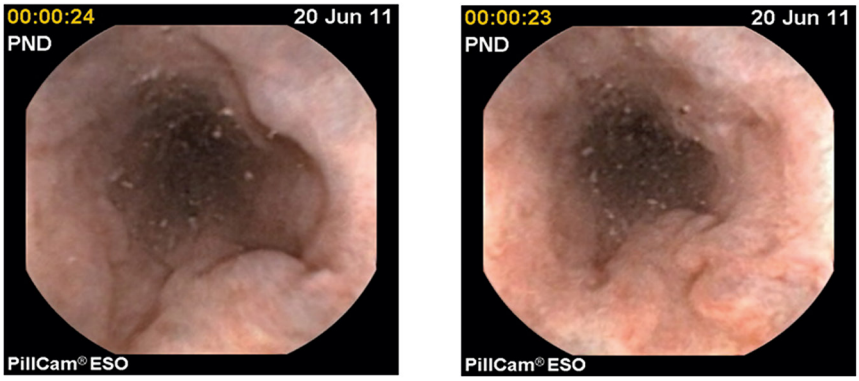

Figure 4. The presence of esophageal varices seen with PillCam ® ESO.

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).

References

1. Ciriza de los Ríos C, Fernández Eroles AL, García Menéndez L, *et al.* Sedation in upper gastrointestinal endoscopy. Analysis of tolerance, complications and cost-effectiveness. *Gastroenterol Hepatol* 2005 ; 28 : 2-9.
2. Abraham NS, Fallone CA, Mayrand S, *et al.* Sedation versus no sedation in the performance of diagnostic upper gastrointestinal endoscopy: a Canadian randomized controlled cost-outcome study. *Am J Gastroenterol* 2004; 99: 1692-9.
3. Gralnek IM, Rabinovitz R, Afik D, *et al.* A simplified ingestion procedure for esophageal capsule endoscopy: initial evaluation in healthy volunteers.

Endoscopy 2006 ; 38 : 913-8.
4. Locke GR, Talley NH, Fett SL, Zinsmeister AR, Melton LJ. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted Country, Minnesota. *Gastroenterology* 1997; 112: 1448-1456.
5. Loffeld RJ, Van der Putten AB. Rising incidence of reflux oesophagitis in patients undergoing upper gastrointetinal endoscopy. *Digestion* 2003 ; 68 : 141-4.
6. Lieberman D, Fennerty MB, Morris CD, Holub J, Eisen G, Sonnenberg A. Endoscopic evaluation of patients with dyspepsia : results from the national endoscopic data repository. G*astroenterology* 2004 ; 127 : 1067-75.
7. Quigley EMM, DiBaise JM. Non-erosive reflux disease: the real problem in gastro-oesophageal reflux disease. *Digest Liver Dis* 2001 ; 33 : 523-7.
8. Connor MJ, Weston AP, Mayo MS, Sharma P. The prevalence of Barrett's esophagus and erosive esophagitis in patients undergoing upper endoscopy for dyspepsia in a VA population. *Dig Dis Sci* 2004 ; 49 : 920-4.
9. Sharma P. Prevalence of Barrett's oesophagus and metaplasis at the gastro-oesophageal junction. *Aliment Pharmacol Ther* 2004 ;20 : S48-54.
10. Mantynen T, Farkkila M, Kunnamo I, *et al.* The impact of upper GI endoscopy referral volume on the diagnosis of gastroesophageal reflux disease and its complications : a 1 year croos sectinal study in a referral area with 260,000 habitants. *Am J Gastroenterol* 2002 ; 97 : 2524-9.
11. Lin OS, Schembre DB, Mergener K, *et al.* Blinded comparison of esophageal capsule endoscopy versus conventional endoscopy for a diagnosis of Barrett's esophagus in patients with chronic gastroesophageal reflux. *Gastrointest Endosc* 2007 ; 65 : 577-83.
12. Sharma P, Wani S, Rastogi A, *et al.* The diagnostic accuracy of esophageal capsule endoscopy in patients with gastroesophageal reflux disease and Barrett's esophagus: a blinded, prospective study. *Am J Gastroenterol* 2008 ; 103 : 525-32.
13. Galmiche JP, Sacher-Huvelin S, Coron E, *et al.* Screening for esophagitis and Barrett's esophagus with wireless esophageal capsule endoscopy: a multicenter prospective trial in patients with reflux symptoms. *Am J Gastroenterol* 2008 ; 103 : 538-45.
14. Bhardwaj A, Hollenbeak CS, Pooran N, Mathew A. A meta-analysis of the diagnostic accuracy of esophageal capsule endoscopy for Barrett's esophagus in patients with gastroesophageal reflux disease. *Am J Gastroenterol* 2009 ; 104 : 1533-9. doi : 10.1038/ajg.2009.86
15. Consensus conference: Complications of portal hypertension in adults. *Gastroenterol Clin Biol*. 2004; 28 : B324-34. [Review. French]
16. De Franchis R. Quand et comment évaluer le risque d'une première hémorragie digestive ? *Gastroenterol Clin Biol* 2004 ; 28 : B203-7.
17. De Franchis R, Prignani M. Natural history of portal hypertension in

patients with cirrhosis. *Clin Liver Dis* 2001 ; 5 : 645-63.
18. Pascal JP, Cales P. Propranolol in the prevention of first upper gastrointestinal tract hemorrhage in patients with cirrhosis of the liver and esophageal varices. *N Engl J Med* 1987 ; 317 : 856-61.
19. D'Amico G, De Franchis R. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. *Hepatology* 2003 ; 3 : 599-612.
20. Kishimoto H, Sakai M, Kajiyama T, *et al*. Clinical trial of prophylactic endoscopic variceal ligation for esophageal varices. *J Gastroenterol* 1997 ; 32 : 6-11.
21. Lapalus MG, Saurin JC. Complications of gastrointestinal endoscopy: gastroscopy and colonoscopy. *Gastroenterol Clin Biol* 2003 ; 27 : 909-21.
22. Eisen GM, Baron TH, Dominitz JA, *et al*. Standards Practice Committe, American Society for Gastrointestinal Endoscopy. The role of endoscopic therapy in the management of variceal hemorrhage. *Gastrointest Endosc* 2002 ; 56: 618-20.
23. Lapalus MG, Dumortier J, Fumex F, *et al*. Esophageal capsule endoscopy versus esophagogastroduodenoscopy for evaluating portal hypertension: a prospective comparative study of performance and tolerance. *Endoscopy* 2006 ; 38 : 36-41.
24. Eisen GM, Eliakim R, Zaman A, *et al*. The accuracy of PillCam ESO capsule endoscopy versus conventional upper endoscopy for the diagnosis of esophageal varices: a prospective three-center pilot study. *Endoscopy* 2006 ; 38 : 31-5.
25. Pena LR, Cox T, Koch AG, *et al*. Study comparing oesophageal capsule endoscopy versus EGD in the detection of varices. *Dig Liver Dis* 2008 ; 40 : 216-23.
26. Frenette CT, Kuldau JG, Hillebrand DJ *et al*. Comparison of esophageal capsule endoscopy and esophagogastroduodenoscopy for diagnosis of esophageal varices. *World J Gastroenterol* 2008 ; 14 : 4480-5.
27. Lapalus MG, Ben Soussan E, Gaudric *et al*. Esophageal capsule endoscopy vs. EGD for the evaluation of portal hypertension: a French prospective multicenter comparative study. *Am J Gastroenterol.* 2009 ; 104 : 1112-8. doi : 10.1038/ajg.2009.66.
28. De Franchis R, Eisen GM, Eliakim A, *et al*. Esophageal capsule endoscopy for screening and surveillance of esophageal varices in patients with portal hypertension. *Hepatology* 2008,47:1595-1603. doi: 10.1002/hep.22227.
29. Sacher-Huvelin S, Calès P, Bureau C *et al*. Screening of esophageal varices by esophageal capsule endoscopy: Results of a French multicentre prospective study. *Endoscopy* 2015 ; 47 : 1438-8812. doi: 10.1055/s-0034-

1391393
30. Lu Y, Gao R, Liao Z, *et al*. Meta-analysis of capsule endoscopy in patients diagnosed or suspected with esophageal varices. *World J Gastroenterol.* 2009 ; 15 : 1254-8. doi : 10.3748/wjg.15.1254
31. Laurain A, de Leusse A, Gincul R *et al*. Oesophageal capsule versus oesophago-gastroduodenoscopy for the diagnosis of recurrent varices : A prospective multicentre study. *Dig Liver Dis* 2014 ; 46 : 535-40. doi : 10.1016/j.dld.2014.02.002.
32. Spiegel BMR, Esrailian E, Eisen G. The budget impact of endoscopic screenoing for oesophageal varices in cirrhosis. *Gastrointestinal Endoscopy* 2007 ; 66 : 679-92.
33. White CM, Kilgore ML. PillCam ESO versus esophagogastroduodenoscopy in oesophageal variceal screening: a decision analysis. *J Clin Gastroenterol* 2009 ; 43 : 975-81. doi : 10.1097/MCG.0b013e3181a7ed09
34. Heresbach D, Leray E, d'Halluin PN *et al*. Diagnostic accuracy of esophageal capsule endoscopy versus conventional upper digestive endoscopy for suspected esophageal squamous cell carcinoma. *Endoscopy* 2010 ; 42 : 93-7. doi : 10.1055/s-0029-1243856.
35. Chandran S, Testro A, Urquhart P *et al*. Risk stratification of upper GI bleeding with an esophageal capsule. *Gastrointest Endosc* 2013 ; 77 : 891-8. doi : 10.1016/j.gie.2013.01.003.

Endoscopic treatment of Barrett's esophagus by radiofrequency ablation

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" Barrett's esophagus (BE) can be associated with the advent of an adenocarcinoma of the lower esophagus, and the detection of a dysplastic section is a predicting factor. The endoscopic treatment of a BE with high-grade dysplasia can be achieved by resection techniques such as endoscopic mucosal resection or submucosal dissection, which must be proposed as a first-line treatment if zones with raised abnormalities are present. However, the treatment of large, circumferential areas may lead to complications, and in particular to the risk of esophageal stricture. The destruction by esophageal radiofrequency ablation of an extended BE with zones of high-grade dysplasia has been evaluated in numerous studies and allows the eradication of the Barrett's mucosa in the short and medium terms, with low morbidity and a very significant reduction in the risk of development of an adenocarcinoma. Treatment of BE with low-grade dysplasia or without dysplasia using this technique is currently being evaluated."

Gastroesophageal reflux can be a contributing factor to the development of Barrett's esophagus (BE), also known as Barrett's mucosa. The prevalence of BE has been estimated at 1% in patients undergoing upper endoscopy, regardless of the indication [1]. BE is a stage with precancerous potential, which can evolve to adenocarcinoma. This risk of malignant transformation is very low in the case of BE without dysplasia (about 0.6% per patient per year) and is also minimal for BE associated with low-grade dysplasia (LGD) (1.7–2% per patient per year). In contrast, it becomes more substantial for high-grade dysplasia (HGD), with a risk determined as 6–10% per patient per year [2-5]. BE with dysplasia can be treated by surgery, but with significant morbidity and mortality, even when performed by highly skilled teams. Endoscopic treatments represent an alternative to surgical treatment. Mucosal resection techniques such as endoscopic mucosal resection or submucosal dissection allow curative treatment and histological analysis but are associated with the onset of esophageal strictures if an extensive resection is performed. Esophageal endoscopic radiofrequency ablation has become the standard treatment for dysplastic BE as it allows the destruction of a large area of the BE without excessive morbidity.

Technique of the esophageal radiofrequency ablation

The treatment is carried out with a radiofrequency catheter and a dedicated generator. The HALO 360 system (BAARx Médical, Covidien, USA) is a method of circumferential thermal destruction of the mucosa using a balloon topped with bipolar electrodes, which is inflated in the esophageal lumen (*figures 1 and 2*).

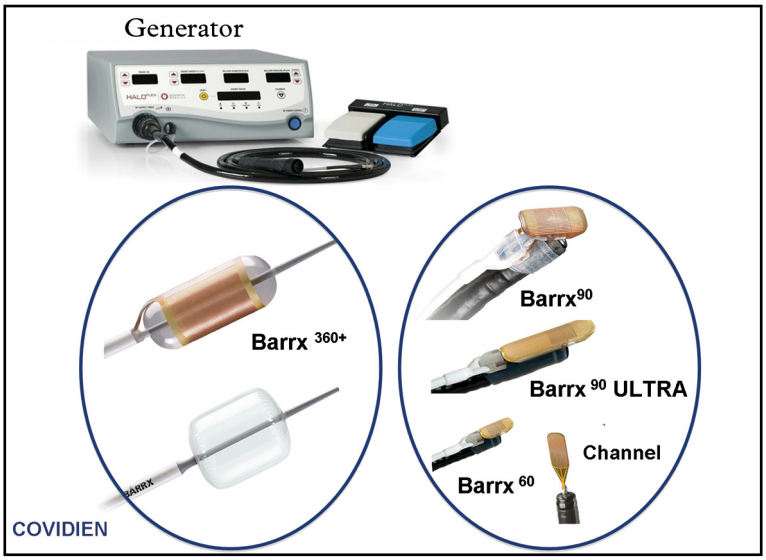

Figure 1. Equipment necessary for esophageal radiofrequency ablation.

The diameter of the balloon is defined through the use of a calibration balloon inflated beforehand in the esophagus. Destruction is homogeneous through the use of a standardized radiofrequency generator. When there is a noncircumferential lesion or a residual island after the first session of radiofrequency ablation, it is possible to use an applicator with bipolar electrodes attached to perform a focal destruction of the mucosa (HALO 90 system) or a smaller radiofrequency catheter inserted through the operating channel (channel catheter). On average, two to three radiofrequency sessions are required to eradicate the entire zone of BE.

The theoretical contraindications of esophageal radiofrequency ablation treatment are: active and/or complicated peptic esophagitis at the time of treatment; an esophagitis due to irradiation; a stricture of the esophagus of any etiology; the presence of esophageal varices; a history of Heller's cardiomyotomy.

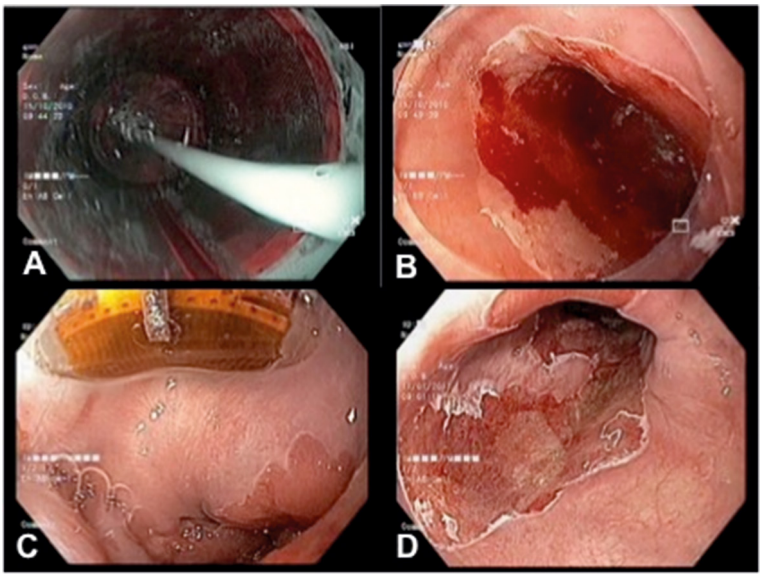

Figure 2. Circumferential radiofrequency ablation treatment with the Barrx 360 system, the balloon being inflated in the esophagus (A and B); and focal ablation treatment with the Barrx 90 system (C and D).

Indications for esophageal radiofrequency ablation

Barrett's esophagus and high-grade dysplasia

Diffuse or multifocal BE in the presence of HGD or of an in situ, non nodular adenocarcinoma is an indication for curative endoscopic radiofrequency ablation that has been well codified and scientifically documented. Macroscopic analysis in white light and with staining (acetic acid or virtual staining) allows the identification of any potential nodular lesion, which should be resected by mucosal resection or submucosal dissection before the remaining BE is treated. In case of doubt regarding a deep malignant invasion, endoscopic ultrasound can be performed beforehand. Only lesions classified as usT1N0 by endoscopic ultrasound can be resected. Histological analysis of the resected section will provide a precise diagnosis of the depth of invasion of the lesion. When the resection is complete and the lesion is intramucosal,

the residual circumferential BE should be destroyed by radiofrequency ablation during a second session of endoscopy (after 2–3 months). When resection is not complete and the depth of invasion reaches the submucosa, a complementary surgical treatment should be proposed. For elderly patients and/or those with significant comorbidities, radiochemotherapy in addition to noncurative endoscopic resection can be discussed.

Barrett's esophagus and low-grade dysplasia

French and international guidelines recommend the monitoring of BE with LGD. This surveillance includes carrying out staged biopsies (Seattle protocol) and biopsies targeted by chromoendoscopy. Radiofrequency ablation treatment in this situation is being evaluated in clinical research protocols that are comparing the evolution of patients treated with radiofrequency ablation with that of patients receiving endoscopic surveillance according to current recommendations. A recent study comparing a group of LGD patients treated with radiofrequency ablation with a control group showed a significant reduction in progression to HGD/cancer in the treated group [6]. In light of the initial results reported in the literature, radiofrequency ablation could be proposed when the presence of LGD is certain (verified after treatment with proton pump inhibitors [PPI], taken at a high dose for 2 months), confirmed (by two different pathologists), multifocal (> 5 LGD crypts in one biopsy; LGD at several levels of the esophagus), and diffuse (> 50% of 200 crypts analyzed show LGD). Other criteria associated with a greater risk of progression are male sex, age 50–75 years, being overweight, and the presence of a hiatus hernia [5].

Barrett's esophagus and intestinal metaplasia (IM)

BE without dysplasia is not an indication for radiofrequency ablation and should just be monitored according to the recommendations currently in place.

Results

A high complete-response rate with few complications

Several studies have demonstrated the effectiveness of radiofrequency ablation in the short and medium terms for the destruction of intestinal metaplasia (IM) and dysplasia in more than 80% of cases [7-10]. Radiofrequency ablation treatment of dysplastic BE also reduces the risk of developing esophageal adenocarcinoma. The first study in the field, by Shaheen et al. [8], showed that neoplastic progression was significantly reduced in the treated group compared with the control group (3.6% versus 16.3%, P = 0.03), with fewer cancers diagnosed (1.2% versus 9.3%, P = 0.045). A meta-analysis including 18 studies and 3,802 patients showed rates for the eradication of intestinal metaplasia and dysplasia of 78% and 91%, respectively [11].
Immediate major complications (hemorrhage, perforation) are extremely rare, whilst minor complications (retrosternal pain, fever, minor bleeding) are rare (between 5% and 10%), with a favorable evolution. The only long-term complication is the occurrence of stenosis, which is observed in 0.5%–10% of cases, depending on the published series. Endoscopic dilation is then an effective treatment. The risk of stenosis is greater in patients with a history of antireflux surgery, and in those who have esophagitis or who are taking oral nonsteroidal anti-inflammatory drugs [12].

Duration of the response and long-term risk of recurrence

The long-term outcomes of esophageal radiofrequency ablation have been less well evaluated, but they appear to persist, both for the eradication of IM and dysplasia [13,14]. Orman et al. [15] analyzed factors predictive of recurrence of dysplasia or IM after a comprehensive and effective radiofrequency ablation treatment in 262 patients. Median follow-up was for 397 days (54–1,668 days). Eight patients had a recurrence and three of these had progression to dysplasia or carcinoma in situ. In this study, the recurrence rates were 4.2% per year for dysplasia and 5.2% per year for IM. A study of 335 patients treated with radiofrequency ablation and endoscopic mucosal resection of nodular zones, for BE with HGD (72%), intramucosal adenocarcinoma (24%), or LGD (4%), showed complete eradication of HGD and IM

in 86% and 62% of patients at 12 months [15]. Phoa et al. reported that in 54 patients treated with radiofrequency ablation, preceded or not by endoscopic mucosal resection, eradication of the HGD or IM persisted in 90% of cases [16]. Finally, in an American study [17], treatment of 448 patients by radiofrequency ablation, for BE with HGD or intramucosal adenocarcinoma (70%), with LGD (15%), or with a simple IM (14%), resulted in complete eradication of the IM in 56% of patients at 24 months, and 71% at 36 months. The recurrence rate for IM at 2 years was 33%. The smaller percentage of eradication rates and the relatively high percentage of IM recurrence in this study could be explained by:

1. the need for two consecutive endoscopies without IM (as opposed to only one in the other studies) to confirm that eradication was complete;
2. the high proportion of BE greater than 8 cm;
3. the systematic collection of biopsies in the region of the gastroesophageal junction (common area of recurrence).

Recurrence of BE could be related to the persistence of glands buried under the squamous neoepithelium after radiofrequency ablation. The prevalence of buried glands varies between different studies. Their histological definition is the presence of a glandular epithelium covered by squamous epithelium, without contact with the esophageal lumen. The Amsterdam group [18] studied the presence of buried glands, as described by the pathologist, in residual BE islands of less than 5 mm. They analyzed biopsies from 69 consecutive patients with follow-up for BE, treated by radiofrequency ablation that was preceded, or not, by mucosal resection. Of 2,515 biopsies of neosquamous epithelium with a normal macroscopic appearance, buried glands were present in 0.1% of cases. Biopsies of the small, residual BE islands showed embedded glands in 21% of cases. These represent, in fact, "pseudo–buried glands" corresponding to the juxtaposition of the glandular epithelium in the BE island and the adjacent squamous epithelium. The authors explain that biopsies of the small BE islands can include an adjacent fragment of squamous epithelium, either because this epithelium partially covers the glandular epithelium or because of the tangential position of the biopsy forceps in the narrow esophageal lumen. This study highlights the risk of false-positive biopsies taken from BE islands. During the endoscopic surveillance of patients treated with radiofrequency ablation, the analysis of the esophageal mucosa

must be scrupulously and precisely performed to be certain to collect biopsies from the neosquamous epithelium and not from residual BE islands, which will be destroyed during the endoscopic follow-up. Nevertheless, these results provide incentive to maintain surveillance, even in patients with complete response after treatment with radiofrequency ablation.

Factors predictive of response to radiofrequency ablation

In the multicenter, prospective study of van Vilsteren et al. [19], independent predictive factors of poor response to circumferential radiofrequency ablation at 3 months (defined as < 50% loss of BE at the surface) were highlighted. In the group of poor responders (n = 36, 13%), the complete-response rates for IM and dysplasia (66% and 86%, respectively) were significantly lower than for good responders (95% and 98%); the average total time necessary to achieve eradication was longer (13 months versus 7 months) and more sessions were required (four versus three). The factors predictive of a poor early response were:

1. active esophagitis despite adequate PPI therapy;
2. Barrett's mucosa on the previous endoscopic resection scar;
3. narrowing of the esophageal lumen before radiofrequency ablation;
4. long-term development of dysplasia prior to treatment.

The presence of esophagitis was the most significant predictive factor and demonstrates the need for control of acid reflux prior to radiofrequency ablation treatment.

Conclusion

BE is a precancerous state that requires endoscopic surveillance to screen for dysplasia. Radiofrequency ablation treatment is indicated for flat esophageal BE with HGD. A rigorous macroscopic endoscopic examination should be performed to identify a possible suspect or nodular infiltration area in a circumferential BE, which can benefit from a prior endoscopic resection by endoscopic mucosal resection or submucosal dissection. The rate of complete response after radiofrequency ablation, in terms of dysplasia and IM, is greater than 80%, and persists after several years. Endoscopic surveillance should, however, be continued, even after complete eradication of BE and dysplasia, in

order to detect any recurrence from buried glands.

Conflicts of interest

None.

References

1. Ronkainen J, Aro P, Storskrubb T, *et al.* Prevalence of Barrett's esophagus in the general population: an endoscopic study. *Gastroenterology* 2005; 129 : 1825-31.
2. Skacel M, Petras RE, Gramlich TL, Sigel JE, Richter JE, Goldblum JR. The diagnosis of low-grade dysplasia in Barrett's esophagus and its implications for disease progression. *m J Gastroenterol* 2000 ; 95 : 3383-7.
3. Curvers WL, Ten Kate FJ, Krishnadath KK, *et al.* Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. *Am J Gastroenterol* 2010; 105 : 1523-1530. doi :10.1001/jama.2014.2512.
4. Bennett C, Vakil N, Bergman J, *et al.* Consensus statements for management of Barrett's dysplasia and early-stage esophageal adenocarcinoma, based on a Delphi process. *Gastroenterology* 2012; 143:336-6. doi : 10.1053/j.gastro.2012.04.032
5. Prasad GA, Bansal A, Sharma P, Wang KK. Predictors of Progression in Barrett's Esophagus: Current Knowledge and Future Directions. *The Am J Gastroenterol* 2010 ; 105 : 1490-1502. doi : 10.1038/ajg.2010.2
6. Orman ES, Li N, Shaheen NJ. Efficacy and durability of radiofrequency ablation for Barrett's Esophagus: systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2013 ; 11 : 1245-55. doi : 10.1016/j.cgh.2013.03.039
7. Vassiliou MC, Von Renteln D, Wiener DC, Gordon SR, Rothstein RI. Treatment of ultralong-segment Barrett's using focal and balloon-based radiofrequency ablation. *Surg Endosc* 2010 ; 24 : 786-91. doi : 10.1007/s00464-009-0639-4
8. Shaheen NJ, Sharma P, Overholt BF, *et al.* Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med* 2009; 360: 2277-88. doi: 10.1056/NEJMoa0808145
9. Lyday WD, Corbett FS, Kuperman DA, *et al.* Radiofrequency ablation of Barrett's esophagus: outcomes of 429 patients from a multicenter community practice registry. *Endoscopy*. 2010; 42: 272-8. doi : 10.1055/s-0029-1243883
10. Sharma VK, Jae Kim H, Das A, Wells CD, Nguyen CC, Fleischer DE. Circumferential and focal ablation of Barrett's esophagus containing dysplasia. *Am J Gastroenterol* 2009; 104 : 310-7.
11. Orman ES, Li N, Shaheen NJ. Efficacy and durability of radiofrequency ablation for Barrett's Esophagus: systematic review and meta-analysis. *Clin*

Gastroenterol Hepatol 2013 ; 11 : 1245-55. doi : 10.1016/j.cgh.2013.03.039
12. Pasricha S, Bulsiewicz WJ, Hathorn KE, *et al.* Durability and Predictors of Successful Radiofrequency Ablation for Barrett's Esophagus. *Clin Gastroenterol Hepatol* 2014 ; epub. doi : 1016/j.cgh.2014.04.034
13. Fleischer DE, Overholt BF, Sharma VK, *et al.* Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. *Endoscopy* 2010 ; 42 : 781-9. doi : 10.1055/s-0030-1255779.
13. Shaheen NJ, Overholt BF, Sampliner RE, *et al.* Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. *Gastroenterology* 2011 ; 141 : 460-8. doi : 10.1053/j.gastro.2011.04.061
14. Orman ES, Kim HP, Bulsiewicz WJ, *et al.* Intestinal Metaplasia Recurs Infrequently in Patients Successfully Treated for Barrett's Esophagus With Radiofrequency Ablation. *Am J Gastroenterol* 2013 ; 108 : 187-95. doi : 10.1038/ajg.2012.413
15. Haidray RJ, Dunn JM, Butt MA, *et al.* Radiofrequency ablation and endoscopic mucosal resection for dysplastic barrett's esophagus and early esophageal adenocarcinoma: outcomes of the UK National Halo RFA Registry. *Gastroenterology* 2013 ; 145 : 87-95. doi : 10.1053/j.gastro.2013.03.045
16. Phoa KN, Pouw RE, van Vilsteren FG, *et al.* Remission of Barrett's esophagus with early neoplasia 5 years after radiofrequency ablation with endoscopic resection: a Netherlands cohort study. *Gastroenterology* 2013 ; 145 : 96-104. doi : 10.1053/j.gastro.2013.03.046.
17. Gupta M, Iyer PG, Lutzke L, *et al.* Recurrence of esophageal intestinal metaplasia after endoscopic mucosal resection and radiofrequency ablation of Barrett's esophagus: results from a US Multicenter Consortium. *Gastroenterology* 2013 ; 145 :79-86. doi : 10.1053/j.gastro.2013.03.008
18. Pouw RE, Visser M, Odze RD, *et al.* Pseudo-buried Barrett's post radiofrequency ablation for Barrett's esophagus, with or without prior endoscopic resection. *Endoscopy* 2014 ; 46 : 105-9. doi : 10.1055/s-0033-1358883
19. van Vilsteren FG, Alvarez Herrero L, Pouw RE, *et al.* Predictive factors for initial treatment response after circumferential radiofrequency ablation for Barrett's esophagus with early neoplasia: a prospective multicenter study. *Endoscopy* 2013 ; 45 : 516-25. doi : 10.1055/s-0032-1326423

The small bowel video capsule: a new device for new levels of performance

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« *Exploration of the small intestine with an endoscopic video capsule is one of the latest technological revolutions in gastrointestinal endoscopy. The main indications are an investigation for occult bleeding after a normal result from a standard endoscopic assessment, and suspected damage to the small intestine in the context of Crohn's disease. The continuous technological development of the capsule has generated a new device (PillCam SB 3 ® system) capable of producing a film with better image resolution and an even greater coverage of the intestinal mucosal surface, with the development of an image capture adapted to the speed of progression of the capsule in the intestine. Finally, the new RAPID 8 ® software associated with this SB 3 ® capsule is even more performant (speed of image interpretation, numerous modes for optimized playback) and represents a valuable aid for the reader.*"

Having for a long time been frustrated at not being able to explore the small intestine optimally, endoscopists have welcomed the small intestinal video capsule as a technological revolution. While this examination is currently in routine use for well-defined indications, the capsule has also been the focus of continuing technological development. New devices are currently being proposed that aim to improve the video image quality, and thus to improve the diagnostic yield of intestinal endoscopic investigations. Another objective is to facilitate the interpretation of video recordings with innovative software. It is with these considerations in mind that the new PillCam SB 3 ® system has been developed. The package comprises: the PillCam SB 3 ® capsule, the PillCam ® Recorder DR3, the PillCam ® Sensor Belt SB3, and the RAPID ® for Pillcam Software v8.0 (*figure 1*).

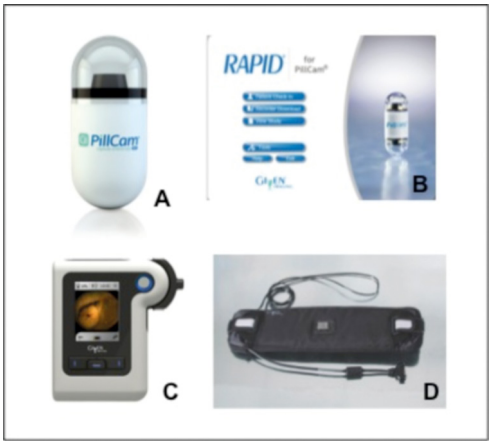

Figure 1. The PillCam SB3 ® system, composed of the following elements: the PillCam SB 3 ® capsule (A), the RAPID ® for Pillcam Software v8.0 (B), the PillCam ® Recorder DR3 (C), and the PillCam ® Sensor Belt SB3(D).

PillCam SB3 system hardware

The PillCam SB3 capsule

The PillCam SB 3 ® capsule proposed by Covidien (GI Solutions) Given Imaging is a new-generation capsule derived from a technological improvement allowing the acquisition of a better image quality and the exploration of the small intestinal surface with an even

greater coverage. The optics and sensor have been modified. This "ecological" capsule does not contain mercury. Its functioning time is approximately 11 hours, which limits the number of incomplete examinations resulting from battery failure during recording.
The improvements in image resolution result in a sharper and brighter image, which allows the details of the intestinal mucosa to be seen more clearly (*figure 2*).
Small intestinal lesions, such as angiodysplasias that are red or ulcers with a whitish, fibrinous background, are thus easier to identify.

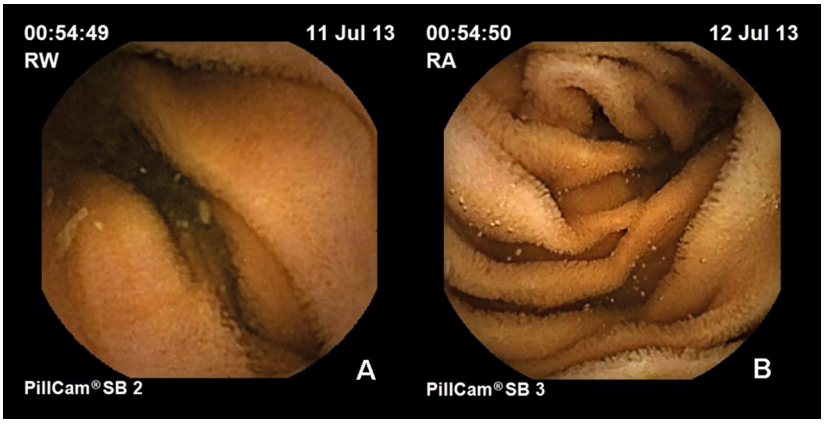

Figure 2. The PillCam SB 3 ® capsule (A): better definition than the PillCam SB 2 ® capsule (B). Images of the small intestine with normal villi, in the same patient and in the same intestinal portion.

This increase in resolution is estimated to be 30% as compared with the previous device, the PillCam SB 2 ® capsule. The smallest object that can be detected with PillCam SB 3 ® is 0.07 mm, *versus* 0.1 mm with PillCam SB 2 ®. This improvement in the image is useful in the detection of submucosal tumors, where the eye is often drawn to a simple deformation of a mucosal fold, and for which diagnosis is often difficult. Furthermore, the contrast is increased, which facilitates analysis of the mucosal surface and the better detection of small bowel polyps, such as in patients with polyposes such as Peutz-Jeghers disease.
Adaptation of the image capture to the capsule speed is one of the most important innovations of the SB 3 ® capsule. Thus, when the capsule is moving fast, as for example in the distal duodenum, proxi-

mal jejunum, or during passage through a descending intestinal loop, the number of images per second increases from two to six. The filming of a greater mucosal surface in these situations thus limits the risk of a lesion being missed. Using this new system, the number of images to process is theoretically greater, however the reading time does not appear to be any longer. This can be explained by a decrease in the number of "stops" or "image replays" needed during the reading, due to a better overall image quality (sharpness, brightness, and contrast), with wider angles of vision and a better depth of field.

The PillCam ® Recorder DR3

The DR3 recorder captures images continuously and is equipped with an LCD screen that allows real-time viewing of the film taken by the capsule. It is no longer necessary to connect a computer to the recorder to identify the location of the capsule.

The PillCam ® Sensor Belt SB3

The Sensor Belt makes the procedure simpler and faster. It helps to improve patient comfort (especially for patients for whom shaving is necessary before electrodes can be attached with skin patches).

The RAPID ® for Pillcam Software v8.0 associated with the PillCam SB 3 ® system

The new reading software, RAPID ® 8, associated with this capsule has a modified user interface and improved software ergonomics. The ribbon, which is an element of the Microsoft user interface, has been designed to help readers to find the software commands quickly. Basic functions are facilitated, such as, for example, drafting a report or identifying a patient. The video-processing algorithm has been improved and the creation of a video is now faster. New reading support tools are available and the «Progress Indicator» program has been improved. In the "QuickView" mode, also available in the previous version of the software, images that are considered to be identical can be removed from the film, allowing the reading of a film containing only the images that the software identifies as relevant. This algorithm has been evaluated in the literature and ensures a very good sensitivity [1]. The

"Complementary QuickView" mode proposed in the new version allows the visualization of all of the images, including those that have been excluded in the QuickView mode. The "Mosaic" mode shows, as a matrix, all the images selected by an algorithm. Only the relevant part of the image is displayed, allowing an easier visualization of the entire video.

The "SBI" (Suspected Blood Indicator) mode automatically flags suspicious images of bleeding when they contain a red spot consistent with blood. The sensitivity, positive predictive value, and accuracy of this function for the detection of active bleeding in the small intestine are 81%, 81%, and 83%, respectively [2]. This analysis represents an aid to the diagnosis of hemorrhagic lesions during the examination but a full reading of the film taken by the capsule remains indispensable.

The utilization of virtual chromoendoscopy (FICE: Flexible Intelligent Color Enhancement) makes it possible to increase the contrast and to better detect certain types of flat lesions, such as angiodysplasias, which will have an enhanced color, or small flat polyps, for which the surface relief is increased. The benefit of this feature has already been investigated using the previous PillCam system [3].

The software contains a large database of Pillcam capsule endoscopy images that allows the comparison of a pathological image found during a reading with the images in the atlas (f*igure 3*).

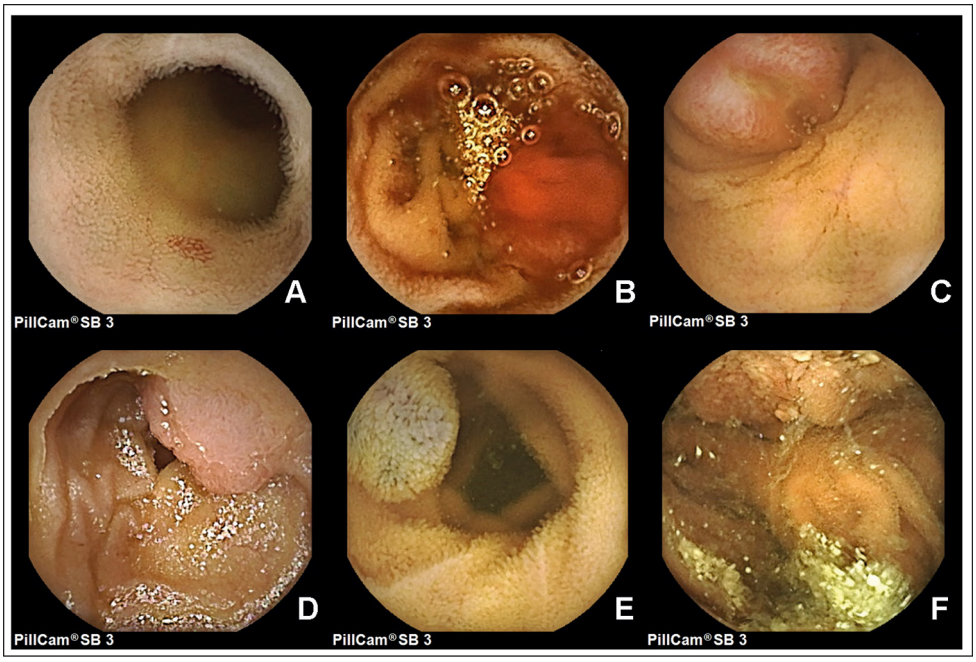

Figure 3. Examples of pathological images identified by the SB3 ® capsule. A: typical angiodysplasia; B: active bleeding with a blood clot in the intestinal lumen; C: suspicious nodular ulceration corresponding to the histology of an adenocarcinoma in the small intestine; D: small submucosal tumor corresponding to a carcinoid tumor; E: jejunal varix in the context of segmental portal hypertension; F: hamartomatous polyp (at the top of the image) in the context of Peutz-Jeghers syndrome.

Conclusion

This new small-bowel video capsule system represents a technological advancement, with the following advantages:
1. increase in the ease and speed of capsule reading;
2. increased diagnostic yield through superior film quality and adaptation of the image capture to the speed of progression of the capsule through the small intestine.
The potential future developments of the capsule are numerous: a "remote-controlled" capsule, a "therapeutic" capsule delivering an active substance in the small intestine, a more efficient method of locating the capsule in the small intestine, visualization of the film in 3D, etc.

Conflicts of interest

None.

References

1. Saurin JC, Lapalus MG, Cholet F, *et al.* Can we shorten the small-bowel capsule reading time with the «Quick-view» image detection system? D*ig Liver Dis* 2012 ; 44 : 477-81. doi : 10.1016/j.dld.2011.12.021
2. Liangpunsakul S, Mays L, Rex DK. Performance of Given suspected blood indicator. *Am J Gastroenterol* 2003 ; 98 : 2676-8.
3. Imagawa H, Oka S,Tanaka S, *et al.* Improved visibility of lesions of the small intestine via capsule endoscopy with computed virtual chromoendoscopy. *Gastrointest Endosc* 2011 ; 73 : 299-306. doi : 10.1016/j.gie.2010.10.016

The small bowel capsule and management of patients with inflammatory bowel disease

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" The management of inflammatory bowel disease (IBD) has changed considerably in recent years with the widespread use of anti-TNF-α antibodies. These treatments have clearly demonstrated their efficacy for the treatment of Crohn's disease (CD) and ulcerative colitis (UC). Unlike previously used molecules – corticosteroids, azathioprine, methotrexate, and 5-aminosalicylates – , anti-TNF-α drugs have the ability to induce healing of endoscopic mucosal lesions in a large number of patients. With their use we have rediscovered the importance of endoscopically visible lesions of the intestinal wall; new management strategies have been developed taking into account these lesions and their evolution with time. In parallel, the renewed interest in morphological exploration of the digestive tract has provided an opportunity to develop noninvasive tools that allow repeated examinations in patients with IBD, and which are effective and acceptable to patients. These modern strategies of management include capsule endoscopy of the small bowel (SBCE), which allows accurate and noninvasive analysis of the gastrointestinal mucosa. This is the only tool that allows a global vision of the lining of the small intestine, which was hitherto impossible because of the lack of a simple tool adapted to this exploration."

The natural history and evolution over time of inflammatory bowel disease

It has been customary to describe inflammatory bowel disease (IBD) as a chronic disease that progresses in successive bursts, interspersed with remission periods of variable length. This description takes into account only the tip of the iceberg, namely clinical symptomatology, and ignores subclinical changes in gastrointestinal inflammation characterized by the presence of persistent intestinal mucosal injury. IBD, especially Crohn's disease (CD), are progressive and destructive diseases; the clinical evaluation of their severity at a given time does not reflect the accumulation of destructive lesions in the intestine. The gradual emergence of stenotic and fistulizing complications, corresponding to subclinical destruction of the gut, has been described in two independent studies performed in reference centers [1, 2]. Patients with a luminal inflammatory disease at the time of diagnosis progressively developed stenotic and/or fistulizing disease. This evolution was also observed in a cohort from the general population, which better reflects the diversity of CD phenotypes outside of reference centers [3].

All anti-TNF-α drugs have the capacity to induce a deep remission, with the disappearance of symptoms and mucosal healing [4-6]. It has been clearly demonstrated in these studies that the percentage of patients with mucosal healing is even greater when the disease is of recent onset. This observation is consistent with the irreversible nature of old lesions, both of inflammatory and scarring origin, for which no treatment can reverse these effects.

The changes in therapeutic goals for IBD originate from the beneficial influence of mucosal healing on the natural history of the disease. In the short and medium terms, it has been demonstrated that the frequency of hospitalization and the need for surgery are significantly reduced when mucosal healing is achieved, in comparison with their frequencies in patients with progressive lesions [7-10]. Conversely, the proportion of patients in remission without corticosteroid treatment, or with neither corticosteroid nor anti-TNF treatment, was higher 2 years after having achieved mucosal healing than in those patients with persistent mucosal lesions [11]. Overall, these data have driven new strategies based on an earlier and more effective treatment of patients with IBD, on obtaining mucosal healing and the disappearance of lesions that are at risk of complications, and finally on an objective mo-

nitoring of the efficacy of the treatments. This monitoring takes into account biological, radiological, and endoscopic data, in which the use of capsule endoscopy will increasingly have a place.

Role of the capsule in the diagnosis of Crohn's disease

Small bowel capsule endoscopy (SBCE) is the examination with the highest diagnostic yield for exploration of the small intestine. Indeed, the meta-analysis of Triester *et al.* [12], updated in 2010 [13], demonstrated the superiority of the capsule in terms of diagnostic yield compared with small bowel transit time: 52% *versus* 16% ($P < 0.0001$); scanner with enterography: 68% *versus* 21% ($P < 0.00001$); and ileocolonoscopy: 47% *versus* 25% ($P = 0.009$) (*table 1*).

A 10% gain was obtained as compared with magnetic resonance imaging enterography (55% *versus* 45%, $P = 0.43$) [13]. It is clear that the SBCE allows the visualization of superficial mucosal lesions that are not visible on conventional radiology, resulting in an increase in diagnostic yield and a better guidance of the diagnostic enteroscopy (oral or rectal route) if this is necessary, in particular to obtain histological samples. The positive and negative predictive values of SBCE were assessed in a recent study [14]. Seventy-five patients suspected of having CD, in spite of a normal colonoscopy and a normal radiological examination of the small bowel, were included in this study. All patients underwent SBCE and were then followed up for an average of 13 months. The positive and negative predictive values of the SBCE for the diagnosis of CD were 87% and 96%, respectively [14].

In light of these results, the joint recommendations of ECCO (the European Crohn's and Colitis Organization) and the World Organization of Digestive Endoscopy (OMED), published in 2009 [15], were amended in 2013 [16]. While in 2009 it was recommended to perform a radiological examination of the small bowel before performing an SBCE, experts now recommend carrying out an examination of the small bowel by capsule endoscopy or by radiology when conventional endoscopy does not permit a diagnosis of CD [16]. Considering its negative predictive value, it is unnecessary to perform further tests if the SBCE is normal.

Table 1. Additional diagnostic yield of the capsule compared with conventional techniques for exploration of the small intestine, from [13].

		Studies (n)	Patients (n)	Additional diagnostic yield (CI) 95 %)
Capsule *vs* enteroscopy	Suspicion of CD	2	46	0.18 (-0.23 – 0.59)
	Known CD	2	56	0.57 (0.43 – 0.71)
Capsule *vs* small bowel transit time	Suspicion of CD	8	155	0.32 (0.16 – 0.48)
	Known CD	10	224	0.38 (0.22 – 0.54)
Capsule *vs* . CT enterography	Suspicion of CD	3	53	0.47 (0.31 – 0.63)
	Known CD	3	66	0.47 (0.31 – 0.63)
Capsule *vs* MRI enterography	Suspicion of CD	3	31	0.10 (-0.14 – 0.34)
	Known CD	4	63	-0.06 (-0.30 – 0.19)

CD: Crohn's disease; MRI: magnetic resonance imaging; CT : computed tomography.

Monitoring of Crohn's disease patients

In the case of known CD, it has also been clearly demonstrated that SBCE has a better performance compared with conventional diagnostic tests. The SBCE is better:

- than enteroscopy: 66% *versus* 9% (P < 0.00001) (*table 1*);
- than small bowel transit time : 71% *versus* 36% (P < 0.00001);
- than computed tomodensitometry enterography (CTE): 71% *versus* 39% (P < 0.0001);
- than MRI with enterography or enteroclysis [13].

Only SBCE allows the detection of early superficial mucosal lesions

that are undetectable by radiological techniques. SBCE is also able to detect lesions of the proximal small bowel, which is not possible with MRI or CT examinations with enteroclysis or enterography [17,18]. In a first study, the sensitivity and specificity of SBCE to diagnose an ileal involvement were 100% and 91%, respectively, while those of MRI were 81% and 86%, and those of CT, 76% and 85%. The other improvement was the detection of proximal lesions in 18 patients, as opposed to 2 patients and 6 patients for MRI and CT, respectively [17]. Similar results were published in a second study that compared MRI and SBCE [18]. The importance of the proximal small bowel mucosal lesions detected by SBCE was recently suggested in a cohort study [19]. In this study, 108 patients with CD had a median follow-up of 24 months (IQ: 8-46) after the completion of a capsule endoscopic examination of the small bowel, and 50% had a relapse during follow-up. The only independent risk factor for relapse was the presence of endoscopic lesions in the proximal small bowel, with a hazard ratio of 1.99 (95% CI, 1.10–3.21). These results highlight the potential value of detecting proximal small bowel lesions to optimize the treatment of patients with CD. Studies evaluating surveillance, with and without capsule endoscopy, of the evolution of the disease, the frequency of complications, of bowel resections, and of hospitalizations, are nevertheless lacking. Some data are available regarding the possibility of observing changes in endoscopic lesions visualized using the capsule, notably following anti-TNF therapy. These preliminary data represent an essential first step before assessing a surveillance of the patients with the capsule [20,21]. In this latter study, there was no correlation between the changes in endoscopic severity score in the small bowel (Lewis score) and the changes in clinical activity and quality of life scores [21]. The authors proposed that endoscopic data be considered as independent surveillance and evaluation criteria. It is also possible that the severity index used in the overall evaluation of the small bowel may not be suitable for the assessment of changes induced by treatments. These facts highlight the importance of defining precisely the evolutive potential of each of the lesions visible with the capsule, and probably of considering differently aphthous erosions and superficial or deep ulcerations. For now, we can only extrapolate the data demonstrating the importance of endoscopic healing observed in colonoscopy and imagine that this will be the same for the capsule
.

Risk of impaction of the capsule in Crohn's disease

One of the limitations to the use of the capsule is the risk of impaction in the event of stenosis of the small bowel. Surgery or endoscopic dilatation may then be necessary to recover the video capsule. The risk of impaction is significantly increased in patients with known CD [22]. In 2009 [15] it was recommended that examination of the small bowel by CT or MRI be performed to rule out stenosis. These recommendations did not take into account the possibility of eliminating the risk of impaction by first ingesting a "dummy" capsule, the Patency Agile ®, whose main feature is its ability to dissolve within a determined time frame. Initial studies tested two generations of Patency Agile ®, with different dissolution times, which explains the conflicting results obtained: in any case these results were insufficient to eliminate the risk of impaction of the video capsule during a stenosis of the small bowel. The latest-generation Patency Agile ® starts to dissolve from the 30th hour after ingestion. Its passage intact within the allotted time, or disappearance on a radiological examination of the abdomen, can almost completely eliminate the risk of impaction, with a yield at least equal, if not superior, to that of conventionally used radiological examinations [23]. In the updated recommendations [16], the Patency Agile ® can be used equivalently to conventional radiological examinations to minimize the risk of capsule impaction. Moreover, if new patient management strategies and the early initiation of effective treatments to heal the mucosa are applied, the risk of digestive stenosis should steadily decrease and eventually disappear. This strategy would give a clear role to capsule endoscopy in the monitoring of patients.

Conclusion

In parallel with the provision of effective new molecules for the treatment of IBD, therapeutic goals will change until macroscopic and even histological healing of the digestive mucosa is achieved. The necessary monitoring of the patients to ensure that these goals are attained requires the development of minimally or non invasive tools allowing repeated follow-up of patients. Capsule endoscopy, given its characteristics and performance, would seem ideally suited to management strategies for patients with IBD, not only in the initial diagnosis but also for patient monitoring, as illustrated in *figure 1*.

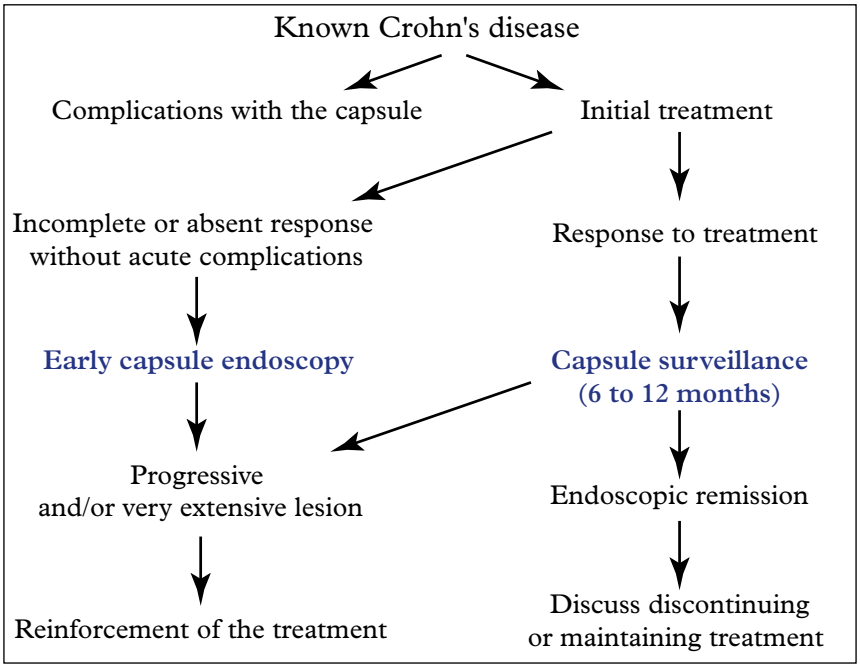

Figure 1. Algorithm for Crohn's disease.

Conflicts of interest

Arnaud Bourreille has links as an expert or as a speaker with the following companies: Abbvie, Ferring, Given Imaging, MSD, Norgine, and Takeda.

References

1. Louis E, Collard A, Oger AF, *et al.* Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. *Gut* 2001 ; 49 : 777-82.
2. Cosnes J, Cattan S, Blain A, *et al.* Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002 ; 8 : 244-50.
3. Thia KT, Sandborn WJ, Harmsen WS, Zinsmeister AR, Loftus EV Jr. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology* 2010 ;139 : 1147-55. doi: 10.1053/j.gastro.2010.06.070
4. Schreiber S, Colombel JF, Bloomfield R, *et al.* Increased response and

remission rates in short-duration Crohn's disease with subcutaneous certolizumab pegol: an analysis of PRECiSE 2 randomized maintenance trial data. *Am J Gastroenterol* 2010 ; 105 : 1574-82. doi: 10.1038/ajg.2010.78
5. Colombel JF, Rutgeerts PJ, Sandborn WJ, *et al.* Adalimumab induces deep remission in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2014 ; 12 : 414-22. doi: 10.1016/j.cgh.2013.06.019
6. Colombel JF, Sandborn WJ, Reinisch W, *et al.* Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010 ; 362 : 1383-95. doi: 10.1056/NEJMoa0904492
7. Rutgeerts P, Diamond RH, Bala M, *et al.* Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc* 2006 ; 63 : 433-42.
8. Schnitzler F, Fidder H, Ferrante M, *et al.* Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. *Inflamm Bowel Dis* 2009 ; 15 : 1295-301. doi: 10.1002/ibd.20927
9. Costa J, Magro F, Caldeira D, *et al.* Infliximab reduces hospitalizations and surgery interventions in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis* 2013 ; 19 : 2098-110. doi: 10.1097/MIB.0b013e31829936c2
10. Beppu T, Ono Y, Matsui T, *et al.* Mucosal healing of ileal lesions is associated with long-term clinical remission after infliximab maintenance treatment in patients with Crohn's disease. *Dig Endosc* 2014 [Epub ahead of print]. doi: 10.1111/den.12313
11. Baert F, Moortgat L, Van Assche G, Caenepeel P, Vergauwe P, De Vos M, Stokkers P, Hommes D, Rutgeerts P, *et al.* Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. *Gastroenterology* 2010 ; 138 : 463-8. doi: 10.1053/j.gastro.2009.09.056
12. Triester SL, Leighton JA, Leontiadis GI, *et al.* A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with non-stricturing Small bowel Crohn's disease. *Am J Gastroenterol* 2006 ; 101 : 954-64.
13. Dionisio PM, Gurudu SR, Leighton JA, *et al.* Capsule endoscopy has a significantly higher diagnostic yield in patients with suspected and established small-bowel Crohn's disease: a meta-analysis. *Am J Gastroenterol* 2010 ; 105 : 1240-8. doi: 10.1038/ajg.2009.713
14. Hall B, Holleran G, Costigan D, McNamara D. Capsule endoscopy: High negative predictive value in the long term despite a low diagnostic yield in patients with suspected Crohn's disease. *United European Gastroenterol J* 2013 ; 1:461-6. doi: 10.1177/2050640613508551
15. Bourreille A, Ignjatovic A, Aabakken L, *et al.* Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED-ECCO consensus. *Endoscopy* 2009 ; 41 : 618-37. doi: 10.1055/s-0029-1214790
16. Annese V, Daperno M, Rutter MD, *et al.* European evidence based consensus for endoscopy in inflammatory bowel disease. *J Crohns Colitis*

2013 ; 7 : 982-1018. doi: 10.1016/j.crohns.2013.09.016
17. Jensen MD, Nathan T, Rafaelsen SR, Kjeldsen J. Diagnostic accuracy of capsule endoscopy for small bowel Crohn's disease is superior to that of MR enterography or CT enterography. *Clin Gastroenterol Hepatol* 2011 ; 9 : 124-9. doi: 10.1016/j.cgh.2010.10.019
18. Böcker U, Dinter D, Litterer C, *et al.* Comparison of magnetic resonance imaging and video capsule enteroscopy in diagnosing small-bowel pathology: localization-dependent diagnostic yield. *Scand J Gastroenterol* 2010 ; 45 : 490-500. doi: 10.3109/00365520903567817
19. Flamant M, Trang C, Maillard O, *et al*. The prevalence and outcome of jejunal lesions visualized by Small bowel capsule endoscopy in Crohn's disease. *Inflamm Bowel Dis* 2013 ; 19 : 1390-6. doi: 10.1097/MIB.0b013e31828133c1
20. Efthymiou A, Viazis N, Mantzaris G, *et al.* Does clinical response correlate with mucosal healing in patients with Crohn's disease of the small bowel? A prospective, case-series study using wireless capsule endoscopy. *Inflamm Bowel Dis* 2008 ; 14 : 1542-7. doi: 10.1002/ibd.20509
21. Niv E, Fishman S, Kachman H, Arnon R, Dotan I. Sequential capsule endoscopy of the small bowel for follow-up of patients with known Crohn's disease. *J Crohns Colitis* 2014 [Epub ahead of print]. doi: 10.1016/j.crohns.2014.03.003
22. Caunedo-Alvarez A, Romero-Vazquez J, Herrerias-Gutierrez JM. Patency and Agile capsules. *World J Gastroenterol* 2008 ; 14 : 5269-73.
23. Yadav A, Heigh RI, Hara AK, *et al.* Performance of the patency capsule compared with nonenteroclysis radiologic examinations in patients with known or suspected intestinal strictures. *Gastrointest Endosc* 2011 ; 74 : 834-9. doi: 10.1016/j.gie.2011.05.038

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 recorder[1]. 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-

1 See chapter V, "*The small bowel video capsule: a new device for new levels of performance* ", Gabriel Rahmi, pages 51-57.

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, κ (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 κ 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-analyzes (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 here[2].

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

2 See chapter VI : "*The small intestine capsule and management of patients with inflammatory bowel disease*", Arnaud Bourreille, pages 58-66.

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.

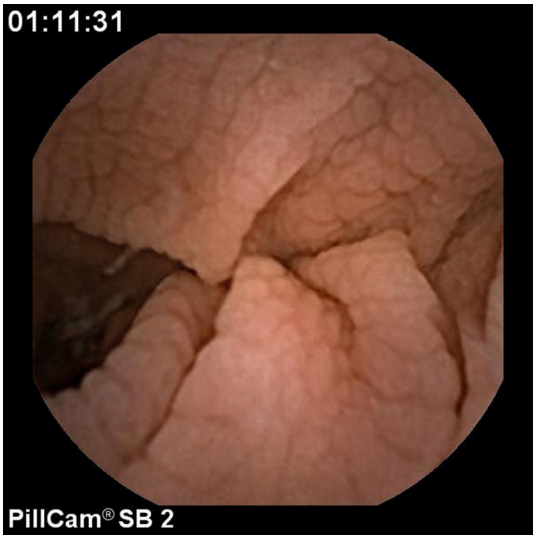

Figure 1. Typical appearance of celiac disease in video capsule endoscopy of the small bowel, showing the surface relief of the squamous mucosa in front view and jagged edges of the folds in profile, reflecting villous atrophy.

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

3 Rameshshanker R, O´Rourke A, Butcher J, *et al. Assessment of small bowel polyps in peutz-jeghers syndrome: should mr enterography be the first line surveillance modality rather than capsule endoscopy?* 21st United European Gastroenterology Week, Berlin, Allemagne.

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

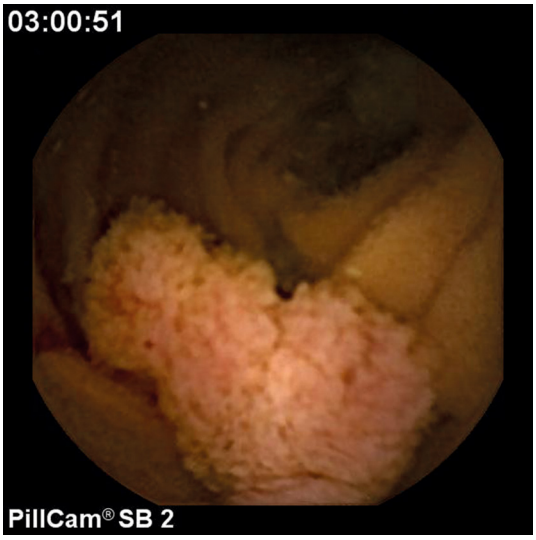

Figure 2. Hamartomatous jejunal polyp, typically pedunculated, observed using video capsule endoscopy in Peutz-Jeghers polyposis.

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 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).

4 Samaha E, Rahmi G, Malamut G, *et al. Impact diagnostique d'une stratégie de surveillance prospective de l'intestin grêle chez les patients ayant un syndrome de Lynch*. JFHOD 2012, Paris, France.

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

1. Pioche M, Vanbiervliet G, Jacob P, *et al*. Prospective randomized comparison between axial- and lateral-viewing capsule endoscopy systems in patients with obscure digestive bleeding. *Endoscopy* 2014 ; 46 : 479-84. doi : 10.1055/s-0033-1358832
2. Choi EH, Mergener K, Semrad C, et al. A multicenter, prospective, randomized comparison of a novel signal transmission capsule endoscope to an existing capsule endoscope. *Gastrointest Endosc* 2013 ; 78 : 325-32. doi : 10.1016/j.gie.2013.02.039
3. Bandorski D, Keuchel M, Brück M, et al. Capsule endoscopy in patients with cardiac pacemakers, implantable cardioverter defibrillators, and left heart devices: a review of the current literature. *Diagn Ther Endosc* 2011 ; 2011 : 376053. doi: 10.1155/2011/376053
4. ASGE Technology Committee, Wang A, Banerjee S, Barth BA, *et al.* Wireless capsule endoscopy. *Gastrointest Endosc* 2013 ; 78 : 805-15. doi: 10.1016/j.gie.2013.06.026
5. Meltzer AC, Ward MJ, Gralnek IM, Pines JM. The cost-effectiveness analysis of video capsule endoscopy compared to other strategies to manage

acute upper gastrointestinal hemorrhage in the ED. *Am J Emerg Med* 2013 Nov 13. doi: 10.1016/j.ajem.2013.11.012
6. Bourreille A, Ignjatovic A, Aabakken L, *et al*. World Organisation of Digestive Endoscopy (OMED) and the European Crohn's and Colitis Organisation (ECCO). Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED-ECCO consensus. Endoscopy 2009 ; 41 : 618-37. doi: 10.1055/s-0029-1214790
7. Rokkas T, Niv Y. The role of video capsule endoscopy in the diagnosis of celiac disease: a meta-analysis. *Eur J Gastroenterol Hepatol* 2012 Mar; 24: 303-8. doi : 10.1097/MEG.0b013e32834fa914
8. Lewis BS, Eisen GM, Friedman S. A pooled analysis to evaluate results of capsule endoscopy trials. *Endoscopy* 2005; 37: 960-5.
9. Ross A, Mehdizadeh S, Tokar J, *et al.* Double balloon enteroscopy detects small bowel mass lesions missed by capsule endoscopy. *Dig Dis Sci* 2008 ; 53 : 2140-3. doi : 10.1007/s10620-007-0110-0
10. Gupta A, Postgate AJ, Burling D, *et al.* A prospective study of MR enterography versus capsule endoscopy for the surveillance of adult patients with Peutz-Jeghers syndrome. *AJR Am J Roentgenol* 2010 ; 195 : 108-16. doi: 10.2214/AJR.09.3174
11. Saurin JC, Pilleul F, Soussan EB, *et al.* Small-bowel capsule endoscopy diagnoses early and advanced neoplasms in asymptomatic patients with Lynch syndrome. *Endoscopy* 2010; 42: 1057-62. doi: 10.1055/s-0030-1255742
12. Schulmann K1, Hollerbach S, Kraus K, *et al*. Feasibility and diagnostic utility of video capsule endoscopy for the detection of small bowel polyps in patients with hereditary polyposis syndromes. *Am J Gastroenterol* 2005; 100 : 27-37.
13. Isomura Y, Yamaji Y, Yamada A, *et al.* Irsogladine improves small-intestinal injuries in regular users of nonsteroidal anti-inflammatory drugs. *Gastrointest Endosc*. 2014; 80 :118-25. doi : 10.1016/j.gie.2013.12.030

PillCam Colon 2 ® capsule endoscopy *versus* standard colonoscopy:

Results of studies in Europe and the United States

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"The colon capsule, PillCam Colon2 ®, has been in development since 2009. As compared with the previous capsule, it incorporates technical advances that improve the quality of the images obtained and the frequency of image capture during sequences in which the capsule is propelled rapidly through a colonic segment. Studies comparing this capsule with colonoscopy have shown a sensitivity of 87% and a specificity of 79% for polyps ≥ 6 mm, with values of 89% and 92% for polyps ≥ 10 mm. These results provide ground to consider PillCam Colon 2 ® for use in colorectal cancer screening. Studies will be required to assess its effectiveness and its impact on healthcare costs, particularly in comparison with immunological tests in the investigation of blood in the stools. Other indications are also being evaluated, notably in the context of inflammatory bowel disease."

Initially developed for the examination of the small intestine, capsule endoscopy has undergone technical developments that have enabled its use for the examination of the colon. The PillCam Colon 2 ® capsule (Given Imaging Covidien GI Solutions) represents the latest generation in capsule endoscopy for the examination of the colonic mucosa. The aim of this overview is to summarize and to discuss studies comparing PillCam Colon 2 ® with colonoscopy.

Technical specifications of the PillCam Colon 2 ® capsule

The PillCam Colon 2 ® capsule has been in development since 2009. As for the previous version, PillCam Colon 1 ®, it differs from the capsule used for exploration of the small intestine by the presence of two optical systems, each capturing 4 images per second. The technical improvements to PillCam Colon 2 ® include an angle of view of 172 ° instead of 156 °, which allows a better examination of the colonic mucosa, and a capture frequency that can vary between 4 and 35 frames per second, providing a better visualization in colonic segments where the capsule progresses rapidly, in particular in the transverse colon. The recorder worn by the patient on his/her belt has also been improved, allowing real time visualization of the images obtained by the capsule, and including algorithms for detecting the presence of the capsule in the small intestine that inform patients of the different stages of the colonic preparation protocol.
In parallel with these technical advances in the capsule, the reading software provided by Given Imaging (Rapid Access 8 ®) has also been improved and includes a function to facilitate the estimation of polyp size as well as the possibility of FICE-type electronic coloration (Fujifilm Inc. Omiya, Japan), which highlights polyp structure and the changes in vasculature, as in conventional colonoscopy.

Comparative studies of the PillCam Colon 2 ® capsule and colonoscopy

Since 2009, several studies have been conducted comparing PillCam Colon 2 with colonoscopy, primarily for the detection of colorectal polyps, with a view to assessing the effectiveness of the capsule in colorectal cancer screening. More recently, several comparative studies

have also been performed in patients with ulcerative colitis.

Comparative studies of colorectal polyp detection

The first comparative study of PillCam Colon 2 ® was carried out by Eliakim et al. [1] and indicated a sensitivity of 89% and a specificity of 76% for the detection of polyps ≥ 6 mm in diameter. The results for the PillCam Colon 2 capsule were considered to be better than those of the Colon 1 capsule reported in several previous studies [2-4]. It should be noted that in this study the discordant cases between capsule endoscopy and colonoscopy were reassessed retrospectively by a panel of experts. This may have contributed to the improvement in results between the two studies carried out by same group – one with the Colon 1 ® capsule [2] and the other with the Colon 2 ® capsule [1]. Furthermore, the specificity reported by these authors reflected a large number of PillCam Colon 2 ® capsule false positives for polyps ≥ 6 mm that were not identified during colonoscopy.
A multicenter European study was subsequently carried out, including 117 patients with an average age of 60 years [5]. In this study, examination of the colonic mucosa involved the entire colon and rectum in 88% of patients. This rate of "complete" examination was comparable to that previously reported with the Colon 1 capsule [2-4,6]. The per-patient analysis showed, for PillCam Colon 2 ®, a sensitivity of 84% for polyps ≥ 6 mm and 88% for polyps ≥ 10 mm. Specificities were, respectively, 64% and 95% for the detection of these polyps. Three cancers were discovered during this study, all detected by PillCam Colon 2 ®. During the analysis of the results, half of the false negatives for PillCam Colon 2 ® were in fact errors in estimation of the size of polyps with a diameter close to 6 mm, which had been noted as < 6 mm from the capsule reading. More recently, a North American study was published as an abstract [7]; this included 884 patients at average risk for colorectal neoplasia. The sensitivity of PillCam Colon 2 ® was 88% for adenomas ≥ 6 mm and 92% for adenomas ≥ 10 mm, with specificities of 82% and 95%, respectively. When the analysis was based on all polyps, including hyperplastic polyps and serrated polyps, the sensitivity was 81% for polyps ≥ 6 mm and 80% for polyps ≥ 10 mm, with specificities of 93% and 97%, respectively. This observation may reflect the difficulty for the capsule to identify flat lesions such as serrated adenomas.

Finally, a recent study assessed the diagnostic yield of PillCam Colon 2 ® and of virtual colonoscopy in patients who were positive for a fecal blood test [8]. Fifty patients with an average age of 59 years were evaluated by the following three methods: capsule endoscopy, virtual colonoscopy, and then conventional colonoscopy, considered as the gold standard. Sixteen patients (32%) had at least one polyp ≥ 6 mm. The sensitivity and specificity of PillCam Colon 2 ® were 88.2% and 87.8%, respectively, comparable to those of virtual colonoscopy: 88.2% sensitivity and 84.8% specificity. This study also included an assessment of patient preference for one examination or the other, indicating that 78% of patients preferred the capsule endoscopy to the virtual colonoscopy.

The colon capsule as a filter test before colonoscopy?

A first study with the Colon 1 ® capsule had tested this hypothesis [6], considering the healthcare costs of the large number of "negative" colonoscopies in everyday practice [9]. In this study, the indication for colonoscopy in light of the colon capsule results was defined as the presence of at least 1 polyp ≥ 5 mm, 3 polyps < 5 mm, or any other significant pathology: cancer, inflammatory bowel disease (IBD)... The positive predictive value of the colon capsule to indicate colonoscopy was 88% and the negative predictive value 76%, the latter being reduced by 8 false negatives with the capsule. Moreover, patient recruitment was not strictly that of a screening in the general population, as many patients with digestive symptoms or a high risk of polyps were included.

In a recent study, 62 patients with a positive immunoassay for detection of blood in the stool were examined by PillCam Colon 2 ®, and then a conventional colonoscopy was performed the next day [10]. Colonoscopy, the reference examination, was completed in 94% of cases and the diagnostic yield was 58%, with 29 adenomas, 1 cancer, 2 cases of colitis, and 1 solitary rectal ulcer. The sensitivity of PillCam Colon 2 ® to detect all types of polyps was 95%, specificity 65%, positive predictive value 79%, and negative predictive value 90%. When only the 18 patients who had a significant lesion by colonoscopy were considered, the sensitivity of PillCam Colon 2 ® was 89%, specificity 96%, positive predictive value 89%, and negative predictive value 96%. The authors concluded that the colon capsule could be considered as

a filter test for the indication of colonoscopy.

Studies comparing colon capsule endoscopy and colonoscopy in ulcerative colitis (UC).

A few recent studies have evaluated the feasibility of examining the colon by colon capsule endoscopy in patients with UC. A first study in 100 patients using the Colon 1 capsule, carried out by Sung et al. [11], showed a rather high rate of incomplete examination, with 10% of patients not having expelled the capsule during the registration time period. Compared with colonoscopy performed on the same day, the capsule had a sensitivity of 89%, specificity 75%, positive predictive value 93%, and negative predictive value 63%, to detect the presence of inflammatory lesions of the colonic mucosa. A study that was also conducted in Asia, including 40 patients with UC and performed using PillCam Colon 2 ®, showed a high rate of capsule retention in the colon, as it was only expelled in 66% of cases [12]. The correlation between conventional colonoscopy and PillCam Colon 2 ® was good for the detection of inflammatory lesions of the colonic mucosa. A single-center Spanish study that included 42 patients also showed a good concordance ($k = 0.75$) for the endoscopic level of severity and the assessment of the extent of lesions ($k = 0.71$) [13]. Finally, a study of 26 patients found a similar concordance between capsule endoscopy and colonoscopy for the severity ($k = 0.75$; $P < 0.001$) and the extent ($k = 0.52$; $P < 0.001$) of lesions [14].

Discussion

Comparison of the results obtained with PillCam Colon 1 ® and PillCam Colon 2 ® for the detection of colorectal polyps shows a better sensitivity of the second-generation capsule, but the number of studies available with the latter capsule is limited and there are differences in colonic preparation protocols between the different studies that may have influenced the results [1-8,15]. The quality of colonic preparation is an important factor that influences the diagnostic yield of the colon capsule as well as the rate of examinations completed (with expulsion of the capsule during the time of recording). A study comparing two preparation protocols [16] showed that the protocol used significantly influenced the rate of full examinations and the transit time of the cap-

sule through the colon, without affecting the diagnostic sensitivity and specificity of the capsule.
The capability of the endoscopic capsule to detect colorectal polyps also depends on the size and type of polyps. Table 1 summarizes the different comparative studies carried out with PillCam Colon 1 ® and PillCam Colon 2 ®, separating polyps into ≥ 6 mm and ≥ 10 mm categories. The variability of the analysis criteria between the studies makes the comparison difficult, in particular for polyps ≥ 10 mm, which were only defined as a specific group in a small number of PillCam Colon 1® studies. Nevertheless, it can noted that PillCam Colon 2 ® shows a better diagnostic yield that can be explained by the technical advances that improve the image quality of this capsule, and in addition by the growing experience of the readers who participated in most of the studies concerning the two types of capsule. Furthermore, the study presented by Rex et al. [7] analyzed polyps ≥ 6 mm, polyps ≥ 10 mm, and all polyps grouped together, regardless of their size and shape. It would seem that capsule endoscopy has a lower sensitivity in this latter category, notably by recognizing less easily flat or serrated polyps.
The colon capsule will find, primarily, a future clinical use in screening for colorectal cancer. Two studies have evaluated the colon capsule as a "filter test" for the indication of colonoscopy [6,10]. These have shown encouraging results, but it should be noted that one study was performed in a group of patients who were symptomatic or at high risk of colorectal cancer [6] and the other study involved patients who had a positive fecal blood test [10]. Nevertheless, in that study, the colonic capsule showed a very high negative predictive value, and therefore reliability for ruling out the indication of colonoscopy. This negative predictive value will increase even further when populations at medium or low risk of colorectal cancer are studied, as is the case in general population screening. Future studies conducted under strict screening conditions should demonstrate the advantages of this approach, in particular in reducing healthcare costs related to screening for colorectal cancer [19]. The effectiveness of the colon capsule in this screening strategy, and its impact on healthcare costs, should be evaluated against fecal blood immunoassays. Colon capsule endoscopy may in fact be proposed for ambulatory use, the recorder being able to warn the patient of the different times of the protocol of colonic washes [20].

Table 1. Detection of colorectal polyps by the PillCam Colon ® capsule: comparison of the PillCam Colon 1 and PillCam Colon 2 capsules.

	Patients (n)	PillCam Colon 1				PillCam Colon 2			
		≥ 6mm		≥ 10mm		≥ 6mm		≥ 10mm	
		Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Eliakim *et al.* [2]	91	56	69	-	-				
Schoofs *et al.* [3]	41	60	73	-	-				
Van Gossum *et al.* [4]	332	64	84	60	98				
Sieg *et al.* [17]	38	55	96						
Gay *et al.* [6]	128	76	76	80	100				
Pilz *et al.* [18]	62	79	55	-	-				
Sacher-Huvelin *et al.* [15]	545	39	88	-	-				
Eliakim *et al.* [1]	104					89	76	88	89
Spada *et al.* [5]	117					84	64	88	95
Rondonotti *et al.* [8]	50					88	84	88	87
Rex *et al.* [7]	884					88	93	92	97
Average		**61**	**76**	**70**	**99**	**87**	**79**	**89**	**92**

Conclusion

Studies conducted to date with PillCam Colon 2 ® have confirmed the results obtained with the previous version and shown a better diagnostic yield for the detection of colorectal polyps. Future studies should focus on demonstrating the effectiveness of PillCam Colon 2 ® in colorectal cancer screening and on evaluating its impact on the healthcare costs associated with this screening. Other indications, notably in patients with inflammatory bowel disease, are currently being evaluated.

Conflicts of interest

Gérard Gay is a consultant for Given Imaging Covidien GI Solutions.

References

1. Eliakim R, Yassin K, Niv Y, *et al*. Prospective multicenter performance evaluation of the second-generation colon capsule compared with colonoscopy. *Endoscopy* 2009 ; 41 : 1026-31. doi : 10.1055/s-0029-1215360
2. Eliakim R, Fireman Z, Gralnek IM, *et al.* Evaluation of the PillCam Colon capsule in the detection of colonic pathology: results of the first multicenter, prospective, comparative study. *Endoscopy* 2006 ; 38 : 963-70.
3. Schoofs N, Deviere J, Van Gossum A. Pillcam colon capsule endoscopy compared with colonoscopy for colorectal diagnosis: a prospective pilot study. *Endoscopy* 2006 ; 38 : 971-7.
4. Van Gossum A, Navas MM, Fernandez-Urien I *et al.* Capsule endoscopy versus colonoscopy for the detection of polyps and cancer. *New Engl J Med* 2009; 361 : 264-70. doi : 10.1056/NEJMoa0806347.
5. Spada C, Hassan C, Munoz-Navas M, *et al.* Second-generation colon capsule endoscopy compared with colonoscopy. *Gastrointest Endosc* 2011 ; 74 : 581-9. doi: 10.1016/j.gie.2011.03.1125
6. Gay G, Delvaux M, Frederic M, Fassler I. Could the colonic capsule PillCam Colon be clinically useful for selecting patients who deserve a complete colonoscopy?: Results of clinical comparison with colonoscopy in the perspective of colorectal cancer screening. *Am J Gastroenterol* 2010; 105 : 1076-86. doi : 10.1038/ajg.2009.624
7. Rex DK, Adler SN, Aisenberg J, *et al.* Accuracy of PillCam COLON 2 for detecting subjects with adenomas ≥ 6 mm. *Gastrointest Endosc* 2013 ; 77 (suppl. 1): AB29 (abstract).
8. Rondonotti E, Borghi C, Mandelli G, *et al.* Accuracy of Capsule Colonos-

copy and Computed Tomographic Colonography in Individuals With Positive Results From the Fecal Occult Blood Test. *Clin Gastroenterol Hepatol* 2014 ; 12 : 1303-10. doi : 10.1016/j.cgh.2013.12.027
9. Canard JM, Debette-Gratien M, Dumas R, *et al.* A prospective national study on colonoscopy and sigmoidoscopy in 2000 in France. *Gastroenterol Clin Biol* 2005 ; 29 : 17-22.
10. Holleran G, Leen R, O'Morain C, McNamara D. Colon capsule endoscopy as possible filter test for colonoscopy selection in a screening population with positive fecal immunology. *Endoscopy* 2014 ; 46 : 473-8. doi : 10.1055/s-0034-1365402
11. Sung J, Ho KY, Chiu HM, Ching J, Travis S, Peled R. The use of Pillcam Colon in assessing mucosal inflammation in ulcerative colitis: a multicenter study. *Endoscopy* 2012; 44 : 754-8. doi : 10.1055/s-0032-1309819
12. Hosoe N, Matsuoka K, Naganuma M, *et al.* Applicability of second-generation colon capsule endoscope to ulcerative colitis: a clinical feasibility study. *J Gastroenterol Hepatol* 2013 ; 28 : 1174-9. doi : 10.1111/jgh.12203.
13. San Juan-Acosta M, Caunedo-Álvarez A, Argüelles-Arias F, *et al.* Colon capsule endoscopy is a safe and useful tool to assess disease parameters in patients with ulcerative colitis. *Eur J Gastroenterol Hepatol* 2014 ; 26 : 894-901. doi : 10.1097/MEG.0000000000000125
14. Ye CA, Gao YJ, Ge ZZ, *et al.* PillCam colon capsule endoscopy versus conventional colonoscopy for the detection of severity and extent of ulcerative colitis. *J Dig Dis* 2013 ; 14 : 117-24. doi: 10.1111/1751-2980.12005
15. Sacher-Huvelin S, Coron E, Gaudric M, *et al.* Colon capsule endoscopy vs. colonoscopy in patients at average or increased risk of colorectal cancer. *Aliment Pharmacol Ther* 2010 ; 32 : 1145-53. doi : 10.1111/j.1365-2036.2010.04458.x
16. Spada C, Riccioni ME, Hassan C, Petruzziello L, Cesaro P, Costamagna G. PillCam colon capsule endoscopy: a prospective, randomized trial comparing two regimens of preparation. *J Clin Gastroenterol* 2011; 45 : 119-24. doi : 10.1097/MCG.0b013e3181dac04b
17. Sieg A, Friedrich K, Sieg U et al. Is PillCam COLON capsule endoscopy ready for colorectal cancer screening? A prospective feasibility study in a community gastroenterology practice. *Am J Gastroenterol* 2009 ; 104 : 848-54.
18. Pilz JB, Portmann S, Peter S, Beglinger C, Degen L Colon Capsule Endoscopy compared to Conventional Colonoscopy under routine screening conditions. BMC Gastroenterol 2010 18 ; 10 : 66. doi : 10.1186/1471-230X-10-66.
19. Hassan C, Benamouzig R, Spada C, *et al.* Cost effectiveness and projected national impact of colorectal cancer screening in France. *Endoscopy* 2011 ; 43 : 780-93. doi : 10.1055/s-0030-1256409
20. Adler SN, Hassan C, Metzger Y, Sompolinsky Y, Spada C. Second-generation colon capsule endoscopy is feasible in the out-of-clinic setting. *Surg Endosc* 2014 ; 28 : 570-5. doi : 10.1007/s00464-013-3206-y
21. Shi HY, Ng SC, Tsoi KK, Wu JC, Sung JJ, Chan FK. The role of

capsule endoscopy in assessing mucosal inflammation in ulcerative colitis. *Expert Rev Gastroenterol Hepatol* 2014 ; 25 : [epub]. doi : 10.1586/17474124.2014.934359

Colon Capsule Endoscopy in incomplete colonoscopy

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"Optical colonoscopy is the standard method for evaluating the colon. However, in routine clinical practice the cecal intubation rate is often suboptimal. CT colonography (CTC) has been recommended as the imaging modality of choice in cases of incomplete colonoscopy. Alternatively, colon capsule endoscopy (CCE) is a new, minimally invasive, painless endoscopic technique that is able to explore the colon without requiring sedation, gas insufflation, and radiation exposure. In several studies, CCE was performed to complement a previous incomplete colonoscopy, being able to visualize the colonic segments not seen by previous incomplete colonoscopy. Recently, a study compared the performance of CCE and CTC. One-hundred consecutive patients with a previous incomplete colonoscopy underwent CCE and CTC followed by colonoscopy in the case of positive findings on either test. CCE and CTC were both able to achieve complete colonic evaluation in 98% of cases. In a per-patient analysis for polyps ≥ 6 mm, CCE detected 24 patients (24.5%) and CTC detected 12 patients (12.2%). Positive predictive values for polyps ≥ 6 mm and ≥ 10 mm were 96% and 85.7%, and 83.3% and 100%, for CCE and CTC, respectively. No missed cancers occurred at clinical follow-up of a mean of 20 months. The overall diagnostic yield of CCE was superior to CTC (mainly because of a higher accuracy for small and/or nonpolypoid lesions). In conclusion, CCE is a highly technically feasible examination for patients with previously incomplete colonoscopy and it should be considered as a first-choice technique in such a setting."

Incomplete colonoscopy: a practical challenge

Optical colonoscopy is the standard method for evaluating the colon [1]. This technique allows evaluation of the entire colon in most patients. Cecal intubation is associated with an increased detection rate of advanced neoplasia, as 33–50% of advanced neoplasias are located in the proximal colon [2]. Despite a recommendation of ≥ 90% and ≥ 95% cecal intubation rates in routine clinical practice and in screening colonoscopies, respectively [3], the actual cecal intubation rate is often suboptimal [4-11]. After an incomplete optical colonoscopy, patients are required to undergo another test in order to exclude clinically relevant lesions and to reduce the risk of proximal cancer, which has been shown to increase twofold when colonoscopy is incomplete [12]. Both endoscopic and radiological options to complete the colon assessment have been available in recent decades. Multiple alternative endoscopic techniques – such as colonoscopy with thinner colonoscopes, gastroscopes, and device-assisted enteroscopes – have been described [13, 14]. However, none of these has been clearly standardized. Alternatively, double-contrast barium enema (DCBE) has traditionally been used to image the colon after failed or incomplete colonoscopy. However, data from the National Polyp Study Work Group already indicated a disappointing 48% sensitivity of DCBE for > 10 mm polyps [15]. CT colonography (CTC) has also been recommended by the American Gastroenterological Association (AGA) as the imaging modality of choice in cases of incomplete colonoscopy [16]. In large, randomized trials in symptomatic patients [17, 18], CTC has been shown to be substantially more effective than DCBE – and equally as effective as colonoscopy – for the detection of large colorectal polyps and already-developed colorectal cancers.

Colon capsule endoscopy: a valid option ?

Colon capsule endoscopy (CCE) (Given Imaging Ltd, Yoqneam, Israel) is a new, minimally invasive, painless endoscopic technique that is able to explore the colon without requiring sedation, gas insufflation, and radiation exposure. Recently, a second-generation CCE has been released that provides a higher frame rate and a larger -angle lens [19,20]. Preliminary data suggest that CCE is a feasible and safe tool for visualization of the colonic mucosa in patients with incomplete

colonoscopy without stenosis, being able to guide further work-up [21-23]. CCE has also recently been approved by the FDA, specifically for a previously incomplete colonoscopy. However, studies comparing CCE with radiological imaging, and in particular with CTC, are lacking. Potential advantages of CCE over CTC are the lack of ionizing radiation, the limited availability of CTC due to saturation of the time-machine with other indications, and the possibility to directly visualize the colorectal mucosa by CCE.
In several studies [21-27], CCE was proven to be able to complement a previous incomplete colonoscopy, being able to visualize the colonic segments not visualized by previous incomplete conventional colonoscopy. Finally, CCE detected additional findings that would have been missed as they were localized in unseen segments(*table 1*).

Table 1. Summary of studies that used Colon capsule endoscopy (CCE) in case of incomplete colonoscopy.

	Number of patients	**Completeness** (%)	**CCE Complementary Findings** (%)
Pioche *et al.* [25]	107	83	34
Alarcon-Fernandez *et al.* [22]	34	85	23.5
Triantafyllou *et al.* [23]	75	90.7	44
Spada *et al.* [26]	100	98	24⋆
Nogales *et al.* (UEGW, 2013)	96	93	45⋆ °°
Baltes *et al.* [27]	74	95	49/28⋆ °°

⋆ significant polyps; °° cancers.
Nogales O, *et al.* Utility of colon capsule endoscopy after an incomplete colonoscopy. Multicentric spanish study. UEGW 2013 P 793
UEGW: United European Gastroenterology Week.

In detail, regarding full papers, few studies, all performed using the first generation of colon capsule, have evaluated the role of CCE in

patients with an incomplete colonoscopy [22, 23, 25]. Pioche *et al.* [25] reported for the first time, in a prospective multicenter series of 107 patients (*i.e.* 77 with a colonoscopy failure and 30 with a contraindication), a 93% capsule completion rate and a 33.6% CCE diagnostic yield. Alarcon-Fernandez *et al.* [22] evaluated the effects of CCE on medical decision-making in patients with incomplete colonoscopy in 34 patients. These authors reported that CCE was able to exceed the most proximal point reached by conventional colonoscopy in 85% of patients and to allow formulation of a specific medical plan in 59% of patients. Triantafyllou *et al.* [23] studied 75 patients who underwent CCE either immediately after incomplete colonoscopy, or rescheduled to a different day. CCE reached or went beyond the colonic segment where colonoscopy stopped in 91% of patients and detected additional findings in 44% of patients . Data available in the literature, thus, homogenously suggest that CCE can be considered as a complementary procedure in cases of incomplete colonoscopy and can yield significant findings

Head-to-head comparison of CCE and CTC

Despite previously published trials on either of the two techniques, the comparison between CCE (using the second generation of colon capsule) and CTC in this group of patients was never evaluated. Recently, a study [26] was published with the aim to compare the performances of CCE and CTC in a prospective cohort of patients with a previously incomplete colonoscopy. Consecutive patients with a previous incomplete colonoscopy underwent CCE and CTC followed by colonoscopy in the case of positive findings on either test (polyps/mass lesions ≥ 6 mm). CTC was performed either after colon capsule excretion or 10–12 hours post ingestion. Since the gold standard colonoscopy was performed only in positive cases, both diagnostic yield and positive predictive values of CCE and CTC were used as study endpoints. As patients underwent CCE and CTC on the same day, the regimen of preparation that is usually recommended was slightly modified [21] (Table 2). Briefly, this consisted of the standard regimen of preparation for CCE as previously described, with the inclusion of sodium-amidotrizoate and meglumine-amidotrizoate (75 mL) (Gastrografin, Bayer, Italy), which was added to the sodium-phosphate booster for fecal tagging.

Table 2. Regimen of preparation for Colon capsule endoscopy (CCE) used in the comparison of CCE and CT colonography (CTC) [26].

	Schedule	Intake
Day -2	Bedtime	Senna, 4 tb (48 mg)
Day -1	All Day	Clear Liquid Diet
Exam-day	Evening	2 L PEG
	7-9 am	2 L PEG
	10 am (~ 1h after last intake of PEG)	Capsule Ingestion*
	After small bowel detection	1st Boost 40 mL NaP + 1 L water with Gastrografin*** (50 mL)
	3 hours after 1st Boost	2nd Boost **20 mL NaP + 0.5 L water with Gastrografin*** (25 mL)
	2 hours after 2nd Boost	Suppository **10 mg Bisacodyl

* 10 mg metoclopramide tablet if capsule delayed in stomach > 1 hour; ** Only if capsule not excreted yet; *** Sodium-amidotrizoate and meglumine-amidotrizoate.

One hundred patients were enrolled. CCE and CTC were both able to achieve complete colonic evaluation in 98% of cases. In a per-patient analysis for polyps ≥ 6 mm, CCE detected 24 patients (24.5%) and CTC detected 12 patients (12.2%). The relative sensitivity of CCE compared with CTC was 2.0 (95% CI, 1.34–2.98), indicating a significant increase in sensitivity for lesions ≥ 6 mm. Regarding diagnostic yield for large polyps (≥ 10 mm), these values were 5.1% for CCE and 3.1% for CTC, respectively (relative sensitivity: 1.67 [95% CI, 0.69–4.00]). Positive predictive values for polyps ≥ 6 mm and ≥ 10 mm were 96% and 85.7%, and 83.3% and 100%, for CCE and CTC,

respectively. No missed cancer occurred at clinical follow-up of a mean of 20 months. The Authors concluded that both CCE and CTC were of comparable efficacy in completing colon evaluation after incomplete colonoscopy. However, the overall diagnostic yield of colon capsule endoscopy was superior to CTC. Interestingly, the superiority of CCE appears mainly to be related to a higher accuracy for small and/or nonpolypoid lesions. This is in line with the suboptimal sensitivity of CTC for such lesions already shown in previous head-to-head CTC-colonoscopy series [28-39]. Such superiority of CCE over CTC challenges the clinical recommendation of CTC for patients with a previously incomplete colonoscopy, with the exception of those with a colonic stricture. In settings where CCE is already available, CCE should always be considered in the case of incomplete colonoscopy and the choice between CCE and CTC will depend on local expertise, patient acceptance, and economic resources.

To note, CCE completion and excretion rates observed in this trial were higher than those observed in previous trials [19; 20]. The volume effect caused by Gastrografin that was included in the regimen of preparation in this trial [26] might have had a role in enhancing the propulsion of the capsule through the colon, and might also have had an effect on the quality of colonic preparation. In this trial, a high rate of good quality examinations was observed with both CCE and CTC. Hence, the overall quality rate was judged adequate in 83% (95% CI 74%-90%) and 90% (95% CI 82%-95%) of cases, respectively [26].

Directions for future research

The role of CCE in cases of a previously incomplete colonoscopy has been widely explored in recent years. To date, there is good evidence that CCE is a highly technically feasible examination for patients with previously incomplete colonoscopy, being able to complete the vast majority of previously incomplete colonoscopies and to detect significant findings not visualized by incomplete colonoscopy. Nevertheless, there are some issues that still need to be clarified. These mainly relate to the timing of capsule endoscopy after incomplete colonoscopy and to how to proceed with the preparation if CCE is performed immediately after colonoscopy. It would be important to know if CCE is feasible and can be performed immediately after an incomplete colonoscopy. This would be crucial since patients would not be asked to

perform an additional preparation and it would allow Endoscopists to complete colonoscopy the same day without referring the patient to other physicians and/or sessions. It is basically unknown how to proceed with the preparation if CCE is feasible immediately after incomplete colonoscopy. In particular, it is not known if in such cases the regimen of preparation for CCE may be limited to the administration of boosters or if additional doses of lavage solutions are required.

Conclusion

Data available in the literature suggest that CCE is a highly technically feasible examination for patients with previously incomplete colonoscopy and that it should be considered as a first-choice technique in such setting.

Conflicts of interest

Cesare Hassan is a consultant for Given imaging Covidien GI Solutions.

References

1. Winawer SJ, Zauber AG, Ho MN, *et al.* Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993; 329: 1977-81.
2. Harrison M, Singh N, Rex DK. Impact of proximal colon retroflexion on adenoma miss rates. *Am J Gastroenterol* 2004; 99 : 519-22.
3. Winawer SJ, Zauber AG, Fletcher RH, *et al.* Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. *Gastroenterology* 2006; 130: 1872-85.
4. Gryspeerdt S, Lefere P, Herman M, *et al.* CT colonography with fecal tagging after incomplete colonoscopy. *Eur Radiol* 2005; 15: 1192-202.
5. Anderson ML, Heigh RI, McCoy GA, *et al.* Accuracy of assessment of the extent of examination by experienced colonoscopists. *Gastrointest Endosc* 1992; 38: 560-3.
6. Aslinia F, Uradomo L, Steele A, *et al.* Quality assessment of colonoscopic cecal intubation: an analysis of 6 years of continuous practice at a university hospital. *Am J Gastroenterol* 2006; 101: 721-31.
7. Bowles CJ, Leicester R, Romaya C, *et al.* A prospective study of colonoscopy practice in the UK today: are we adequately prepared for national

colorectal cancer screening tomorrow? *Gut* 2004; 53: 277-83.
8. Imperiale TF, Wagner DR, Lin CY, *et al.* Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. *N Engl J Med* 2000; 343: 169-74.
9. Lieberman DA, Weiss DG, Bond JH, *et al.* Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med* 2000; 343: 162-8.
10. Mitchell RM, McCallion K, Gardiner KR, *et al.* Successful colonoscopy; completion rates and reasons for incompletion. *Ulster Med J* 2002; 71: 34-7.
11. Regula J, Rupinski M, Kraszewska E, *et al.* Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. *N Engl J Med* 2006; 355: 1863-72.
12. Brenner H, Chang-Claude J, Jansen L, *et al.* Role of colonoscopy and polyp characteristics in colorectal cancer after colonoscopic polyp detection: a population-based case-control study. *Ann Intern Med* 2012; 157: 225-32. doi : 10.1007/s00384-010-1016-4
13. Morini S, Zullo A, Hassan C, *et al.* Endoscopic management of failed colonoscopy in clinical practice: to change endoscopist, instrument, or both? *Int J Colorectal Dis* 2011; 26: 103-8. doi : 10.1007/s00384-010-1016-4
14. Gawron AJ, Veerappan A, McCarthy ST, *et al.* Impact of an incomplete colonoscopy referral program on recommendations after incomplete colonoscopy. *Dig Dis Sci* 2013; 58: 1849-55. doi: 10.1007/s10620-013-2605-1
15. Winawer SJ, Stewart ET, Zauber AG, *et al.* A comparison of colonoscopy and double-contrast barium enema for surveillance after polypectomy. National Polyp Study Work Group. *N Engl J Med* 2000; 342: 1766-72.
16. Atkin W, Dadswell E, Wooldrage K, *et al.* Computed tomographic colonography versus colonoscopy for investigation of patients with symptoms suggestive of colorectal cancer (SIGGAR): a multicentre randomised trial. *Lancet* 2013; 381: 1194-202. doi : 10.1016/S0140-6736(12)62186-2
17. Halligan S, Atkin WS. CT colonography for diagnosis of symptomatic colorectal cancer: the SIGGAR trials and their implication for service delivery. *Clin Radiol* 2013; 68: 643-5. doi : 10.1016/j.crad.2013.02.008
18. Position of the American Gastroenterological Association (AGA) Institute on computed tomographic colonography. *Gastroenterology* 2006; 131: 1627-8.
19. Eliakim R, Yassin K, Niv Y, *et al.* Prospective multicenter performance evaluation of the second-generation colon capsule compared with colonoscopy. *Endoscopy* 2009; 41: 1026-31. doi : 10.1055/s-0029-1215360
20. Spada C, Hassan C, Munoz-Navas M, *et al.* Second-generation colon capsule endoscopy compared with colonoscopy. *Gastrointest Endosc* 2011;

74: 581-9. doi : 10.1016/j.gie.2011.03.1125
21. Spada C, Hassan C, Galmiche JP, *et al.* Colon capsule endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2012; 44: 527-36. doi : 10.1055/s-0031-1291717
22. Alarcon-Fernandez O, Ramos L, Adrian-de-Ganzo Z, *et al.* Effects of colon capsule endoscopy on medical decision making in patients with incomplete colonoscopies. *Clin Gastroenterol Hepatol* 2013; 11: 534-40. doi : 10.1016/j.cgh.2012.10.016
23. Triantafyllou K, Viazis N, Tsibouris P, *et al.* Colon capsule endoscopy is feasible to perform after incomplete colonoscopy and guides further work-up in clinical practice. *Gastrointest Endosc* 2014; 79: 307-16. doi: 10.1016/j.gie.2013.07.061
24. Spada C, De Vincentis F, Cesaro P, *et al.* Accuracy and safety of second-generation PillCam COLON capsule for colorectal polyp detection. *Therap Adv Gastroenterol* 2012; 5: 173-8. doi : 10.1177/1756283X12438054
25. Pioche M, de Leusse A, Filoche B, *et al.* Prospective multicenter evaluation of colon capsule examination indicated by colonoscopy failure or anesthesia contraindication. *Endoscopy* 2012; 44: 911-6. doi : 10.1055/s-0032-1310008
26. Spada C, Hassan C, Barbaro B, *et al.* Colon capsule versus CT colonography in patients with incomplete colonoscopy: a prospective, comparative trial. *Gut* 2014: epub. doi: 10.1136/gutjnl-2013-306550.
27. Baltes P, Bota M, Albert JG. Tu1557 PillCam Colon2® After Incomplete Colonoscopy- a Prospective Multi-Center Study. *Gastrointestinal Endoscopy* 2014; 79: AB584. doi: 10.1016/j.gie.2014.02.1003
28. Park SH, Ha HK, Kim MJ, *et al.* False-negative results at multi-detector row CT colonography: multivariate analysis of causes for missed lesions. *Radiology* 2005; 235: 495-502.
29. Park SH, Ha HK, Kim AY, *et al.* Flat polyps of the colon: detection with 16-MDCT colonography--preliminary results. *AJR Am J Roentgenol* 2006 ; 186 : 1611-7.
30. Fidler J, Johnson C. Flat polyps of the colon: accuracy of detection by CT colonography and histologic significance. *Abdom Imaging* 2009; 34: 157-71. doi : 10.1007/s00261-008-9388-4
31. Macari M, Bini EJ, Jacobs SL, *et al.* Significance of missed polyps at CT colonography. *AJR Am J Roentgenol* 2004; 183: 127-34.
32. Arnesen RB, Adamsen S, Svendsen LB, *et al.* Missed lesions and false-positive findings on computed-tomographic colonography: a controlled prospective analysis. *Endoscopy* 2005; 3: 937-44.
33. Cotton PB, Durkalski VL, Pineau BC, *et al.* Computed tomographic colonography (virtual colonoscopy): a multicenter comparison with standard colonoscopy for detection of colorectal neoplasia. *JAMA* 2004; 291:

1713-9.
34. Pickhardt PJ, Levin B, Bond JH. Screening for nonpolypoid colorectal neoplasms. *JAMA* 2008; 299: 2743-4.
35. Pickhardt PJ, Nugent PA, Choi JR, *et al*. Flat colorectal lesions in asymptomatic adults: implications for screening with CT virtual colonoscopy. *AJR Am J Roentgenol* 2004; 183: 1343-7.
36. Pickhardt PJ, Kim DH. Colorectal cancer screening with CT colonography: key concepts regarding polyp prevalence, size, histology, morphology, and natural history. *AJR Am J Roentgenol* 2009; 193: 40-6. doi : 10.2214/AJR.08.1709.
37. Park SH, Lee SS, Choi EK, *et al.* Flat colorectal neoplasms: definition, importance, and visualization on CT colonography. *AJR Am J Roentgenol* 2007; 188: 953-9.
38. Park SH, Ha HK, Kim AY, *et al.* Flat polyps of the colon: detection with 16-MDCT colonography--preliminary results. *AJR Am J Roentgenol* 2006; 186: 1611-7.
39. Halligan S, Park SH, Ha HK. Causes of false-negative findings at CT colonography. *Radiology* 2006; 238: 1075-6.

French National Colon Capsule Endoscopy Observatory (ONECC)

Evaluation and first lessons

Jean-Christophe Saurin

On behalf of the *comité scientifique de l'Oservatoire national de l'endoscopie par capsule colique (ONECC)* : Robert Benamouzig, Antoine De Leusse, Edouard Chabrun, Christophe Cellier (France).

" Diagnostic endoscopy by colon capsule endoscopy is now capable of detecting significant colorectal neoplastic lesions (> 6 mm) with a sensitivity of around 90%. One very specific organization in France, the ONECC, has promoted the training of hundreds of gastroenterologists, the routine use of the capsule in 145 active centers, and the inclusion of 1,200 patients in a prospective cohort. Although the scientific potential of this observatory is still far from fully exploited, the development of colon capsule endoscopy in France is a model of efficiency and rigor. The potential of this observatory in terms of research and analysis of current practices is substantial. The rapidity of case inclusions and the practical feasibility clearly show that there is a role in clinical practice for this diagnostic tool. The place of colon capsule endoscopy in the colorectal cancer screening arsenal remains to be defined. However its use in indications which are currently those for virtual colonoscopy is now unquestionable, due to its simplicity, safety, absence of irradiation, and sensitivity, in comparison with other modalities."

French National Colon Capsule Endoscopy Observatory: history and rationale

The French National Colon Capsule Endoscopy Observatory ("*Observatoire national de l'endoscopie par capsule colique*", ONECC) was conceived and established in 2011 as a monitoring center equipped with an e-CRF (electronic case report form) platform, jointly managed by the French Society of Digestive Endoscopy ("*Société française d'endoscopie digestive*", SFED), the Gastroenterological Groups Reflection Team ("*Club de réflexion des cabinets et groupes d'hépato-gastroentérologie*", CREGG), and the firm, Given Imaging. The reasons justifying the establishment of this monitoring center were:
- the commercialization of Pillcam Colon 2 ® in France, authorized by the CE (European conformity) mark (September 2009);
- reliable scientific data regarding the good sensitivity of the second-generation colon capsule for the detection of polyps of a significant size (> 5 mm) [1,2];
- substantial pre-existing experience of the use of colon capsule endoscopy in France, through the implementation of prospective, multicenter national studies for indications of colorectal cancer screening, as well as for the indications endorsed by the ONECC [3,4];
- the need to regulate the use of this new device in current practice, to define the indications and standardized modalities for use.

The ONECC was structured into a Steering Committee, responsible for the overall organization and management of the monitoring center, and a Scientific Committee comprising individuals recognized as experts (through experience and publications) in the field and who are, to a large extent, representatives of SFED. The organization respects the rule, at the Steering Committee level, of an equal representation of the public and private sectors. The ONECC, and in particular its Scientific Committee, works closely with the SFED "Capsule Committee", especially in the development of colon capsule training modules.

Indications for colonoscopy by video capsule endoscopy endorsed by the ONECC Scientific Committee

Several medical conditions endorsed by the SFED, which correspond to valid indications for virtual colonoscopy as recommended by the

French National Authority for Health ("Haute autorité de santé", HAS), may be within the scope of a colon video capsule examination:
1. incomplete optical colonoscopy, not related to the presence of an organic colorectal stenosis or a poor preparation (except in cases of poor compliance of the preparation protocol by the patient);
2. severe comorbidities, contraindicating the performance of an optical colonoscopy, in particular where there are risks and contraindications related to anesthesia;
3. refusal of the optical colonoscopy examination by the patient after receiving information regarding the risks of not performing optical colonoscopy and the current limitations of colon capsule endoscopy (CCE).

Activity of the ONECC

Training

Around 20 ONECC training courses have been carried out, each involving 20 to 30 gastroenterologists, with over 500 practitioners trained in the use of CCE (principles, implementation, preparation, reading, interpretation). In France, 145 centers are currently active in this procedure, each with at least one trained gastroenterologist. This includes an equal representation in public and private centers.
Training in the use of colon capsule endoscopy has been evaluated in part, and this has resulted in a conference communication emphasizing the importance of training dedicated specifically to the use of CCE. This CCE training should be clearly distinct from training and evaluation of competence in capsule endoscopy in general [5]. These courses are expected to evolve towards a quantified assessment of the practices using software developed for training in the use of CCE. This CCE practice may be incorporated into the ongoing professional development program of gastroenterologists. The practical skills that will be assessed and that will be taught to the current state of the art are: quality of detection of adenomas and other polyps; specificity of this detection; evaluation of the bowel preparation. The teaching program also includes the modalities of the procedure, the principles of the ONECC charter, and, finally, an update on scientific knowledge concerning CCE.

Practice of colon capsule endoscopy

As of June 1st 2014, 1,250 CCE examinations had been carried out under the framework of the ONECC in France, in 145 active centers including practitioners who have signed the ONECC partnership agreement [6]. The rate of inclusion (*figure 1*) clearly highlights the practical value and role of the examination in the diagnostic arsenal of the gastroenterologist.

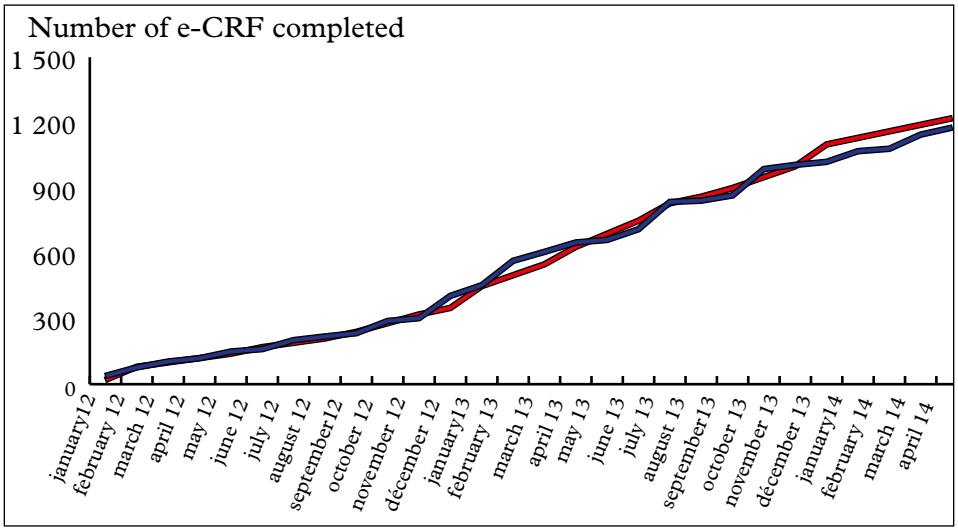

Figure 1. ONECC inclusion curve in France (actual in blue, theoretical in red).

The indications for these examinations have been perfectly respected and are divided in almost equal parts between the three recommended indications. One single examination was performed outside of these indications, in a heart-transplant patient after the approval of the Scientific Committee of ONECC was obtained, as specified in the ONECC regulations. Technically, relatively few problems have been reported, confirming the feasibility of use of this examination in everyday practice, under the right conditions. Finally, bowel preparation was estimated as good (data not verified by a second reading) in 80% of examinations (excellent or good on a scale of 4). Impressively, relatively few second opinions regarding the images obtained from the capsule have been requested from the Scientific Committee (in contrast to the multitude of requests relating to current use of the small bowel capsule). One possible explanation for this is the relative simplicity of

interpretation of these images by practitioners who are experienced in the analysis of colorectal images, in addition to the relative similarity of capsule images with colonoscopic images.

Evaluation of colon capsule endoscopy practice

The ONECC observatory is not closed in terms of inclusions, thus the collection of results relating to diagnostic performance is partial. These results will be the subject of a scientific publication. As of December 31st 2013, examination by video capsule from the colon to the anus had been complete in 829 patients, allowing the detection of polyps larger than 5 mm in 16–25% of patients for whom the use of colon capsule endoscopy had been justified (failure of, contraindication to, or refusal of, colonoscopy) (*figure 2*). The capsule is thus useful in practice, detecting lesions of a significant size in around 20% of patients (and at least one polyp in 38% of patients)..

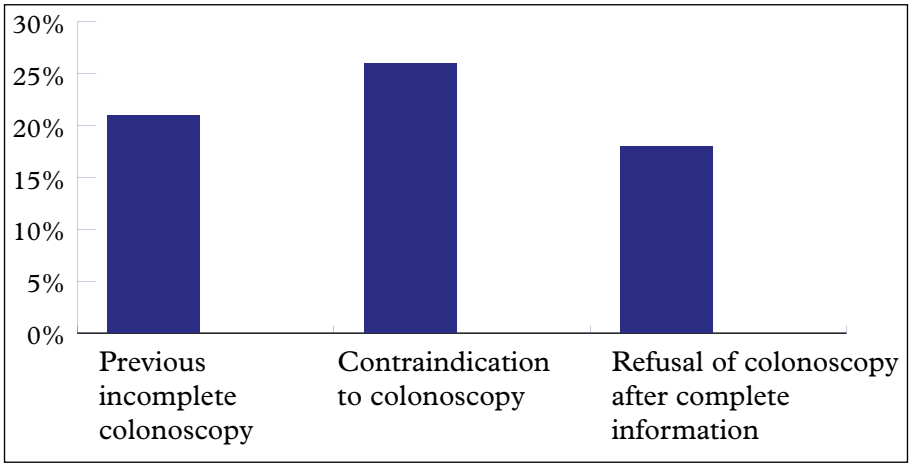

Figure 2. Prevalence of significant colorectal polyps (> 5 mm diameter) according to the ONECC indications for colon capsule endoscopy.

Concerning the analysis of practice, it is interesting to note that 23% of examinations, despite showing no significant polyp (> 6 mm) nevertheless led the gastroenterologist to perform a colonoscopy. The analysis of these 45 cases was carried out using data from the e-CRF. This indicates that the principal practical problem encountered is the question of how to proceed in cases where small polyps are present (43/45 cases, 95.5%). Gastroentero-

logists tend to privilege the option of colonoscopy, even for small colorectal lesions. The results of these colonoscopies are still pending, and the important goal of the ONECC is (as soon as possible) to be able to complete this data collection.

Perspectives

The aims of the ONECC in 2015 are as follows:

- complete the data collection, in particular data regarding colonoscopies, lesions detected, lesions treated, and histological results. These tasks will require time and effort and are currently being organized;
- continue clinical activity, which appears to be important and useful in light of the rapid constitution of the cohort, both in the public and private sectors;
- develop collaborative research projects based on existing centers of expertise (cancer screening, bowel preparation, comparison with virtual colonoscopy, new indications) and the IT network already in place, probably with an upgrade of the e-CRF;
- optimize and evaluate training and competence in CCE.

Conflicts of interest

Jean-Christophe Saurin is a speaker and consultant for: Covidien (GI Solutions) Given Imaging, Intromedic, and Caspovision.

References

1. Eliakim R, Yassin K, Niv Y, *et al.* Prospective multicenter performance evaluation of the second-generation colon capsule compared with colonoscopy. *Endoscopy* 2009 ; 41 : 1026-31. doi: 10.1055/s-0029-1215360
2. Spada C, Hassan C, Munoz-Navas M, *et al.* Second-generation colon capsule endoscopy compared with colonoscopy. *Gastrointest Endosc* 2011 ; 74 : 581-9 e1. doi : 10.1016/j.gie.2011.03.1125
3. Pioche M, Leusse A de, Filoche B, *et al.* Prospective multicenter evaluation of colon capsule examination indicated by colonoscopy failure or anesthesia contraindication. *Endoscopy* 2012 ; 44 : 911-6. doi : 10.1055/s-

0032-1310008
4. Sacher-Huvelin S, Coron E, Gaudric M, *et al.* Colon capsule endoscopy vs. colonoscopy in patients at average or increased risk of colorectal cancer. *Aliment Pharmacol Ther* 2010 ; 32 : 1145-53. doi : 10.1111/j.1365-2036.2010.04458.x
5. Danset J, Bejou B, Saurin JC, *et al.* Colon Capsule Endoscopy by Expiremented Gastroenterologists Practicing the Small Bowel Capsule Endoscopy Requires a Specific Training. *Gastrointest Endosc* 2014 ; 79 : AB307. doi : 10.1016/j.gie.2014.02.263
6. Saurin JC, Benamouzig R, Ponchon T. Observatoire national de l'endoscopie par capsule colique: résultats à 2 ans de la pratique en France. *Endoscopy* 2014 ; 46 : A8693. doi : 10.1055/s-0033-1364108

Current issues in colorectal cancer screening in France

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“ Colorectal cancer is a major public health issue. Colorectal cancer screening should be adapted to the level of risk. In subjects with high or very high risk, screening is carried out by colonoscopy. Where there is average risk, the basis of screening is an immunological fecal test performed every two years. This test, which is now available in 2015, can detect 7–8 out of 10 cancers, instead of just 3–4 for the Hemoccult ® test previously used. Increasing the participation of the target population is the major challenge in this action. The role of general practitioners and their corresponding gastroenterologists is central to this increase in participation. Colonoscopy could also be considered for people at average risk if there is a particular demand and if the risk–benefit ratio is clearly stated. Other tools may also be useful in specific circumstances: the fecal DNA test, rectosigmoidoscopy, and colon capsule endoscopy.”

A public health issue

Approximately 42,000 new cases of colorectal cancer are diagnosed each year in France. The lifetime risk for an individual of developing a colorectal cancer is in the order of 3–4%, with a very low risk before the age of 50 years that then steadily increases. Despite significant therapeutic advances and the possibility of earlier detection at a stage when the prognosis is more favorable, colorectal cancer remains the second leading cause of cancer mortality.

Increased risk

Individuals who have already had an adenoma or colorectal cancer, and those with at least one first-degree relative with a colorectal polyp or cancer have an increased relative risk, of between 2 and 4, depending on the age of onset and the type of index lesion [1].

The risk of colorectal cancer is also increased in Crohn's disease and ulcerative colitis (relative risk of approximately 2). This risk is observed when the inflammation has been poorly controlled, when it has been present for more than 10 years, when more than half of the colon is affected, and when sclerosing cholangitis or a family history of colon cancer are present [2].

The risk of colorectal cancer is very high in certain rare genetic conditions, such as familial adenomatous polyposis – linked to mutations in the APC gene (almost 100% risk of developing a cancer) or linked to MYH gene defects (relative risk greater than 30) – as well as Lynch syndrome (greater than 60% risk of developing a cancer).

The cancers diagnosed in these groups at high and very high risk represent approximately 20% of all colorectal cancers. The systematic identification of these circumstances and the implementation of regular surveillance by colonoscopy should allow for the management of most of this risk. The establishment of organized networks has facilitated progress, which should be further pursued [3].

It is recommended that all people over 40 years of age who have symptoms suggestive of colorectal cancer, both clinical – such as recent changes in bowel frequency (positive predictive value 14%) or rectal bleeding (positive predictive value 8%) –, or biological – such as iron-deficiency anemia without a gynecological explanation (positive predictive value 10%) –, consider undergoing a colonoscopy [4].

How to screen the "average-risk" population?

A "slow" natural history facilitating the screening

Most colorectal cancers are described as sporadic, that is they develop in subjects with none of the risk factors that are currently clearly identified. These sporadic cancers develop slowly over several years from benign precancerous lesions, or from adenomatous or serrated polyps. At the asymptomatic stage, advanced polyps and cancers can be the basis of intermittent occult bleeding. This bleeding can be identified in the stool by chemical (guaiac test, such as Hemoccult ®) or immunological (antibody against human hemoglobin) methods. The current screening program is based on this principle.

Hemoccult® : France at the forefront of organized screening

Performance of the Hemoccult ® test every two years can lead to a reduction of around 30% in colorectal cancer mortality in subjects participating in the screening program. This screening test has the advantage of being relatively simple and acceptable, safe, inexpensive, and with a proven efficacy. When the Hemoccult test is positive, which is the case in 2–3% of the subjects tested, a colonoscopy should be performed, which will generally reveal a cancer in just under 1 in 10 cases. After pilot programs were implemented in the early 2000s, colorectal cancer screening was generalized throughout the whole territory from 2008. France is thus one of the first countries to have proposed this test to all persons covered by social insurance aged between 50–74 years, as part of an organized program. One of the principal limitations of this program is insufficient participation, which has declined over time to around 32% of the target population according to the most recent estimates by the French National Institute for Health Surveillance ("Institut national de veille sanitaire"). This can be compared with the participation observed in the United Kingdom, which is of the order of 60%. The efficiency of a screening program depends not only on the performance of the test but also on the participation rate. The active involvement of general practitioners, which is an essential element of effectiveness in colorectal cancer screening, varies widely between different French "departments" (administrative regions) and

would seem to be diminishing over time.

Immunological tests; technical and conceptual progress

The French National Authority for Health ("*Haute autorité de santé*", HAS) recommended a switch to the use of immunological blood tests from 2008 onwards, as this method of detection of blood in the stool is more effective. However, a tender procedure was only implemented by the Public Health Insurance Fund ("*Caisse nationale d'assurance maladie*"), on government instruction, in 2014. The deployment of the new test is scheduled at the beginning of 2015. Whilst these immunological tests are still fecal tests, they require only a single stool sample, collected with a swab, as opposed to the Hemoccult ® test that requires six samples: two samples from three consecutive stools, collected using a spatula that is less easy to use. This test should, thus, be better accepted and better achieved by target individuals; an increase in participation somewhere between 0% and 15% is anticipated. Unlike that of the Hemoccult ® test, reading of the immunoassays is automated, which reduces the risk of human error. The cost will be broadly similar: although the unit cost is a little higher, the cost-effectiveness is similar.
At the chosen positivity threshold, the immunoassays can detect 7–8 cancers in 10, instead 3–4 cancers in 10 for the Hemoccult ® test (Table 1). They also detect three to four times as many advanced adenomas [5]. This ability to detect cancers at an early stage as well as advanced adenomas should allow not only the prevention of cancer deaths (cancers detected at an early stage), but also, ultimately, a reduction in the number of cancers (adenomas detected being removed during colonoscopy). General practitioners are at the heart of this screening program, as a test is performed more than 8 times out of 10 when it is actually prescribed by them. They must, therefore, be heavily involved in this change. Gastroenterologists, who are key partners in this action, as shown by the investment of their learned societies, need to motivate their general practitioner colleagues to increase participation.

Table 1. Comparison of the key characteristics of the Hemoccult ® test and immunological tests.

	Hemoccult ®	Immunological test
Estimated sensitivity to detect a cancer (%)	30 to 40	70 to 80
Estimated sensitivity to detect an advanced adenoma (%)	10	35
Number of colonoscopies to detect a cancer (after a positive test)	15	10 to 15

Other screening methods

Many other biological and morphological methods are available or being evaluated.

The detection of anomalies in fecal DNA (investigation of deleterious mutations and/or methylation anomalies associated with colon carcinogenesis) coupled with an immunological fecal blood test has been proven to be superior in terms of sensitivity compared with the immunological fecal blood test alone [6]. The specific contribution of seeking such DNA abnormalities remains moderate, however, in comparison with the completion of a fecal immunological test alone (18% gain in sensitivity for detecting cancer). The contribution of this approach will show its cost-effectiveness when the proposed cost is known.

Several blood tests have been developed, mostly based on the detection of abnormalities in circulating DNA, in particular abnormal methylation, with promising results. However, the results are still insufficient (positive predictive value in the order of 30%) for these tests to be considered for use at the level of large populations, despite their advantages in terms of acceptability [7]. Moreover, none of the available blood tests have a good detection for advanced adenomas. Alternative blood tests based on RNA or proteome analysis are still at the stage of preliminary studies [8].

Colonoscopy proposed as a first-line screen from the age of 50 or 55 years is considered as an option for colorectal cancer screening in countries such as Germany, Poland, and the United States. The acceptability of this method is low when it is systematically proposed to the general population, with a rate of between 20% and 25% [9]. Participation seems to be higher, around 50%, when the examination is proposed by a general practitioner [10]. The number of colonoscopies that need to be performed in order to detect a cancer or advanced adenoma depends on age and sex, varying from 46 colonoscopies for a 45-year-old woman to 10 colonoscopies for a 60-year-old man, figures that are close to those observed after a positive fecal test [9, 11]. The decrease in specific mortality expected after undergoing a screening colonoscopy remains to be quantified precisely, available estimates varying between 50–90%, depending on the study [12]. Ongoing interventional studies, NordiCC, COLONPREV, CONFIRM, and SAVE, should allow a clarification of these figures. Colonoscopy first-line screening strategies appear to be less cost-effective than screening based on fecal tests (fecal immunochemical test, FIT) [13]. The contribution of new endoscopic techniques – such as the increased lateral viewing allowed by the Fuse (Full Spectrum ™ Endoscopy; vision at 330 °) or "Third Eye", technologies, or by use of a centering balloon and vital or electronic chromoendoscopy – and also the contributions of policies facilitating the better quality of the colonoscopies performed, need to be clarified in the context of screening.

The protective role of a screen by rectosigmoidoscopy, once or repeated every 10 years, has been demonstrated by several randomized studies, with a decrease of around 20% in specific mortality [12]. The main problem of this technique, as for colonoscopy, is its poor acceptability (30% uptake).

The coloscanner with air insufflation has been proposed by some authors for use in colorectal cancer screening [14]. Its sensitivity to detect patients having at least one adenoma greater than 6 mm has been estimated as 76%, but this varies depending on the center and technique [15]. Assessments by the French National Authority for Health, and by the US authorities for the Medicare and Medicaid programs have not selected this technique for colorectal cancer screening [16]. Its role in screening in high-risk cases is thus confined to subjects unable or unwilling to undergo a colonoscopy.

The sensitivity of colon capsule endoscopy to detect adenomas larger

than 6 mm is about 85%, which is higher than that of the coloscanner. The capsule is currently proposed as a second-line option, after a positive fecal test and when colonoscopy is not possible or refused. The value of colon capsule endoscopy as a first-line screen for colorectal cancer remains to be assessed in the general population. Preliminary studies are in progress. The anticipated participation rate might be higher than that observed for conventional colonoscopy, which would render this approach cost-effective. [17]. "New" capsules are at a preliminary study stage, including one that uses a very low level of X-rays to allow 3D visualization of the colon without the need for bowel preparation (Check-Cap).

A false "average risk"

Age and male gender are risk factors for colorectal cancer, as well as insufficient physical activity, obesity, diabetes, high cholesterol, chronic alcohol consumption, smoking, a diet high in red and cured meats and/or low in fruits and vegetables, calcium, and possibly folate and phenols, and the absence of chronic exposure to aspirin. These factors appear to be particularly harmful in combination or when there is a predisposing genetic background, characterized by certain polymorphisms affecting sensitive metabolic or immune pathways. In these situations, the risk level approaches that of "known" high-risk populations and colonoscopy screening could be envisaged. Scores have been proposed to better define risk levels, some of which are available online [18-20]. These scores are still insufficiently discriminating for use in the clinic and have not been validated for the French population. An original approach to the prediction of colorectal cancer risk using a mathematical algorithm based on the evolution of data from repeated complete blood counts is currently being evaluated.

Conflicts of interest

Robert Benamouzig, head of Avicenne University hospital and the director of a clinical research center, is principal investigator for several studies promoted by "Assistance Publique-Hôpitaux de Paris" and INRA. He is a member of the Scientific Board of Given Imaging, Covidien.

References

1. Imperiale TF, Ransohoff DF. Risk for Colorectal Cancer in Persons With a Family History of Adenomatous PolypsA Systematic Review. *Annals of Internal Medicine* 2012 ; 156 : 703-9. doi: 10.7326/0003-4819-156-10-201205150-00006
2. Andersen NN, Jess T. Has the risk of colorectal cancer in inflammatory bowel disease decreased? *World J Gastroenterol* 2013 ; 19 : 7561-8. doi: 10.3748/wjg.v19.i43.7561.
3. Lowery JT, Horick N, Kinney AY, *et al.* A randomized trial to increase colonoscopy screening in members of high-risk families in the colorectal cancer family registry and cancer genetics network. *Cancer Epidemiol Biomarkers Prev* 2014 ; 23 : 601-10. doi : 10.1158/1055-9965.EPI-13-1085
4. Astin M, Griffin T, Neal RD, Rose P, Hamilton W. The diagnostic value of symptoms for colorectal cancer in primary care: a systematic review. *Br J Gen Pract* 2011 ; 61 : e231-43. doi: 10.3399/bjgp11X572427
5. Lee JK, Liles EG, Bent S, Levin TR, Corley DA. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. *Ann Intern Med* 2014 ; 160 : 171. doi : 10.7326/M13-1484
6. Imperiale TF, Ransohoff DF, Itzkowitz SH, *et al.* Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med* 2014 ; 370 : 1287-97.
7. Johnson DA, Barclay RL, Mergener K, *et al.* Plasma Septin9 versus fecal immunochemical testing for colorectal cancer screening: a prospective multicenter study. *PLoS One* 2014 ; 9 : e98238. doi: 10.1371/journal.pone.0098238
8. Schaaij-Visser TB, de Wit M, Lam SW, Jiménez CR. The cancer secretome, current status and opportunities in the lung, breast and colorectal cancer context. *Biochim Biophys Acta* 2013 ; 1834 : 2242-58.
9. Salas D, Vanaclocha M, Ibáñez J, *et al.* Participation and detection rates by age and sex for colonoscopy versus fecal immunochemical testing in colorectal cancer screening. *Cancer Causes Control* 2014 ; 25 : 985-97. doi: 10.1007/s10552-014-0398-y
10. Boguradzka A, Wiszniewski M, Kaminski MF, *et al.*, The effect of primary care physician counseling on participation rate and use of sedation in colonoscopy-based colorectal cancer screening program - a randomized controlled study. *Scand J Gastroenterol* 2014 ; 49 : 878-84. doi : 10.3109/00365521.2014.913191
11. Regula J, Rupinski M, Kraszewska E, *et al.* Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. *N Engl J Med* 2006 ; 355 : 1863-72.
12. Kuipers EJ, Rösch T, Bretthauer M, Colorectal cancer screening--optimizing current strategies and new directions. Nat Rev Clin Oncol, 2013.

10 : 130-42. doi : 10.1038/nrclinonc.2013.12
13. Sharaf RN, Ladabaum U. Comparative effectiveness and cost-effectiveness of screening colonoscopy vs. sigmoidoscopy and alternative strategies. *Am J Gastroenterol* 2013 ; 108 : 120-32. doi : 10.1038/ajg.2012.380
14. Hanly P, Skally M, Fenlon H, Sharp L. Cost-effectiveness of computed tomography colonography in colorectal cancer screening: a systematic review. *Int J Technol Assess Health Care* 2012 ; 28 : 415-23. doi : 10.1017/S0266462312000542
15. Meertens R, Brealey S, Nightingale J, McCoubrie P. Diagnostic accuracy of radiographer reporting of computed tomography colonography examinations: a systematic review. *Clin Radiol* 2013 ; 68 : e177-90. doi: 10.1016/j.crad.2012.11.005
16. Gandon Y. Screening for colorectal cancer: the role of CT colonography. *Diagn Interv Imaging* 2014 ; 95 : 467-74. doi : 10.1016/j.diii.2014.03.012
17. Holleran G, Leen R, O'Morain C, McNamara D. Colon capsule endoscopy as possible filter test for colonoscopy selection in a screening population with positive fecal immunology. *Endoscopy* 2014 ; 46 : 473-8. doi : 10.1055/s-0034-1365402
18. Ma GK, Ladabaum U, Personalizing Colorectal Cancer Screening: A Systematic Review of Models to Predict Risk of Colorectal Neoplasia. *Clinical Gastroenterology and Hepatology* 2014 ; epub. doi: 10.1016/j.cgh.2014.01.042.
19. Wells BJ, Kattan MW, Cooper GS, Jackson L, Koroukian S. ColoRectal Cancer Predicted Risk Online (CRC-PRO) calculator using data from the Multi-Ethnic Cohort Study. *J Am Board Fam Med* 2014 ; 27 : 42-55. doi: 10.3122/jabfm.2014.01.130040.
20. Kaminski MF, Polkowski M, Kraszewska E, *et al*. A score to estimate the likelihood of detecting advanced colorectal neoplasia at colonoscopy. *Gut* 2014 ; 63 : 1112-9. doi: 10.1136/gutjnl-2013-304965

Online E-Learning Course
An Innovative, New Training Tool for Reading Colon Capsule Endoscopy Videos

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" Colon capsule endoscopy with the PillCam Colon ® system is a relatively new, minimally invasive method for colorectal imaging. When reading the capsule video, identification of polyps and other significant lesions is dependent on the reader skills, and adequate reading training is necessary to ensure high quality reports. We have developed a structured e-learning training course for reading colon capsule endoscopy videos. The course focuses on improving skills for reading and analyzing colon capsule videos, and includes a blend of theoretical learning, reading practice with interactive feedback, and knowledge assessments. The course automatically optimizes reading practice according to individual skill level. The Japanese Association of Capsule Endoscopy (JACE) endorsed the e-learning course during early 2014. Twenty Japanese physicians completed a full online pilot course, of whom 67% indicated that the e-learning course was extremely helpful, and 33% indicated that it was very helpful in improving their reading skill. The new e-learning course appears to be a promising training tool which provides an efficient and flexible online learning method optimized according to the trainee skill level. The course is being used in Japan, and ongoing work is being carried out to expand its usage worldwide. A French version is currently being prepared with the intent to introduce it to France during 2015."

Colon capsule endoscopy with the PillCam Colon ® system is a relatively new, minimally invasive method for colorectal imaging. The system includes an ingestible capsule with two camera heads, sensors, a small data recorder, and a software package called Rapid ®. The data recorder is carried by the patient and receives and stores images from the capsule as it propagates through the colon. The recorded images are viewed as video on a workstation using the Rapid software, which also allows the creation of procedure reports.
When reading the capsule video, the identification of polyps and other significant lesions is dependent on the reader skills, and adequate reading training is necessary to ensure high quality reports.
Capsule endoscopy for small bowel visualization has been available for over 15 years, and courses including reading training have been offered worldwide. However, colon physiology presents new challenges to the colon video reader such as complex, non-insufflated anatomy, complex capsule transit patterns, and turbid or cloudy colon fluid. In addition, the colon capsule has two camera heads *versus* the single camera of the small bowel capsule, which increases reading complexity.
Therefore a new reading method is needed. Furthermore, a recent study in France [1] concluded that training and experience in small bowel capsule video reading is not sufficient for colon reading, and reading training specific to the colon capsule is needed to ensure the quality of the report

An e-learning course

We have developed an e-learning training course for reading colon capsule endoscopy videos. The course focuses on improving skills for reading and analyzing colon capsule videos, and includes a blend of theoretical learning, interactive reading practice with the Rapid ® software, and knowledge assessments. There are six steps in the course (*figure 1*).

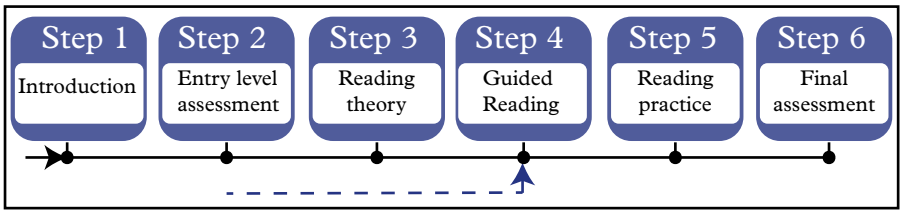

Figure 1. Six steps of the the e-learning course. The trainee progresses through the steps until completion of the training. The course supports both full on-line and blended learning; trainees that attended an instructor-led training in a class, can prove their knowledge in Step 2 (Entry Level Assessment) and skip Step 3 (Reading Theory), as marked with the blue arrow in the figure.

Step 1: Introduction

This step introduces the trainee to the course and reading challenges.

Step 2: Entry Level Assessment

This step allows experienced readers or trainees who attended an instructor-led training in a class, to test their knowledge and skip Step 3, reading Theory, if they obtain a score of 80% or higher.

Step 3: Reading Theory

This step includes five sessions that cover the recommended reading method. Some sessions include interactive practice with the Rapid software, in which the trainee can practice with real Rapid video and get feedback.

Step 4: Guided Reading

This step offers the trainee a chance to read and analyze a full-length video and eight short video segments using the Rapid software, emphasizing specific skills and professional issues, and providing the trainee with feedback.

Step 5: Reading Practice

In this step, the trainee practices full-length video reading with the Rapid software until becoming eligible to take the Final Assessment. When the trainee is ready to submit each report, Rapid reviews the report and displays current accuracy in a percentage range with no additional information. The trainee may continue reading the video to improve the report accuracy. After submitting the report, the trainee can no longer improve the score. Rapid evaluates the report, provides a detailed evaluation feedback, and grants a score based on report accuracy. The score takes into account successful reporting of polyps, including polyp size, shape and location, cleansing level, and false-positive reports. The greater the challenge, the higher the score. The number of videos read is automatically set according to the individual skill level. The score granted for each video is accumulated by Rapid, and after reaching a predefined target score or reaching a maximum number of videos read (n = 14), the trainee can proceed to the next step and perform the Final Assessment. Therefore, a highly skilled reader may need to read a relatively small number of videos prior to performing the Final Assessment.

Step 6: Final Assessment

This step includes reading two full-length videos and two short video segments with the Rapid software. The score granted for each video is accumulated but not shown, and a final assessment score in percentile units is provided upon completion of the course.

Development perspectives

The e-learning training course offers several major advantages:

- It supports full practice of theoretical learning with interactive feedback,
- It provides efficient and flexible on-line learning,
- The trainee is not confined to a fixed schedule,
- It automatically optimizes reading practice according to individual skill level,
- It supports both blended and full online learning,
- It allows cost savings *vs* an equivalent course with full practice.

Following the completion of development, the Japanese Association

of Capsule Endoscopy (JACE) reviewed and accepted the e-learning course during early 2014. Twenty Japanese physicians completed a full online pilot course. The majority of the physicians (78%) did not read any colon video prior to the course, 11% read 1-5 videos, and 11% read 6-15 videos. Two of the feedback questionnaire results are shown in *figure 2*.

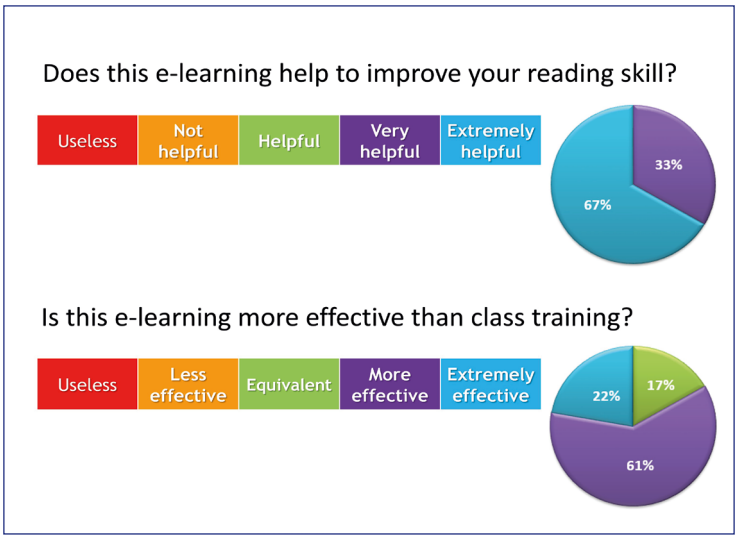

Figure 2. Two sets of questionnaire results obtained from 20 Japanese physicians who took the e-learning pilot course.

Sixty-seven percents of the trainees indicated that the e-learning course was extremely helpful, and 33% indicated that it was very helpful in improving their reading skill. When asked if the e-learning course is more effective than class training, 22% of the trainees indicated that the e-learning is very much more effective, 61% of the trainees indicated that the e-learning is more effective, and 17% indicated that it is equivalent.

A French version of the e-learning course is currently being prepared with the intent to evaluate and introduce it to France during 2015.

Conclusion

In summary, the new e-learning course for reading colon capsule endoscopy videos appears to be a promising training tool that provides an

efficient and flexible online learning method optimized according to the trainee skill level. The course is being used in Japan, and ongoing work is being carried out to expand its usage worldwide.

Conflict of interest

The authors are employees of Given Imaging, a Covidien Company.

Reference

1. Danset JB, Bejou B, Saurin JC, Ponchon T, Benamouzig R. Colon capsule endoscopy by experimented gastroenterologists practicing the small bowel capsule endoscopy requires a specific training. *Gastrointest Endosc* 2014 ; 79: Supplement, AS307. doi: 10.1016/j.gie.2014.02.263