When and How to Perform Surveillance

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Introduction

The distinction between medical screening and surveillance was comprehensively described in 1968 by Wilson and Jungner. Screening refers to the cross-sectional collection of data from a population at risk of disease resulting in separation of high- and low-risk groups. Alternatively, surveillance conveys the idea of a long-term process where screening examinations are repeated at intervals for early disease detection in individuals or a population [1]. In the context of chronic liver diseases, surveillance for the complications of portal hypertension and hepatocellular carcinoma has become a tenet in the model of care for those with an established diagnosis of cirrhosis.

The onset of clinically significant portal hypertension (CSPH), as defined by a hepatic venous pressure gradient (HVPG) of greater than or equal to 10 mmHg, is a critical event in the clinical course of chronic liver disease as it heralds the development of oesophageal varices and the potential for clinical decompensation. Gastro-oesophageal varices develop at a rate of approximately 7 % per year, with a 1-year bleeding risk of 12 % [2]. Upper gastrointestinal endoscopy (UGIE) has traditionally been the mainstay of diagnostic, surveillance and therapeutic algorithms for oesophageal varices, while HVPG remains the gold standard in assessment for CSPH. Both have the disadvantages of being invasive, costly and in the case of HVPG, available only in specialised centres.

Since Baveno V, there have been a number of developments in the evaluation of non-invasive markers of CSPH; however, these are yet to find their place in consensus guidelines. Current algorithms have many unresolved issues, particularly

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agreement on surveillance intervals, consensus on endoscopic criteria, the economic impact of surveillance and whether currently available non-invasive tests can reduce unnecessary procedures. This chapter aims to "fill the gap" between the preceding Baveno consensus meeting by summarising the literature to date.

Is Surveillance Needed?

The benefits of endoscopic surveillance have translated to improved clinical outcomes with a decline in both the mortality and incidence of variceal haemorrhage in population-based studies. A recent national database analysis of patients who presented to acute care hospitals in the USA with upper gastrointestinal bleeding from 1989 to 2009 demonstrated a reduction in the annual incidence of variceal haemorrhage from 2.9 cases to 1.3 cases per 100,000 over the study period. In-hospital mortality decreased from 10.7 to 5.6 % during this time [3]. A decline in mortality has also been demonstrated in other countries [4, 5]. A previous analysis of US national databases found that the outpatient diagnosis of non-bleeding oesophageal varices had increased from 5.5 to 6.6 per 100,000 from 1997 to 2003, respectively [6]. This increase in detection and reduction in overall mortality rates cannot be solely explained by improvements in the acute management and secondary prophylaxis of variceal haemorrhage, indicating that screening, surveillance and prophylaxis algorithms are likely contributors.

Despite the improvements in short-term outcomes, the mortality rate associated with variceal haemorrhage is still unacceptably high and particularly so when considering longer-term survival after the bleeding event. Mortality at 6 weeks is estimated at 10–20 %, while 1-year mortality is estimated at 50–60 % [2, 7–9]. Optimising preventative and surveillance strategies is therefore of paramount importance if these outcomes are to be improved.

However, the economic burden of these interventions is significant, with one Markov model estimating a total cost of $37,300 (US dollars in the year 2000) per patient for an endoscopic surveillance strategy [10]. Further modelling studies have had conflicting conclusions regarding the most cost-effective strategy for prevention, with universal beta-blocker prophylaxis without endoscopy being suggested in certain simulated models [10–14]. The idea of universal beta-blocker prophylaxis has been controversial in the real-world setting for a variety of reasons, and thus endoscopic surveillance is still recommended in consensus guidelines [15–17].

The issue of financial costs associated with endoscopy may be addressed through better risk-stratification of patients who are at risk of progression of liver disease, thereby limiting the number of patients entering into surveillance programmes. The potential for currently available non-invasive tests of CSPH to function in this role is discussed in detail below. Additionally, current surveillance strategies have more to improve upon, particularly regarding the standardisation of endoscopic criteria, surveillance intervals and whether surveillance can be withdrawn.

Available Tools for Surveillance

Hepatic Venous Pressure Gradient

HVPG measurement has been the reference standard for the diagnosis and prognosis of patients with CSPH. However, it has not been widely adopted outside specialised centres due to its invasive nature, cost and the technical expertise required to perform the procedure. HVPG measurement is safe, with a minor complication rate reported between 0 and 1 % and a negligible risk of major complications [18, 19]. In cost-effectiveness models, HVPG appears to be more expensive than endoscopic screening strategies [20, 21]. For these reasons, HVPG does not have a role in surveillance directly but should be used as a reference in validating other non-invasive modalities of detecting CSPH.

Upper Gastrointestinal Endoscopy (UGIE)

UGIE continues to be the ideal screening and surveillance tool as it is widely available and the risk of variceal haemorrhage can be estimated by endoscopically assessable criteria. Specifically, bleeding risk has been correlated with the presence of high-risk endoscopic stigmata such as red signs and variceal size [22, 23]. Furthermore, endoscopic assessment also provides information regarding other causes of portal hypertension-associated bleeding such as portal hypertensive gastropathy, gastric or duodenal varices and gastric antral vascular ectasia. Primary prophylaxis with endoscopic band ligation can also be administered during the diagnostic procedure. However, a universal standard for the endoscopic classification of oesophageal varices is yet to be adopted. Currently, two major classification systems are commonly used: the two-stage Italian Liver Cirrhosis Project [24] and the three-stage Japanese Research Society of Portal Hypertension [25]. Both classification systems rely on subjective criteria, which carry an inherent risk of interobserver variability. Endoscopic assessment has a number of other disadvantages, including being invasive and as aforementioned, expensive. Furthermore, certain patient groups may never develop high-risk endoscopic features despite regular surveillance, which confers an unnecessary burden on patients and endoscopy services.

Wireless Capsule Endoscopy

Wireless capsule endoscopy (WCE) has recently been investigated as a screening and surveillance tool, but lacks the diagnostic capability to be used as a first-line investigation. A Cochrane review with a pooled study population of 936 from 15 studies, including patients with portal vein thrombosis, found that both the sensitivity and specificity of WCE for the detection of varices were approximately 84 % [26]. A more recent prospective multicentre trial yielded sensitivities of 76 % and

64 %, to diagnose and stage oesophageal varices, respectively. The specificity of diagnosis and staging were reported as 91 % and 93 %, respectively [27]. Thus, WCE could be used where UGIE is contraindicated or not possible but lacks the sensitivity to be used routinely in this setting.

Conventional Imaging

Conventional imaging modalities including computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound scanning (USS) also do not have the accuracy to be used as primary screening tools for the presence of CSPH and oesophageal varices. Splenomegaly can be easily identified as a marker of CSPH using imaging modalities, but is a non-specific sign. Conversely, the finding of abdominal portosystemic collaterals on cross-sectional imaging or USS lacks sensitivity, but has a specificity approaching 100 % [28, 29]. USS has been proposed to have the potential to avoid screening endoscopy for varices in compensated cirrhosis; however the data are conflicting [30–32]. CT scanning is reliable in detecting large oesophageal varices with a sensitivity of 84–100 % and specificity of 90–100 % and has been suggested to be more cost-effective than endoscopy. Alternatively, the sensitivity of diagnosing small varices is lower and with moderate interobserver variability [33]. Other modifications to standard imaging techniques that have been recently investigated to predict oesophageal varices are the presence of Gamna-Gandy bodies on splenic MRI [34] and the use of effervescent powder to enhance multi-detector CT scanning [35]; however, these require further study and are unlikely to be used as stand-alone surveillance tools.

Liver Stiffness Measurement

Liver stiffness measurement techniques such as transient elastography (TE), acoustic resonance force impulse imaging (ARFI), real-time shear wave elastography (SWE) or magnetic resonance elastography (MRE) have all been shown to correlate with HVPG with varying accuracy [36–40]. Transient elastography, as measured by FibroScan® (Echosens, Paris, France), is the most widely studied and adopted modality in clinical practice for the non-invasive detection of liver fibrosis. However, the correlation between liver stiffness measurements and portal pressure is less robust once HVPG exceeds 10–12 mmHg. This results in poor prediction of the development and stratification of oesophageal varices and CSPH [36, 41, 42]. Furthermore, interobserver variability has been demonstrated to occur when TE is used as a screening tool for oesophageal varices [43]. As a result, liver stiffness alone is not suitable for surveillance strategies, but has been shown to be more effective in combination algorithms, which will be discussed in detail below.

Spleen Stiffness Measurement

Since Baveno V, there has been a concerted effort to investigate the spleen as a marker of CSPH. Spleen stiffness (SS) measurement with TE was initially shown to be superior to liver stiffness measurement when correlated with HVPG in 100 patients with hepatitis C cirrhosis ($R^2 = 0.78$ and 0.70, respectively) [41]. Measurement of SS with ARFI to determine the presence of oesophageal varices has also been investigated and has a sensitivity of up to 98.5 %, but has a suboptimal specificity of 60.1 % [44]. A subsequent meta-analysis of 12 studies measuring SS using TE, ARFI, real-time tissue elastography or virtual touch tissue quantification found lower sensitivity and higher specificity in the detection of varices at 78 % and 76 %, respectively. Nine studies were included in the meta-analysis for clinically significant varices, which yielded 81 % sensitivity and 66 % specificity [45]. More recently, there has been a suggestion that SWE may have a higher technical success rate and diagnostic accuracy than TE in predicting CSPH with a sensitivity and specificity of 81 % and 88 %, respectively [40]. MRE has been used to measure SS and correlated with HVPG as well as the presence of varices in a cohort of 36 patients but requires further study [39]. The overall diagnostic capability of SS as a single modality is still insufficient to be an adequate surveillance tool.

Combined Algorithms

Varying combinations of non-invasive markers for the detection of CSPH have been developed in an effort to improve accuracy. The platelet count/spleen diameter ratio (PSR) is determined by dividing the platelet count by the maximum bipolar splenic diameter on conventional ultrasound. A meta-analysis of 20 studies found the sensitivity and specificity for detecting oesophageal varices were 92 % and 87 %, respectively; however, there was statistically significant heterogeneity across studies indicating that further prospective evaluation is required [46]. The LSPS index (liver stiffness platelet spleen index = LS × spleen diameter/platelet count) showed promising results in the detection of oesophageal varices with an AUROC (area under the receiver operating characteristic curve) of 0.954 in 280 patients with hepatitis B cirrhosis. However, two cut-off values were established to delineate those who may avoid endoscopy (LSPS < 3.5) and those who should be considered for prophylactic intervention (LSPS > 5.5), which results in ambiguity for those who fall between these values [47]. Additional parameters were added to the LSPS in a prospective cohort of 117 compensated cirrhotics, resulting in the development of the PH (portal hypertension) risk score and VRS (variceal risk score), which resulted in AUROCs of 0.935 and 0.909 for the detection of CSPH and varices, respectively [48]. SS has also been combined with LS and most recently Lok Score plus LS, which all have resulted in similar data [45, 49]. Finally, SS and the Model for End-Stage Liver Disease (MELD) score have been combined to predict clinical decompensation with compelling results that are similar to the predictive ability of HVPG [50].

Combined algorithms have resulted in improved diagnostic accuracy, but still require further validation before widespread use can be recommended for surveillance.

Others

Other emerging non-invasive tools to detect CSPH that have been described are indocyanine green (ICG) clearance, von Willebrand factor antigen and CT esophagography. The ICG 15-min retention (ICG-r15) parameter demonstrated sensitivity and specificity of 97.8 % and 90 %, respectively, for the detection of oesophageal varices in 96 compensated cirrhotic patients using the cut-off values of <10 % (rule out) or >22.9 % [51]. A von Willebrand factor antigen cut-off of >241 % has been correlated with HVPG ($r = 0.69$) and clinical decompensation using a second cut-off of >315 % [52]. Dedicated multi-detector CT oesophagography using air insufflation has been described in a study of 90 patients and differentiated low- and high-risk oesophageal varices with an AUROC 0.931–0.958, depending on the radiologist [53]. Needless to say, these emerging modalities will need ongoing evaluation to determine their clinical utility.

Current Surveillance Algorithms

The majority of international variceal surveillance strategies are largely based on the consensus reached at the Baveno meetings. Most guidelines advise annual surveillance for patients with decompensated cirrhosis and between 2 and 3 yearly for those with compensated disease. The established threshold for initiating primary prophylaxis with non-selective beta-blockade or band ligation is the presence of large varices or high-risk endoscopic stigmata. Adequate beta-blockade should ameliorate the need for ongoing surveillance, while endoscopic follow-up at 6–12 monthly intervals has been suggested once a band ligation course has been completed [15–17].

A number of issues exist with these guidelines: the reliance on subjective endoscopic criteria, the cost of endoscopic surveillance, the lack of consensus on surveillance intervals and the lack of provision for gastric or ectopic varices. Current guidelines risk "over-surveillance" of those with compensated liver disease that are at low probability of progression. Moreover, surveillance strategies have omitted the impact of the persistence, or the removal, of the cause of liver injury. For example, viral eradication in chronic hepatitis C infection has been associated with a reduction in HVPG and the development of varices [54–56]. Similarly, abstinence in alcoholic liver disease or directed weight loss in non-alcoholic fatty liver disease are factors that are more likely to reduce the progression of portal hypertension. Conversely, the removal of the aetiological factor does not infallibly halt the clinical trajectory, especially in decompensated disease. However, stratifying patients who are at a lower risk of disease progression once their aetiological factor is

controlled may be another component in reducing the burden of endoscopic variceal surveillance.

Non-invasive markers have the potential to fill the void and address these issues pertaining to surveillance for both CSPH and varices. Additionally, the assessment of response and adequacy of non-selective beta-blockade is another potential application. However, as discussed, a more extensive evidence base is required before these tools can be adopted into consensus guidelines.

Conclusions

Surveillance for the development of both CSPH and oesophageal varices is a necessary intervention that has led to improvements in clinical outcomes. Despite the many advances in the 5 years since the previous Baveno meeting, the ideal non-invasive portal venous "manometer" that can be used in surveillance strategies is regrettably yet to be found. Combination algorithms involving spleen stiffness hold the most promise and required further validation. In the interim, however, there is still much to be done. The endoscopic classification of varices should be simplified into a single system, minimising interobserver and intraobserver variability. Further study is needed to investigate the impact of aetiologically specific treatments on the natural history of different chronic liver diseases, enabling better risk stratification. Emerging tools, such as ICG clearance, require ongoing development and evaluation. Cost-effectiveness models should be encouraged to assess the effect of implementation of non-invasive surveillance. Surveillance strategies for gastric and ectopic varices also need to be developed. The ideal surveillance algorithm should involve non-invasive markers that are widely available, easily reproducible, economically viable, have excellent diagnostic capability and that provide objective data. The momentum to achieve this is increasing and will only be aided by international collaboration.

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