Esophageal Capsule Endoscopy vs. EGD for the Evaluation of Portal Hypertension: A French Prospective Multicenter Comparative Study

M.G. Lapalus, MD[1,9], E. Ben Soussan, MD[2,9], M. Gaudric, MD[3,9], J.C. Saurin, MD, PhD[4,9], P.N. D'Halluin, MD[5,9], O. Favre, MD[6,9], B. Filoche, MD, PhD[7,9], F. Cholet, MD[8,9], A. de Leusse, MD[1,9], M. Antonietti, MD[2,9], J.L. Gaudin, MD[4,9], P. Sogni, MD[3,9], D. Heresbach, MD, PhD[5,9], T. Ponchon, MD, PhD[1,9] and J. Dumortier, MD, PhD[1,9]

OBJECTIVES: **Esophagogastroduodenoscopy (EGD) is the standard method for the diagnosis of esophago-gastric varices. The aim of this prospective multicenter study was to evaluate the PillCam esophageal capsule endoscopy (ECE) for this indication.**

METHODS: **Patients presenting with cirrhotic or noncirrhotic portal hypertension underwent ECE followed by EGD at the time of diagnosis. Capsule recordings were blindly read by two endoscopists.**

RESULTS: **A total of 120 patients (72 males, mean age: 58 years; mean Child–Pugh score: 7.2) were included. Esophageal varices were detected in 74 patients. No adverse event was observed after either EGD or ECE. Seven (6%) patients were unable to swallow the capsule. The mean recording time was 204 s (range 1–876). Sensitivity, specificity, negative predictive value, and positive predictive value of ECE for the detection of esophageal varices were 77%, 86%, 69%, and 90%, respectively. Sensitivity, specificity, negative and positive predictive values of ECE for the indication of primary prophylaxis (esophageal varices ≥grade 2 and/or red signs) were 77, 88, 90, and 75%, respectively, and 85% of the patients were adequately classified for the indication (or not) of prophylaxis. Interobserver concordance for ECE readings was 79.4% for the diagnosis of varices, 66.4% for the grading of varices, and 89.7% for the indication of prophylaxis.**

CONCLUSIONS: **This large multicenter study confirms the safety and acceptable accuracy of ECE for the evaluation of esophageal varices. ECE might be proposed as an alternative to EGD for the screening of portal hypertension, especially in patients unable or unwilling to undergo EGD.**

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INTRODUCTION

Esophagogastroduodenoscopy (EGD) is the most effective method to investigate disorders affecting the upper digestive tract, and, in particular, EGD is used for evaluation of portal hypertension in cirrhotic patients, for both screening and surveillance purposes (1). The procedure, however, is costly, may be unpleasant, and still has a small but potential risk for complications. Moreover, the procedure is often performed under sedation (2–4), with its own cost and complications, which may be more severe in patients with cirrhosis. The use of an alternative safe and comparable method for evaluating the esophagus, especially in the setting of a screening strategy (i.e., esophageal varices), is needed. Unsedated EGD using small-diameter endoscopes is being evaluated as an alternative to conventional

[1]Fédération des Spécialités Digestives, Hôpital Edouard Herriot, Lyon, France; [2]Service de gastroentérologie, Hôpital Ch. Nicolle, Rouen, France; [3]Service de gastroentérologie, Hôpital Cochin, Paris, France; [4]Service de gastroentérologie, Centre Hospitalier Lyon Sud, Pierre-Benite, France; [5]Service de gastroentérologie, Centre Hospitalier Pontchaillou, Rennes, France; [6]Hôpital privé Les Franciscaines, Nimes, France; [7]Service de gastroentérologie, Hôpital Saint Philibert, Lomme, France; [8]Service de gastroentérologie, Hôpital de la Cavale blanche, Brest, France; [9]Société Française d'Endoscopie Digestive, Paris, France.
Correspondence: J. Dumortier, MD, PhD, Fédération des Spécialités Digestives, pavillon H, Hôpital Edouard Herriot, 69437 Lyon Cedex 03, France.
E-mail: Jerome.dumortier@chu-lyon.fr
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endoscopy to avoid the direct and indirect costs resultant from conscious sedation (5,6). During the past decade, several methods have been proposed as alternatives to conventional EGD for the non-invasive or minimally invasive diagnosis of esophageal varices (7). The platelet count/spleen diameter ratio, Fibrotest, and Fibroscan are non-invasive. Multidetector computed tomographic (CT) esophagography and esophageal capsule endoscopy (ECE) are minimally invasive.

Initial small pilot studies have suggested that ECE may be useful in the detection and assessment of the size of esophageal varices (8–11). The aim of the present large multicenter prospective study was to assess the feasibility, tolerance, and accuracy of ECE for evaluating esophageal varices in patients with portal hypertension.

METHODS

Material

Endoscope. Standard or small-diameter (<6.0 mm) forward-viewing upper gastrointestinal videoendoscopes were used, according to the center's standard procedures.

Capsule. The PillCam Eso device currently available (Given Imaging Ltd., Yoqneam, Israel) is a sealed outer plastic capsule that measures 26 mm in length by 11 mm in diameter. The size and shape allow for easy ingestion and convenient passive passage through the gut. A complementary metal oxide silicone chip camera that has lower power and illumination needs than do conventional endoscopes generates the images at both extremities of the capsule. Four pulsing white, light-emitting diodes generate the necessary illumination on both sides. In addition, there are two silver oxide batteries followed by an ultra high-frequency band radio telemetry transmitter. The image generated has a 140° viewing field and a 1:8 magnification of objects from 1 to 30 mm depth of view. The cameras transmit 14 color images per second as the capsule moves through the esophagus. Images are transmitted to an antenna array over the abdomen, which in turn is connected to a portable hard drive and power source worn on a belt. After the recording is completed, the recorded images are downloaded into a customized personal computer workstation and then reviewed and interpreted. The device is eliminated in the stools.

Endoscopy procedure

All procedures were performed by senior endoscopists experienced in conventional and transnasal EGD. EGDs were conducted with or without premedication or sedation. In case of unsedated transnasal EGD, topical anesthesia of the nasal cavities or pharynx was conducted by applying 5% lidocaine (Astra France, Nanterre, France).

In all cases, the endoscope was inserted under visual control, through the nose or the mouth, to the pharynx. The upper esophageal sphincter was crossed under direct vision, and the esophagus, stomach, and first and second portions of the duodenum were examined as usual.

Capsule endoscopy procedure

No sedation or topical anesthetic was used. Patients fasted for 6 h before swallowing the PillCam Eso. Three sensor arrays were strategically placed on the patient's chest and connected to a data recorder worn on a belt around the waist. A smooth plastic capsule was swallowed with water while the patient lay on his or her back. After swallowing PillCam Eso, patients were raised by 30° angles every 2 min over a 6-min ingestion period until they were sitting upright. Patients did not speak during the procedure and were asked to not swallow after the capsule crossed the upper esophageal sphincter.

Study design

The protocol of the study was approved by the ethics committee of Hospices Civils de Lyon. Patients with recently diagnosed cirrhosis were invited to participate in this study and did so after signing an informed consent. They were both inpatients and outpatients.

Within 48 h after the ECE, subjects underwent the EGD.

Exclusion criteria. Exclusion criteria were age below 18 years, pregnant women, patients with known or suspected gastrointestinal obstruction or strictures, patients with cardiac pacemaker or other implanted electromedical devices, patients with swallowing disorders or dysphagia. Patients with previous endoscopic or surgical esophageal treatment were also excluded.

Feasibility of capsule endoscopy and EGD. The operator indicated the success or failure of the procedure, the reason for failure, and the side effects of the procedure.

Evaluation of portal hypertension. Esophageal varices were graded with ECE and EGD according to the size of varices. Varices are divided into 4 grades: 0 = no varices; 1 = varices that flatten with insufflation; 2 = non-confluent varices that protrude into the esophageal lumen at full insufflation of the esophagus; 3 = confluent varices that protrude into the esophageal lumen at full insufflation of the esophagus. The presence or absence of red spots on esophageal varices was also noted.

The presence or absence of gastric (or gastroesophageal) varices was also noted. Portal hypertensive gastropathy was classified as absent, mild, or severe according to the New Italian Endoscopic Club (12).

Evaluation of capsule endoscopy examination. Esophageal and gastric transit times were noted.

Two independent experienced endoscopists, unaware of the patients' diagnoses, reviewed the pictures obtained with the ECE and rendered an opinion as to whether or not the patient had evidence of esophageal varices, and as to whether or not there was an indication for β-blockers (varices ≥ grade 2 and/or red signs). Despite the main limitation for grading esophageal varices with capsule endoscopy being the lack of air inflation, a specific grading system was not developed and we used the

conventional EGD grading system for esophageal varices, on the basis of estimated size and convergence of the varices and the presence of red signs.

Interobserver agreement of the ECE recordings was evaluated by taking into account two independent readers.

Statistical analysis

Continuous variables were compared by using Student's *t*-test and categorical variables by using the χ^2-test. Results were considered significant if *P* values were <0.05.

RESULTS

Study population

From June 2006 to April 2007, 120 patients (72 men and 48 women; median age, 58 years; range, 23–84 years) were included from nine centers in France, with a mean model for end-stage liver disease (MELD) score of 11.5 and a mean Child–Pugh score of 7.4 (Child–Pugh A, 48%; Child–Pugh B, 30%; Child–Pugh C, 22%). All the patients had their procedures performed for screening purposes. Portal hypertension was related to cirrhosis in 113 patients. The etiology of their underlying liver disease included hepatitis C virus (HCV) infection in 17 patients, alcohol in 78, non-alcoholic steatohepatitis in 14, and other causes in 9. The patients had the EGD on the same day as the ECE in 105 patients; ECE was always performed first.

Comparative study

Feasibility of capsule endoscopy and EGD. Esophago-gastro-duodenoscopy was feasible in all the 120 patients. EGD was performed under sedation or general anesthesia in 37 cases, and was transnasal (unsedated) in 23. A small-diameter endoscope was used in 30 cases (including 23 transnasal EGD). No severe adverse event occurred.

Capsule endoscopy procedure was feasible in 113/120 patients (94%). The mean swallowing time of capsule endoscopy was 39 s per patient (range: 10–196). No severe adverse event occurred.

Diagnostic accuracy of capsule endoscopy examination. Esophagus: The mean recording time of capsule endoscopy in the esophagus was 204 s per patient (range: 1–876). **Figure 1** illustrates the recording times observed in the study. The recording time was <2 min in 47% of the patients. There were 74/120 patients with varices found on the EGD and 61/113 patients with varices found on the ECE. Considering the result of EGD as the standard, the sensitivity, specificity, negative predictive value, and positive predictive value of ECE for the detection of esophageal varices were 77% (95% CI 66–86%), 86% (95% CI 71–94%), 69% (95% CI 55–81%), and 90% (95% CI 79–96%), respectively. All data are summarized in **Table 1**. Similarly, sensitivity, specificity, negative predictive value, and positive predictive value of ECE for the detection of large (>grade 1) esophageal varices were 77% (95% CI 59–89%), 88% (95% CI 79–94%), 90% (95% CI 80–95%), and 75% (95% CI 57–87%), respectively. Positive and negative likelihood ratios (LR) were 6.69 (95% CI 3.52–12.69) and 0.26 (95% CI 0.14–0.48), respectively. In addition, 85% of the patients were adequately classified (global predictive value) for the indication of β-blockers or band ligation (varices grade >1 and/or red signs) from ECE examination. The mean recording time of capsule endoscopy in the esophagus was 201 s per patient (range: 1–876) in patients with diagnosis agreement in comparison to the EGD vs. 216 s per patient (range: 2–665) in patients without diagnosis agreement. Active hemorrhage from esophageal varices was observed in one patient.

Figures 2 and **3** illustrate some cases with or without agreement between the ECE and the EGD.

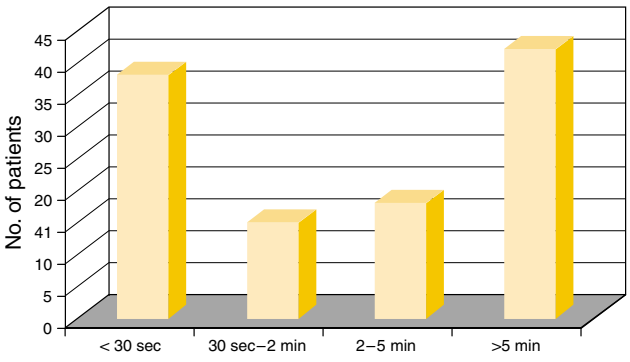

Figure 1. Esophageal recording time from capsule endoscopy examination in the 113 patients of the study.

Table 1. Classification of esophageal varices from EGD and ECE

113 Patients	ECE grade 0	ECE grade I	ECE grade II	ECE grade III
EGD grade 0	36	4	2	0
EGD grade I	14	15	7	0
EGD grade II	2	6	17	7
EGD grade III	0	0	1	2

ECE, esophago-gastro-duodenoscopy; EGD, esophageal capsule endoscopy; pts, patients.

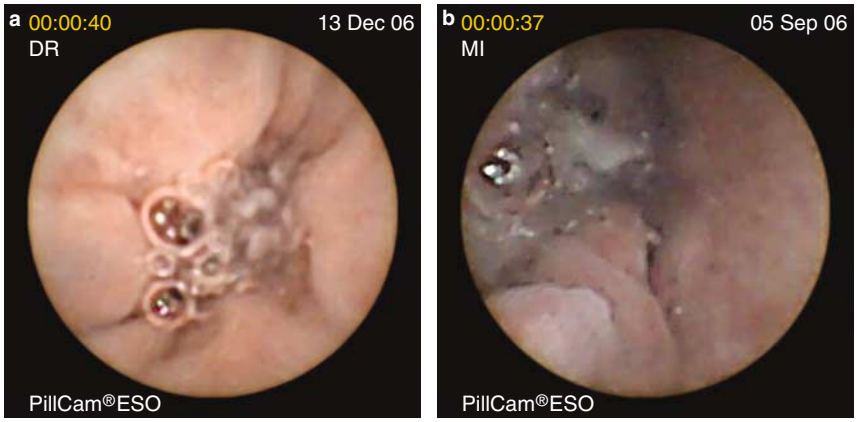

Figure 2. Set of pictures obtained with capsule endoscopy: examples of well-classified patients with grade 1 (**a**) or grade 2 (**b**) esophageal varices.

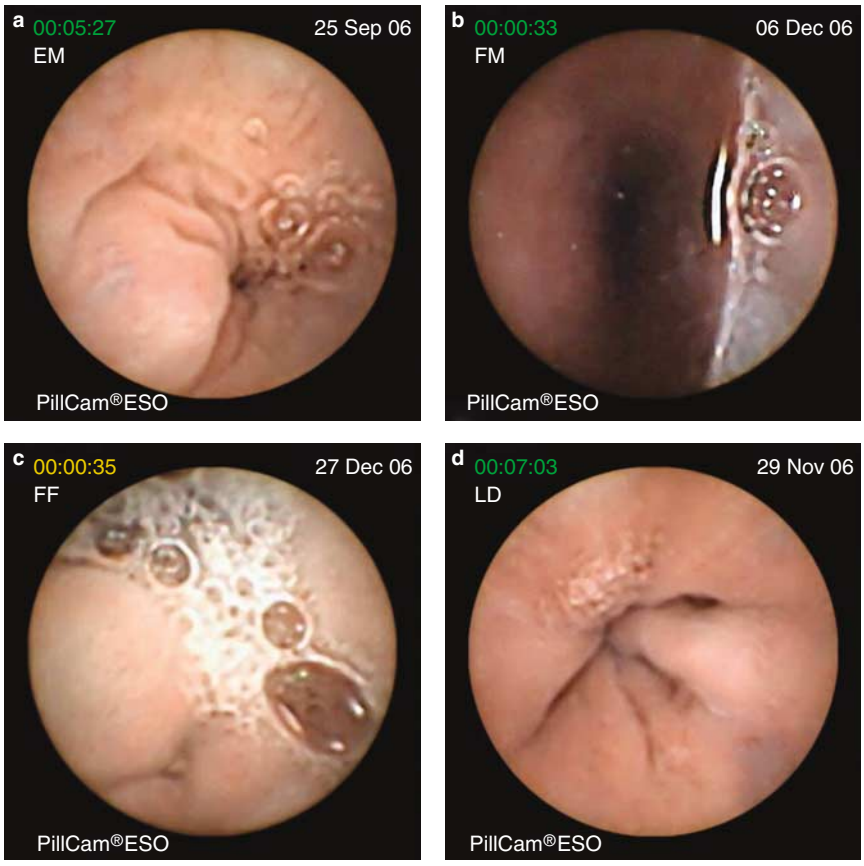

Figure 3. Set of pictures obtained with esophageal capsule endoscopy (ECE): examples of misclassified patients—without varices at esophagogastroduodenoscopy (EGD) and with grade 1 varices at ECE (**a**), with grade 1 varices at EGD and without varices at ECE (**b**), with grade 1 varices at EGD and with grade 2 varices at ECE (**c**), and with grade 2 varices at EGD and with grade 1 varices at ECE (**d**).

Stomach: The mean recording time of capsule endoscopy in the stomach was 491 s per patient (range: 221–1200).

Eight patients presented with gastric varices from the EGD that were diagnosed by capsule endoscopy in one case. Portal hypertensive gastropathy was diagnosed from the EGD in 83/120 patients and from capsule endoscopy in 70/113 patients. Considering the result of EGD as the standard, the sensitivity, specificity, negative predictive value, and positive predictive value of ECE for the detection of portal hypertensive gastropathy were 72, 61, 49, and 81%, respectively. Positive and negative LR were 1.85 and 0.46, respectively. All data are summarized in **Table 2**.

Table 2. Classification of portal hypertensive gastropathy from EGD and ECE

113 Patients	ECE absent	ECE mild	ECE severe
EGD absent	21	12	1
EGD mild	22	37	6
EGD severe	0	6	8

ECE, esophago-gastro-duodenoscopy; EGD, esophageal capsule endoscopy.

Interobserver variability of capsule endoscopy recordings. The interobserver agreement of the recordings was evaluated by taking into account the two readings of each recording that were available for 107 patients. (For six patients, the ECE recordings were lost after the first reading.)

Diagnostic agreement between the two readers was 79.4% for the detection of esophageal varices ($\kappa = 0.582$), 89.7% for the detection of large (>grade 1) esophageal varices ($\kappa = 0.322$), and 66.4% for the grading of esophageal varices ($\kappa = 0.790$).

DISCUSSION

Portal hypertension and the related complications are one of the major concerns during the evolution of cirrhosis. The measurement of the hepatic vein pressure gradient is the most reliable method for the estimation of both the portal pressure and the risk of variceal development and bleeding (13). Nevertheless, this method is invasive and not widely available, and the EGD is therefore usually used to evaluate the presence of esophageal varices and other consequences of portal hypertension (1). Ultrathin endoscopes have been used for the specific purpose of diagnosis of esophageal varices, yielding to accurate results for both the detection and grading of esophageal varices, with safety and enhanced patients' tolerance (5,14). Despite this, the major drawback of EGD is that patients must repeatedly undergo a procedure that is perceived as unpleasant, requires sedation in many cases, may lead to decreased work productivity in addition to its inherent cost, and has a small but not insignificant risk of complications (15). All these factors have led to the development of non-invasive or minimally invasive new methods in the past recent years, to replace or reduce the need for EGD.

The diagnostic value of platelet count is of great interest owing to it of being very simple and has been extensively studied. However, the optimal threshold varies markedly from study to study, from 68,000 to 160,000/mm^3 (16). The use of the platelet count/spleen diameter ratio has also been proposed as a pertinent non-invasive tool to predict the presence of varices. This ratio is calculated by dividing the platelet number/mm^3 by the maximum spleen diameter in mm as estimated by abdominal ultrasound. Using a cutoff value of 909, Giannini *et al.* (17) found that the positive and negative predictive values of platelet count/spleen diameter ratio for the presence of varices were 96 and 100%, respectively, and the area under receiver operating characteristic curve (AUROC) was 0.981. When the analysis was limited to the population on which the index should be routinely used (i.e. patients with compensated cirrhosis), the positive and negative predictive values were 74 and 100%, respectively. In an independent multicenter cohort, the positive and negative predictive values were less impressive at 76.6 and 87%, respectively (18). In summary, despite these promising data, the available evidence has not been considered sufficient to recommend the replacement of endoscopy by such a simple test based on platelet count (19). Another option is to use blood markers of fibrosis to identify patients with large varices. Thabut *et al.* evaluated in 99 patients with cirrhosis the ability of the Fibrotest to detect large varices in comparison to platelet count and Child–Pugh score. The Fibrotest performance was better than the other two tests, but with a poor AUROC of 0.77. The use of transient elastography (Fibroscan) for the detection of esophageal varices was evaluated in 165 patients (20). The AUROC for the discrimination between patients with or without medium–large varices was 0.83, with a sensitivity of 90% and a specificity of 60%. In summary, regarding LR, the performance of these two techniques can be considered, on the basis of our present knowledge, as insufficient (1).

Different from all these non-invasive methods, CT scan and ECE must be considered as minimally invasive methods. Owing to the major technical improvements, the use of multidetector CT esophagography to grade esophageal varices has been evaluated recently (21,22). It is important to remember that such radiological procedure requires the insufflation of air into the esophagus via a catheter passed through the mouth. In the study of Kim *et al.* that included 90 patients with cirrhosis, 30 patients had large esophageal varices. CT scan performance for the diagnosis of large varices was 0.931–0.958 (estimated by the AUROC). Perri *et al.* prospectively evaluated 102 patients who underwent both CT and endoscopic screening for gastroesophageal varices. CT was found to have approximately 90% sensitivity for the identification of large esophageal varices, but only about 50% specificity. Interestingly, the sensitivity of CT in detecting gastric varices was 87%. In addition,the use of CT as the initial screening modality for the detection of varices was significantly more cost-effective compared with endoscopy irrespective of the prevalence of large varices. In these two studies, CT scan was preferred by the patients.

The first experience for the exploration of esophagus with capsule needed the attachment of a string to the "standard" capsule (for small bowel exploration) to obtain a longer transit time (23). This "string–capsule" endoscopy was well tolerated by the patients: Only 1 (3.5%) of the patients had severe difficulty in swallowing the capsule (related to the capsule's size); the majority of patients (82.8%) had no or mild discomfort associated with the retrieval of the capsule at the end of the procedure, and 83.3% of patients would choose a string capsule over EGD. This technique was also evaluated in the areas of screening for Barrett's esophagus (24) and dysphagia (25).

The new and specific device PillCam Eso became available in 2004. Regarding the promising results for the detection of

esophageal varices in initial pilot studies (8–11), large multicenter studies were prompted, including our present one. The mean esophageal recording time was approximately 3–6 min in all reports. An international multicenter trial including 288 patients reported comprehensive data, in accordance with this study (26). In this study, a specific ECE classification for esophageal varices was used, grading varices as no varices (C0), small varices (C1), and large varices (C2), and this can explain some small differences in comparison with our results, including a significant number of grade 1/grade 2 misclassification in our study. For the diagnosis of large varices, the sensitivity, specificity, positive predictive value, and negative predictive value of ECE were 78% (77% in our study), 96% (88% in our study), 87% (75% in our study), and 92% (90% in our study), respectively. In addition, positive LR was better than in our study (19.5 vs. 6.4) and negative LR was similar to ours (0.2). The overall agreement on treatment decision was good in the two studies: 91% in the study by de Franchis and 85% in ours. Some drawbacks of ECE still persist, especially secretions that may interfere with the pictures obtained (this can be minimized by the ingestion of water) and the presence of bubbles (from saliva and/or air swallowed with water). In addition, esophageal transit time is unpredictable, and is less than a few seconds in some cases (<2 min in 47% of the patients in this study); this undoubtedly precludes a satisfactory examination of the esophagus. The major drawback of ECE for the diagnosis of esophageal conditions (varices in our report) is transit time. We observed some patients, with or without diagnosis agreement with EGD, in whom the transit times were 1 or 2 s. Nevertheless, making any diagnosis in such a short period of time is highly unpredictible. As a major consequence, using a device that is costly with uncertainty that it may or may not give accurate information may not be cost effective at all. In addition, ECE is not able to detect gastric varices (1/8 in this study). Regarding portal hypertensive gastropathy, the performance of ECE was good, exceptfor a poor negative predictive value in our study (49%). Interestingly, patients' perceptions *a priori* and *a posteriori* were significantly better for the ECE than for the EGD (26). The major limitation of ECE use in our experience is a significant rate of failure: 6% in this study. Nevertheless, de Franchis *et al.* experienced only one case of vomiting (qwing to esophageal stricture) from their cohort of 288 patients (26). The large size of the capsule remains a limiting factor in some patients when swallowing it in a dorsal decubitus position. Another limitation of ECE is the poor interobserver agreement, despite our observing a good agreement for the diagnosis of large varices ($\kappa = 0.790$). The classification for esophageal varices used by de Franchis *et al.* seems to be probably beneficial (26). In the comprehensive study of Delvaux *et al.*, the authors compared the diagnostic yield of capsule endoscopy and EGD in 98 patients with suspected esophageal disease; EGD was normal in one-third of the patients (27). The interobserver agreement between capsule endoscopy readings was moderate for both findings ($\kappa = 0.39$) and quality assessment ($\kappa = 0.24$). Last but not least, the cost-effectiveness of ECE needs further evaluation, taking into account patients' preferences for screening modality and adherence, which would clearly be in favor of ECE.

In conclusion, our results strongly confirm that ECE is feasible, safe, well tolerated, and accurate for the diagnosis of esophageal varices. Its accuracy may prove to be a cost-effective alternative to standard EGD in the evaluation of esophageal varices for the screening of cirrhotic patients and indication of primary prophylactic treatment (β-blockers or ligation).

CONFLICT OF INTEREST

Guarantor of the article: J. Dumortier, MD, PhD.
Specific author contributions: Study coordination, writing, statistical analysis, and patient inclusion: J. Dumortier; patient inclusion, and capsule examination: M.G. Lapalus, E. Ben Soussan, M. Gaudric, J.C. Saurin, P.N. D'Halluin, O. Favre, B. Filoche, A. de Leusse, M. Antonietti, J.L. Gaudin, P. Sogni, D. Heresbach, and T. Ponchon.
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Potential competing interests: Given Imaging provided all the capsules necessary for the study.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Esophagogastroduodenoscopy (EGD) is the most frequently used method for the evaluation of portal hypertension.
- ✓ Several methods have been proposed as alternatives to conventional EGD for the noninvasive or minimally invasive diagnosis of esophageal varices, including the platelet count/spleen diameter ratio, Fibrotest and Fibroscan, computed tomographic esophagography, and esophageal capsule endoscopy (ECE).

WHAT IS NEW HERE

- ✓ ECE is feasible, safe, well tolerated, and accurate for the diagnosis of esophageal varices.
- ✓ The limitations of ECE are the following: (1) the presence of secretions and bubbles may interfere with the pictures obtained; (2) the esophageal transit time is unpredictable; (3) ECE is not able to detect gastric varices; (4) there is a significant rate of failure (6% in this study); and (5) there is poor interobserver agreement.
- ✓ ECE may be an alternative to EGD for patients who do not want to undergo EGD.

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