Abstract

Currently, oesophago-gastroduodenoscopy is the standard method to diagnose the presence of oesophageal varices and to estimate the risk of bleeding. It is recommended that all patients undergo endoscopic screening for varices at the time when cirrhosis is diagnosed. After screening endoscopy, patients with medium or large varices should be treated to prevent bleeding, while all other patients should undergo periodic surveillance endoscopy. However, at a given point in time a variable proportion of patients will not have varices, since the prevalence of varices is variable. Thus, screening all cirrhotic patients with endoscopy to detect the presence of varices implies a number of unnecessary endoscopies. In recent years a wealth of new methods have been proposed as alternatives to conventional oesophago-gastroduodenoscopy for the non-invasive or minimally invasive diagnosis of oesophageal varices. Three of these methods (the platelet count/spleen diameter ratio, Fibrotest and Fibroscan) are truly non-invasive. Of these, the former is promising and needs a proper validation, Fibrotest appears to be insufficiently precise, while Fibroscan needs further evaluation. Multidetector CT oesophagography and capsule endoscopy are not entirely “non-invasive”, since the first requires air insufflation into the oesophagus via an orally passed tube, and the latter requires swallowing the capsule. Multidetector CT oesophagography is promising, but needs further evaluation; capsule endoscopy is safe and reliable and might be proposed as an alternative to oesophago-gastroduodenoscopy in patients unable or unwilling to undergo oesophago-gastroduodenoscopy.

Keywords: Biochemical parameters; Capsule endoscopy; Diagnosis; Endoscopy; Multidetector CT oesophagography; Non-invasive methods; Oesophageal varices; Portal hypertension; Transient elastograph

1. Introduction

Portal hypertension (PH) plays a crucial role in the transition from the pre-clinical to the clinical phase of cirrhosis. PH is a contributing factor for the development of ascites and hepatic encephalopathy and a direct cause of variceal haemorrhage and of bleeding related death. The increase of portal pressure leads to the development of a collateral circulation, of which oesophago-gastric varices are the most important feature from a clinical standpoint. Varices tend to increase in parallel with the increase in portal pressure, and rupture when variceal wall tension exceeds a critical level. Bleeding from oesophago-gastric varices is the most important complication of cirrhosis, marking the progression of decompensation of the disease to a stage with an extremely high risk of death [1]. It should be noted that, despite the advances achieved in the last decades in its treatment, variceal bleeding still carries a mortality of around 20% within 6 weeks of the bleeding episode [2].

Every decision concerning the diagnosis, control and surveillance of patients with portal hypertension must be based on the knowledge of the natural history of this condition.

2. Diagnosis of portal hypertension and of clinically significant portal hypertension (CSPH)

Portal pressure can only be measured by invasive methods; the most widely used method is based on the catheterisation of a hepatic vein via the femoral or jugular route. A balloon-
that the risk of bleeding is related to variceal size \cite{17,22}. Formed, they tend to increase in size \cite{21} and to bleed, and develop in all cirrhotic patients \cite{20}, and that, once they have vascular ectasia. Such as portal hypertensive gastropathy and gastric antral \cite{19}. In addition, endoscopy allows the identification of other complications. Several cross sectional \cite{5–7} and longitudinal \cite{8–14} studies have shown that varices neither develop nor bleed when the HVPG is below the threshold value of 10–12 mmHg. In addition, it has recently been shown that patients with a HVPG <10 mmHg have a 90% probability of not developing clinical decompensation of cirrhosis \cite{15}. As a consequence, the following definition of clinically significant portal hypertension has been given at a recent international consensus development workshop on portal hypertension \cite{16}: “CSPH is defined by the increase of the HVPG above a threshold value of about 10 mmHg. The presence of oesophago-gastric varices, of variceal bleeding and/or ascites indicate the presence of CSPH”. Hence, the strategy of identifying and surveying the patients with portal hypertension should be mainly focused on patients with CSPH.

### 3. Evaluation of patients to identify clinically significant portal hypertension

HVPG measurement is an accurate and reproducible method: when it is done correctly, the coefficient of variation of the technique is 2.6 ± 2.6\% \cite{6}. However, at present, HVPG measurement cannot be done routinely, and therefore, alternative methods must be used.

#### 3.1. Endoscopy

Complete endoscopic examination of the oesophagus, stomach and duodenum, which is far more widely available than HVPG measurement, is an appropriate method, since the size of varices is clearly related to the risk of bleeding \cite{17}; by this technique, a good degree of interobserver agreement for the assessment of variceal size can be achieved \cite{17,18}, together with a good accuracy for the diagnosis of cirrhosis \cite{19}. In addition, endoscopy allows the identification of other potentially bleeding lesions related to portal hypertension, such as portal hypertensive gastropathy and gastric antral vascular ectasia.

Longitudinal studies have shown that varices eventually develop in all cirrhotic patients \cite{20}, and that, once they have formed, they tend to increase in size \cite{21} and to bleed, and that the risk of bleeding is related to variceal size \cite{17,22}.

Knowledge of the rate of development and growth of varices would be important, since it would help defining the optimal intervals for surveillance endoscopy, with the aim of identifying varices at risk of bleeding before they bleed, in order to start a prophylactic treatment. Too short intervals would unnecessarily increase the workload of endoscopic units, while too long intervals would increase the risk of bleeding of patients between surveillance endoscopies. The yearly rate of development of “new” varices is about 5–10\% \cite{20,23}; the rate of growth of varices from small to large is 5–30\% in different studies \cite{23–26}. Accordingly, practice guidelines \cite{16,27–29} for the treatment of portal hypertension recommend that all patients should undergo endoscopic screening for varices at the time when cirrhosis is diagnosed. After screening endoscopy, patients with medium or large varices should be treated to prevent bleeding, while all other patients should undergo periodic surveillance endoscopy. The recommended intervals are 2–3 years for patients with compensated disease and no varices, 1–2 years for those with small varices \cite{19} and 1 year for those with decompensated disease, with or without varices \cite{19,28}.

However, since the prevalence of varices is variable \cite{23,30}, at a given point in time a variable proportion of patients will not have varices. Thus, screening all cirrhotic patients with endoscopy to detect the presence of varices implies a number of unnecessary endoscopies, which increase the workload of endoscopy units. In addition, practice guidelines require that patients repeatedly undergo a procedure that is perceived as unpleasant, requires conscious sedation in most cases, may lead to decreased work productivity, and has a small but not insignificant risk of complications \cite{31}. These factors may decrease patient compliance leading to a decrease in the effectiveness of the screening program.

#### 3.2. Possible alternatives to endoscopy

Predicting the presence of oesophageal varices by non-invasive means would restrict the performance of endoscopy to those patients with a high probability of having varices. Several studies \cite{32–48} have addressed the issue of identifying patients with varices by non-invasive or minimally invasive means, with the aim of avoiding endoscopy in those at low risk of having varices. These studies have assessed the potential of biochemical, clinical and ultrasound parameters, blood markers of fibrosis, transient elastography, multidetector CT oesophagography and video capsule endoscopy.

#### 3.3. Biochemical and ultrasound parameters

Several biochemical and ultrasound parameters have been found to be related to the presence of varices. They include a low platelet count, splenomegaly, a portal vein diameter on ultrasound scan of ≥13 mm, advanced Child–Pugh class, low prothrombin activity and the presence of telangiectasias. Differences in the populations examined (i.e. the
Several diagnostic indexes based on panels of blood markers of fibrosis have been recently proposed: they are non-invasive and suitable for repeated testing, thus allowing to monitor the evolution of liver disease. One study in particular [42] addressed the issue of identifying patients with large varices by means of the Fibrotest, which is a combination of several blood markers. In 99 patients with cirrhosis, the ability of the Fibrotest to detect large varices was compared with that of platelet count and Child–Pugh score. The Fibrotest performed better than the other two tests, with an AUROC of 0.77. However, when the likelihood ratios (LR) were calculated for the different thresholds of the Fibrotest, they fell short of what is required for a “good” test. It appears thus that the Fibrotest is not an adequate means of reliably identifying patients at risk of having large varices in a non-invasive manner.

3.5. Transient elastography

Transient elastography (Fibroscan) is an ultrasound technique that uses pulse-echo ultrasound acquisitions to measure liver stiffness. The use of Fibroscan in patients with liver disease is based on the assumption that fibrosis results in increased stiffness of the liver parenchyma. Fibroscan is attractive because it is non-invasive and measures stiffness in a volume of the liver which is approximately 100 times bigger than liver biopsy, and thus might be less prone than biopsy to sampling error. The ability of the Fibroscan to predict the presence and grade of oesophageal varices in cirrhosis was evaluated in 165 patients [43]. The AUROC for the discrimination between patients with and without medium-large varices was 0.83, with a sensitivity of 90% and a specificity of 60%, with a positive and negative LR values of 2.2 and 0.18, respectively. Again, these values fall short of what is required from a “good” test. In conclusion, transient elastography might be of value for the non-invasive diagnosis of portal hypertension; however, the available data are too limited to allow reaching a conclusion. In addition, the reproducibility of the technique within centres and across centres needs to be further validated.

3.6. Multidetector CT oesophagography

Multidetector computer tomographic oesophagography (MCTE) allows the examination of hollow viscera both in two-dimensional images and in 3D reconstruction. A recent paper [44] has examined the potential of this technique in detecting oesophageal varices and discriminating between large and small varices in 90 patients with cirrhosis. Conventional endoscopy served as the gold standard. The AUROC for the differentiation between small and large varices ranged between 0.931 and 0.958, with sensitivity ranging between 90 and 93.3% and specificity between 81.7 and 96.6%. The ranges of the LR ratios were: LR+: 4.91–27.4; LR−: 0.12–0.07, respectively. The Authors also showed that the patients largely preferred MCTE over un sedated oesophageal gastroduodenoscopy (EGD). However, MCTE requires the insufflation of an average of 1300 mL of air into the oesophagus via a catheter passed through the mouth, and one wonders where patients preference would lie if MCTE was compared with sedated EGD.
Nevertheless, if the data from this study are confirmed, multidetector CT oesophagography might prove to be a suitable tool for the diagnosis of high risk varices.

3.7. Video capsule endoscopy

Video capsule endoscopy, originally developed for the study of the small bowel has become suitable for the oesophagus with the development of a video capsule specifically designed to image this organ. Three pilot studies [45–47] carried out with this capsule showed a very good degree of correlation between the capsule and standard EGD in the detection of varices. A large international multicentre trial has been recently presented [48], including 288 patients with portal hypertension. Using conventional EGD as the gold standard, capsule endoscopy had a sensitivity of 84% and a specificity of 88% for the detection of varices. The LR ratios were: LR+: 7.0, LR−: 0.18. For the discrimination between medium-large varices and small-no varices the corresponding figures were: sensitivity 78%, specificity 96%; LR+: 19.5; LR−: 0.2. A questionnaire evaluating pre-test patients’ perception and post-test patients satisfaction showed that the capsule was preferred over EGD. These data suggest that capsule endoscopy might become a suitable alternative to EGD for diagnosing and grading oesophageal varices, especially in patients unable or unwilling to undergo conventional endoscopy.

4. Conclusions

The measurement of the hepatic vein pressure gradient is the most reliable method for the estimation of portal pressure and of the risk of variceal development. However, HVPG measurement is not widely available, and therefore, upper GI endoscopy is usually used to evaluate the presence and size, and to monitor the evolution of oesophageal varices with time. Endoscopy is appropriate, since the size of varices is clearly related to the risk of bleeding. By endoscopy, a good degree of interobserver agreement for the assessment of variceal size can be achieved, and other potentially bleeding lesions related to portal hypertension, such as portal hypertensive gastropathy and gastric antral vascular ectasia can be diagnosed.

In recent years a wealth of new methods have been proposed as alternatives to conventional EGD for the non-invasive or minimally invasive diagnosis of oesophageal varices. Three of these methods (the platelet count/spleen diameter ratio, Fibrotest and Fibroscan) are truly non-invasive. Of these, the former is promising and needs a proper validation, Fibrotest appears to be insufficiently precise, while Fibroscan needs further evaluation. Multidetector CT oesophagography and capsule endoscopy are not entirely “non-invasive”, since the first requires air insufflation into the oesophagus via an orally passed tube, and the latter requires swallowing the capsule. Multidetector CT oesophagography is promising, but needs further evaluation; capsule endoscopy is safe and reliable and might be proposed as an alternative to EGD in patients unable or unwilling to undergo EGD.

Whether capsule endoscopy, MCTE or any other non-invasive method will ultimately replace conventional endoscopy is, at present, a matter of speculation.

Practice points
• All cirrhotic patients should undergo upper GI endoscopy at the time of diagnosis of cirrhosis.
• Patients with compensated disease and without varices at screening endoscopy should undergo surveillance endoscopy at 3 years intervals.
• Patients with small varices at screening endoscopy should undergo surveillance endoscopy at 1–2 years intervals; the interval should be 1 year for patients with hepatic decompensation, with or without varices.
• All patients with medium-large varices should be treated to prevent the first variceal haemorrhage.

Research agenda
• The value of transient elastography for the non invasive diagnosis of the presence of esophageal varices should be further investigated,
• MCTE needs to be validated in independent patient series,
• The performance characteristics of capsule endoscopy for diagnosing and grading esophageal varices need to be assessed in large scale studies.

Conflict of interest statement
Roberto de Franchis is a consultant for Given Imaging, Yoqneam, Israel.

References


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