REVIEW

Status of, and strategies for improving, adherence to HCC screening and surveillance

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Abstract: Hepatocellular carcinoma (HCC) represents the second leading cause of cancer deaths worldwide and the main cause of death in patients with cirrhosis. Secondary prevention of HCC can be accomplished through the serial application of screening tests (ultrasound with or without alpha-fetoprotein) to detect the presence of subclinical lesions amenable to potentially curative treatment, such as surgery and ablation. The efficacy of HCC screening is accepted by hepatologists in terms of decline in cancer-specific mortality, but its translation into clinical practice is less than ideal. The effectiveness of HCC screening is hampered by several factors: failure to identify at-risk patients, failure to access care and failure to detect HCC. For each of these steps, possible improvements are discussed in order to face the changing etiology of cirrhosis and expand the screening of at-risk populations by including selected nonalcoholic fatty liver disease patients.

Keywords: cirrhosis, hepatocellular carcinoma, ultrasound, alpha-fetoprotein, screening

Introduction

Hepatocellular carcinoma (HCC) represents a leading cause of cancer mortality, being the 5th most common cancer in men and representing the second leading cause of cancer death worldwide.[1,2] HCC incidence in the United States and Europe has doubled over the past two decades, and HCC is the main cause of death in patients with cirrhosis.[3]

Surveillance represents a typical tool for secondary prevention of cancer and entails the serial application of screening tests to detect the presence of HCC among at-risk populations before the neoplasm becomes clinically suspected or evident.

When detected at a symptomatic stage, HCC is almost invariably fatal. By this stage, the cancer is usually large and untreatable, with rapid progression and an interval from diagnosis to death of 3–6 months.[4] This pattern characterized the large majority of patients in the era before the development of ultrasound (US) and computed tomography (CT) scan and is still the pattern of presentation where these techniques are either not available or not applied.

However, HCC has a prolonged subclinical growth period[5–8] during which curative treatments are often possible. The principal objective of surveillance is, therefore, the detection of subclinical lesions that might be amenable to potentially curative treatment.[9–11]

Although the efficacy of HCC screening is accepted by hepatologists, its effectiveness, ie, the benefits achieved in real practice and broader populations, is far from ideal. This explains why nonliver scientific societies have not endorsed HCC screening due to the lack of high-quality data. The US Preventive Services Task

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Force has not adopted an HCC practice guideline, the American Cancer Society makes no recommendation on HCC screening[12] and the National Cancer Institute found no evidence that screening decreases mortality from HCC but did find evidence that screening could result in harm.[13]

Another major issue is the low adherence to screening programs: in order to achieve outcome improvements in HCC, at least 34% of individuals within a cirrhosis population must undergo surveillance to capture an early-stage diagnosis rate of at least 42%.[14] In real life, reported HCC surveillance rates in most observational studies in the United States and Europe are far from these values.[15–18]

The latest meta-analysis, including 22 studies from North and South America, Europe and Asia and 19, 511 patients with advanced fibrosis or compensated cirrhosis (Ishak score≥3), was published in 2018.[19] It revealed an overall adherence rate to HCC surveillance of 52% with wide differences in compliance rates between studies: in fact, it is higher in studies from Europe than in studies from the United States and Asia (70%, 42%, 33%, respectively) and in those patients with cirrhosis compared to patients without (52% and 32%, respectively). However, in the multivariate analysis, the study design (retrospective vs prospective) turned out to be the only independent predictor accounting for differences in adherence levels. Indeed, the true real-life adherence rate was of 39% based on estimates from retrospective studies where selection bias of patients was deemed to be less relevant.

Therefore, there is a need to improve quality data on HCC screening and to recognize the levels at which the screening fails in order to introduce corrections.

HCC screening: current status

In recent years, guidelines for HCC screening and surveillance have been issued by major liver disease scientific societies in Europe, the United States and Asia.[9–11] Such endorsement relies on the assumption that HCC surveillance fulfills all the pre requisites that make the screening policy cost-effective, according to WHO recommendations.

First, HCC is a common cancer that is the 5th most common cancer in the world and is the third cause of cancer-related mortality, as estimated by the WHO (globacan. iarc.fr).

Second, the risk of disease in the target population is great enough to justify the costs (Box 1). Cirrhosis is considered the most important risk factor for the development of HCC, and, therefore, cirrhotics of any etiology are the patients who may

Box I Population group at high risk for HCC

Cirrhosis regardless of etiology
Viral*
Alcoholic
NAFLD
Genetic hemochromatosis
Alpha 1 – antitrypsin deficiency
Primary biliary
HBV carriers
Asian males >40 years old
Asian females >50 years old
Family history of HCC
Non cirrhotic: at intermediate (PAGE-B** score 10–17) or high (PAGE-B score ≥18) risk for HCC

Notes: **See the Papatheorodidis et al reference for score information.[105]
Abbreviations: NAFLD, nonalcoholic fatty liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; SVR, sustained viral response.

benefit most from screening surveillance. Conventionally, the risk of developing HCC refers to the incidence rate of the disease per year in the target population. Several studies of cost-efficacy or cost-utility analysis have been carried out in the last 20 years.[20–29] Although these models differed in terms of the inception cohort, input values and assumptions (surveillance techniques and surveillance intervals, the follow-up after identification of HCC, rate of patients undergoing curative treatment and costs), virtually all concluded that surveillance is cost effective and enables a reduction in mortality. All these studies confirmed that the cost efficacy of surveillance is critically dependent on the annual incidence of HCC even though an absolute cut off to institute surveillance was not achieved. Averaging out these studies suggests that surveillance is effective for patients with cirrhosis if the annual incidence of HCC exceeds 1.5–2%. This threshold is currently recommended by the most important international guidelines.[9,10]

An HCC annual incidence equal to or exceeding 1.5–2% characterizes viral cirrhosis worldwide. A significant risk of cancer, although drastically reduced, still persists for both hepatitis B virus (HBV)- and hepatitis C virus (HCV)-related cirrhosis following viral suppression (HBV) or viral clearance (HCV) by direct-acting antivirals (DAA). For these reasons, both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommend maintaining successfully treated patients under surveillance.[9,10]

An elevated risk above the threshold has been reported in cirrhosis due to genetic hemochromatosis irrespective of iron depletion.[30] In patients with primary biliary cholangitis (PBC) at an advanced fibrotic stage (cirrhosis) the risk of HCC is similar to that seen in cirrhotic hepatitis C;[31] hence, these patients also warrant surveillance.

For other types of liver diseases such as autoimmune, Wilson's disease or α-1 antitrypsin deficiency, the risk of HCC is thought to be below the above mentioned threshold, and the guidelines do not recommend surveillance. In these instances, HCC incidence is thought to be increased only if cirrhosis is present. Concerns have been raised about the opportunity to offer regular surveillance to alcoholic cirrhotic patients who stopped drinking. A recent French study,[32] however, showed that the incidence of HCC in alcohol-related cirrhosis is sufficient (being the lowest risk estimation in the best scenario of 1.4%) to justify performing HCC screening with regular imaging techniques, mainly US. The main problem is the high rate of noncompliant patients in this at-risk subgroup, given the large proportion of dropouts registered in the study.[33]

Surveillance of non alcoholic fatty liver disease (NAFLD) is still a matter of debate. The most recent epidemiological data[34] provided two kinds of evidence: 1) although the risk of HCC is higher in NAFLD patients than that observed in the general clinical population without major liver disease risk factors, the absolute risk of HCC is too low to recommend universal HCC surveillance in the total NAFLD population; 2) cirrhosis is the major risk factor for HCC development in NAFLD patients, given that the risk of HCC in this subset of patients reached or exceeded the cut offs (0.8–2.3% per year) beyond which HCC surveillance becomes cost-effective.

In the NAFLD context, however, solid prospective information on the real cancer risk is still missing, and the precise indication to begin surveillance still remains unsettled.[35] This conclusion also takes into account the notion that the accepted tool for screening (ie, US) is expected to under diagnose HCC at an early stage owing to the difficult assessment of severe fatty liver and/or obese patients. Moreover, first-line curative treatments (especially surgery) may be hampered in such a population where most of these patients are obese and carry concurrent cardiovascular diseases. However, it is conceivable that in the near future the population at risk for HCC will be broader due to the large number of NAFLD patients.

In non cirrhotic chronic viral hepatitis, the estimated risk of HCC is variable. In the absence of cost-efficacy modeling, expert opinion indicates that surveillance would be warranted if the annual incidence of HCC is at least 0.2%.[36–38]

In the HBV setting, the guidelines recommend surveillance in male patients aged >60 years, with a family history of HCC and higher levels of HBV replication.[39,40] These patients carry a risk greater than the threshold as compared to the general population. Accordingly, international guidelines suggest that in non cirrhotic HBV patients, regular 6-month surveillance may not begin at baseline, but may be initiated whenever the abovementioned risk factors develop. This implies that these patients should undergo regular re assessment for entry into a surveillance program.

In the HCV setting, the incidence of HCC in F3 patients is too low to warrant regular surveillance.[41] However, the exact staging of fibrosis is a challenge even at histological examination since fibrosis is a dynamic process which can either progress or regress over time. These patients should be regularly monitored with Fibroscan even if a cut off threshold to begin surveillance remains to be defined.

In summary, surveillance should be offered to patients in whom cirrhosis has etiology due to viral infection, hemochromatosis, PBC, or alcohol (with ongoing alcohol consumption). In viral cirrhosis, the risk of HCC is not totally eliminated in patients at risk after achieving sustained viral response (SVR) with both PegIFN-based and DAA-based therapies; therefore, surveillance should invariably be carried out. In HBV non cirrhotic patients, surveillance should be carried out only in the presence of additional risk factors, while in non cirrhotic HCV patients standard surveillance is not recommended unless bridging fibrosis is histologically documented. In non cirrhotic viral (HBV and HCV) chronic liver disease, transient elastography has been proposed as a useful tool to stratify the variable risk of HCC.[42,43]

Third, available test procedures are acceptable, safe, relatively inexpensive and offer a good balance between sensitivity (for early HCC detection) and specificity (to reduce false positive-related harm). The above-mentioned professional societies[9–11] agree that US is the cornerstone of HCC screening, due to its widespread availability, low costs, lack of ionizing radiation, repeatability and acceptability by patients. However, limits of US should be considered: operator and US equipment dependency and technical limitations (coarse liver echo-texture, severe steatosis and obesity) explain why early HCC may be

detected only in approximately one-third of patients with cirrhosis by using US alone.[44,45] In order to increase the diagnostic performance of screening, other imaging techniques, such as CT or magnetic resonance imaging (MRI) have been proposed. However, their use in clinical practice is hampered by several limitations including the dangerously high rate of false-positive results, low availability, radiation risk, long duration of scan and, primarily, elevated costs (see the Failure to detect HCC section). Indeed, the AASL and EASL guidelines[9,10] do not recommend the routine use of CT or MRI as they are not considered cost-effective for screening programs.

Whether adding α-fetoprotein (AFP) to US improves screening performance is a matter of debate. Conflicting results are reported in the literature, and the variable suggestions from liver disease societies across the world reflect such uncertainty: EASL guidelines[9] do not recommend AFP in addition to US given its insufficient sensitivity and specificity; in contrast, AASLD[10] states that is not possible to establish whether US should be coupled with AFP for HCC surveillance. A recent meta-analysis showed that, in studies comparing sensitivity for HCC with or without AFP, the pooled sensitivity of US alone was poor (63%) for early HCC and even worse in the subgroup of prospective studies (42%).[46] By adding AFP measurement, a significant gain in pooled sensitivity (63%) was achieved in the subgroup of early HCCs, and this advantage of AFP was maintained in the subgroups of prospective studies (pooled sensitivity of 60%).

On the other hand, adopting AFP as a single tool for screening cannot be recommended since it is both a tumor marker and a regeneration marker. In chronic liver disease, elevated AFP serum levels may indeed simply reflect inflammation and subsequent regeneration.

Fourth, curative treatments are available to patients in whom HCC is discovered at an early stage owing to regular surveillance. Potentially curative treatments include orthotopic liver transplantation (OLT), resection and ablation and offer survival rates at 5 years ranging from 50% to 70%.[9–11] In population-based series and in large prospective cohorts worldwide, the rate of patients receiving curative treatments is steadily increasing, thanks to the expansion of surveillance programs.[16,47–49] Conversely, to avoid futility, this pre requisite would also imply that patients with either decompensated cirrhosis or severe co morbidities would not benefit from surveillance, and therefore they should not be offered any.[50]

HCC screening: limits

Although the efficacy of screening for HCC detection at an early stage has been affirmed by several studies and constitutes the basis of guidelines on HCC surveillance delivered by specialist societies, its translation into clinical practice is less than ideal.

This poor effectiveness might represent one of the reasons why HCC mortality has increased over the last two decades.[51]

A recent study by Moon et al[52] failed to demonstrate a relationship between HCC screening and the decline in cancer-specific mortality, ie, one of the main goals of a screening program. These authors applied a matched case–control study design by selecting patients from the largest integrated health care system in the United States (Veterans Affairs): cirrhotic patients with fatal cancer (cases) were compared to those who did not die from it (controls), on the assumption that a lower adherence to screening programs in the cases should be expected. This analysis did not provide any evidence for a protective effect of specific mortality. The authors ascribed these findings to the low diagnostic performance of diagnostic tests which allow the identification only of slow-growing tumors (length bias) and/or the inadequacy of current treatments.

These results seem to reinforce those concerns raised regarding HCC surveillance which has been adopted in the United States in the absence of sufficient data to demonstrate its efficacy.[53,54]

In addition, potential screening-related undesired effects have recently been highlighted: in a retrospective cohort study 27.5% of patients under surveillance experienced physical harm, defined as CT or MRI scans or biopsies performed for false-positive or indeterminate surveillance findings.[55] Similarly, Konerman et al[56] found that 17% of 999 patients under a well-structured surveillance program had suspicious nodules without a final HCC diagnosis and experienced severe harm (eg, CT/MRI tests ≥4 or a liver biopsy). Although these two studies highlighted the potential harm mainly as multiple imaging evaluation, it should be pointed out that a detection rate of early HCC as high as 70–75%, allowing curative treatments, was reported in both papers. To date, albeit data on harm (including the not yet explored psychological and financial aspects) related to HCC screening are scanty, it seems that advantages of surveillance programs outweigh potential harm.

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Indeed, benefits of well-structured surveillance programs have recently been confirmed by a prospective study[57]: in a large cohort of patients, the adherence to a HCC surveillance program after correction for lead-time bias played a pivotal role in the outcome of screened patients. Indeed, a timeframe <7 months was associated with a median survival twice as long as the survival observed in non compliant patients.

HCC screening: possible improvements

These conflicting results should prompt investigators and health care authorities to evaluate the topic of HCC screening limits and explore possible improvements at various levels.

Failure to identify at-risk patients

It is well known that up to 40% of patients present with HCC without having previously recognized liver disease and/or cirrhosis.[58,59] In addition, the failure to recognize cirrhosis is strongly associated with advanced HCC stage at diagnosis and may be related to patient evaluation by non specialist care providers.[60]

In order to improve the recognition of those subjects at risk, a number of measures could be implemented:

1. Increasing the use of electronic medical records to facilitate the recognition of patients with positive viral markers and the assessment of non invasive laboratory markers of liver disease and/or fibrosis such as the AST to platelet ratio index (APRI)[58,61–63] in order to trigger the cascade of instrumental and/ laboratory screening modalities (see below) in a larger population of patients;

2. Reduce under-recognition of HCV-positive cases: Centers for Disease Control and Prevention and the US Public Health Task Force recommended one-time testing for anti-HCV for people born between the years 1945 and 1965, a period of time when the highest incidence of HCV was found.[64,65] Recently, in France and the United States, universal screening for HCV has been proposed based on the assumption that it is cost-effective in terms of increased life expectancy and quality-adjusted life years, provided that early therapy is started with direct-acting Antivirals (DAA) regardless of the stage of fibrosis.[66–68]

3. Inclusion of other subsets of patients at risk: in NAFDL/non-alcoholic steatohepatitis (NASH)

patients (especially those with obesity and/or diabetes) HCC may occur in the absence of cirrhosis[69] in approximately 15% of cases, and is often recognized at an advanced stage when survival times are shorter.[70] These poor outcomes do not result from a greater biological aggressiveness of NAFLD-related HCC but from delayed referral to tertiary care (or specialist) centers.[71] What kind of NAFLD patients at risk for HCC should undergo regular surveillance is likely to be the huge health care question over the next few years. This will occur due to a decline in HCV infection as a consequence of effective eradicative therapy and the reduction of baby boomers, who are the major reservoir of HCV. On the basis of the most recent epidemiological data,[34] it seems logical to assume that at least NAFLD-related cirrhosis warrants surveillance. Alcoholic etiology of cirrhosis should be reconsidered as well in the light of recent epidemiological evidence that annual HCC incidence in this specific population is well above the threshold which makes screening programs cost-effective.[32]

4. Education of primary care providers (PCPs): it is maintained that PCPs under-recognize chronic liver disease and cirrhosis and may have misconceptions about how best to perform surveillance (timing and/or type of screening tools) and report several barriers to implementation (eg, not being up-to-date with current guidelines, lack of reminder systems for HCC surveillance).[72] It is not by chance that the adherence rate improves dramatically if patients seek hepatogastroenterologic visits.[59,72,73] Therefore, efforts should be undertaken to educate PCPs regarding at-risk populations with chronic liver disease of any etiology, the correct use of screening tools and the benefit of HCC surveillance. Since PCPs are one of the main steps toward improving screening, automated reminders could also be a mean to increase their awareness of HCC screening.[74] A pilot study in Italy[75] showed that implementation of a training program targeting PCPs, aimed at improving the identification of cirrhotic patients living in an area with a high prevalence of disease, led to improved HCC patient survival.

Failure to access care

Although patients' adherence is not considered a major barrier to HCC screening, patient non compliance accounted for <10% of cases in which surveillance was

not completed.[73] Difficulty with the scheduling process, costs of surveillance testing and transportation difficulties may prevent access to screening especially in socio economically disadvantaged patients.[76] Conversely, high levels of instruction and income, living in urban areas, and insurance coverage are all associated with more regular and effective surveillance.[15,16,73]

In this context, the type of health care system plays a pivotal role: wherever government health care authorities cover patient expenses and offer more screening tests and shorter screening intervals, a higher compliance to HCC surveillance is expected. This is the case of Japan, one of the few countries which carried out a national screening program.[77] In contrast, in the United States different health care insurance systems exist, which explains, at least in part, the HCC screening adherence rate widely ranging between 12% and 80%.[44,59,78–82] In addition, participation in screening campaigns of cirrhotic patients may be improved by mailed outreach strategies by providing information about HCC risk and the importance of semi annual surveillance, as well as direct patient telephone interviews aimed at encouraging those who did not adhere to surveillance.[83] However, these strategies were not capable of either pushing surveillance rate above 30% in the enrolled population or significantly increasing the detection rate of early-stage HCC compared to standard surveillance modality (ie, HCC surveillance ordered by clinicians during any outpatient visit).

Failure to detect HCC

1. To overcome the above mentioned US limitations, CT- or MRI-based surveillance has been proposed.[84,85] MRI proved the best method of surveillance for early HCC (sensitivity of 83.7%)[85] but high costs, long scan times and low availability prevent the widespread use of MRI as an imaging technique for screening. An abbreviated MRI protocol (AMRI) which comprises two sequences performed approximately 20 mins after the intravenous injection of gadoxetate disodium[86,87] can be performed at a lower cost in a shorter time than a complete examination, thus making it more suitable for routine HCC surveillance. In retrospective studies,[86,88] AMRI has proven superior to US in diagnostic per-patient and per-lesion performance. Another AMRI protocol utilizing only T1-weighted pre contrast and dynamic post contrast images using an extracellular gadolinium contrast agent has recently been proposed.[89] In this retrospective study conducted on 164 consecutive screenings, this AMRI protocol afforded examination time (7–10 mins) even shorter than an

accurate US examination and showed a strong agreement with conventional MRI in categorizing newly detected lesions according to liver imaging reporting data system (LI-RADS). In addition, it is likely that AMRI would prove especially useful in the NAFLD populations where the diagnostic accuracy of US is greatly reduced.

In a recent mathematical model, bi annual contrast-enhanced AMRI showed a higher sensitivity than US and proved affordable when applied to high-risk patients, resulting in improvement of early tumor detection in a cost-effective manner.[90] If these data are confirmed in controlled trials, AMRI could become a cost-effective alternative to conventional MRI for screening in cirrhosis even though scarce availability and costs of MRI remain problems to be solved.

2. AFP performance can be improved by monitoring longitudinal patterns of AFP over time: if the rate of increase of AFP and the degree of fluctuation of all AFP-values recorded within each patient are used rather than the last value of AFP, the accuracy of the test in detecting HCC among patients with hepatitis C and either advanced fibrosis or cirrhosis may increase.[91,92] Several other tumor markers have been reported as good complements to AFP and have been used in clinical diagnosis, including lens culinaris agglutinin reactive AFP (AFP-L3%), des-γ-carboxy prothrombin (DCP), fucosylated biomarkers (such as Golgi protein 73 and AFP), osteopontin, glypican-3, and micro-RNAs.[93–101] Albeit these biomarkers have been evaluated as potential tools for HCC screening in some studies,[94,100,101] so far they have not met the clinical requirements for HCC surveillance. Prospective studies are needed to externally validate their accuracy for early detection of HCC.[102]

Future directions

In the era of precision medicine and limited resources, screening programs have to accomplish the difficult task of personalized surveillance according to the risk of disease since HCC risk is not uniform across all patients with the same clinical conditions such as cirrhosis owing to different etiologies.

Risk scores providing a numerical cut off for the 5- and 10-year risk of developing HCC have been proposed. These scores have been developed for hepatitis B and for hepatitis C separately, as well as for cirrhosis (of any etiology). Several risk scores have been developed for hepatitis B.[40,103–105] Among them the Risk Estimation for Hepatocellular Carcinoma in chronic hepatitis B (REACH-B)[40] and the Platelets, Age, Gender in chronic hepatitis B (PAGE-B)[105] and their recent

modifications[106,107] are the most popular. The first has been developed and validated in Asian patients without cirrhosis using clinical parameters such as sex, age, serum alanine aminotransferase (ALT) concentration, HBeAg status plus HBV-DNA status.[40] Accordingly, atminimum score values (0–6), the 10-year risk of having HCC is negligible (<1%), while at the value of 16 the 3-, 5-, 10-yeas risk is 15%, 32%, 64%, respectively. Recently, HBV-DNA status has been replaced by liver stiffness (as a measure of liver fibrosis) based on the assumption that HBV clearance can easily be achieved in the era of effective antiviral therapy, therefore leading to overestimation of the incidence of HCC.[106]

PAGE-B score was first developed in Caucasian patients with chronic hepatitis without HCC and treated with first-line oral antivirals for ≥12 months. Based on simple clinical variables (age, gender, and platelets), this score proved useful in the assessment of the 5-year risk of HCC: a high PAGE-B score (≥18) should prompt continuous and careful surveillance in that the 5-year cumulative risk of HCC is 17% in this subgroup of patients. Recently, a modified PAGE-B score by adding serum albumin levels has been validated in Asian populations.[107]

A risk score for HCV patients has been developed using the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) cohort.[41]This model includes age, alkaline phosphatase (ALP), black race, albumin, gastroesophageal varices and platelets. The calculation is complex, and the score has not been validated so far. For these reasons, its use is not recommended.

To further refine HCC prediction, the combination of serum concentrations of three biomarkers (AFP, AFP-L3% and DCP), with patient sex and age has been proposed as a diagnostic model (GALAD),[108] and preliminary clinical results seem to support a widespread use in clinical practice.[109] Improvement of the GALAD score has recently been reported by adding US results (presence of a solid lesion on surveillance).[110] Another risk score, the Doylestown algorithm, incorporates biomarkers (AFP and fucosylated biomarkers) and relevant clinical variables (age, gender and ALT) with ALP.[111] Although promising, these clinical scores have not yet been widely approved for HCC screening.

To supplement these imperfect clinical scores, new molecular biomarkers have been explored.[112,113] Several germline single-nucleotide polymorphisms in epidermal growth factor and myeloperoxidase genes have been associated with elevated HCC risk.[114,115] Similarly, a prognostic 186-gene signature has been identified and validated as an HCC risk predictor in patients with chronic liver disease with different etiologies.[116,117]

Once again, all these molecular biomarkers are far from being in widespread use in clinical practice.

In summary, although there is evidence of the benefits of HCC surveillance in terms of improved specific cancer mortality, improving modality of, and tools for, screening is necessary in order to cope with future scenarios where the etiology of cirrhosis is changing and the population at risk is becoming larger.

Disclosure

The authors certify that they have no affiliations with, or involvement in, any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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