GFM Gastroenterology and Functional Medicine

REVIEW

Hepatocellular carcinoma surveillance in cirrhotic patients: Beyond guidelines

Mohammed Omar Khalifa Elsayed*, Mohamed Gamal Talkhan

Department of Gastroenterology, South Tees Hospitals NHS Foundation Trust, North Yorkshire, TS4 3BW, UK

ABSTRACT

Hepatocellular carcinoma (HCC) surveillance of individuals with cirrhosis or other conditions that confer a high risk of HCC development is essential for early detection and improved overall survival. HCC surveillance is a complex process, with failure at any step in the process contributing to a gap between its efficacy and effectiveness. Biannual ultrasonography with or without alpha-fetoprotein is widely recommended as the standard method for HCC surveillance, but it has limited sensitivity in early disease and may be inadequate in certain individuals. HCC surveillance implementation can be affected by either provider or patient-related factors. Proper screening for HCC is a continuum of services, extending from initial patient screening, diagnosis, treatment and ultimately surveillance. As one may expect, there are numerous chances for failure in the delivery of cancer screening care. When considering the risk versus benefits of HCC surveillance, we must consider the possible harm to the patient. Such concerns include false-positive testing resulting in unnecessary and risk-associated procedures such as liver biopsy, overdiagnosis of HCC among patients with cirrhosis, as well as false-negative investigations resulting in delayed diagnosis of HCC. The development of tools to enhance our ability in optimizing available surveillance is likely to improve the prognosis of patients with HCC. This review article will provide a comprehensive overview of the rationale behind current HCC surveillance guidelines, their utilisation, effectiveness, limitations, benefits, and harms as well as methods to improve the outcome of HCC surveillance.

Key words: hepatocellular carcinoma, surveillance, cirrhosis, guidelines

INTRODUCTION

Liver cancer is among the leading causes of global cancer incidence and is the second-most common cause of cancer mortality.[1,2] Hepatocellular carcinoma (HCC) is the most dominant form of primary cancer, accounting for roughly 80% of all cases of liver cancer and occurs in patients with chronic liver diseases of various causes.[3]

In 2020, more than 900,000 cases of liver cancer were diagnosed globally, with more than 830,000 liver cancer—related deaths, underscoring the high mortality index of this cancer.[4] HCC accounts for 75%–85% of primary liver cancers. The global incidence of HCC has increased by more than 75% in the last 30 years, especially in Western countries,[5–7] and is expected to continue to grow in the near future.

Although the 5-year survival for HCC has improved over time, it remains less than 20% among all patients—related to many patients presenting with advanced tumor burden and/or poor liver function. Patients who present with early-stage HCC are amenable to curative therapies such as surgical resection or liver transplantation and can achieve 5-year survival exceeding 70%. In contrast, patients presenting with more advanced tumor burden are only amenable to

***Corresponding Author:**
Mohammed Omar Khalifa Elsayed, Department of Gastroenterology, South Tees Hospitals NHS Foundation Trust, North Yorkshire, TS4 3BW, UK. E-mail: mohammed.omar@nhs.net. https://orcid.org/0000-0003-2898-9781

Received: 11 August 2023; Revised: 25 September 2023; Accepted: 26 September 2023; Published: 24 October 2023
https://doi.org/10.54844/gfm.2023.439

palliative therapies and have a median survival of approximately 2 years.[8]

The strong association between early detection and improved survival has been the impetus behind professional society guidelines for HCC surveillance among at-risk individuals, including those with cirrhosis. The American Association for the Study of Liver Disease (AASLD), the European Association for the Study of Liver (EASL) and Asian Pacific Association for the Study of Liver (APASL) recommend HCC surveillance for patients with cirrhosis with liver ultrasound with or without serum alpha-fetoprotein (AFP) test every 6 months.[8–10]

This strategy has been shown to increase early detection and improve survival in a large randomized controlled trial (RCT) in hepatitis B virus (HBV) patients and several cohort studies in patients with cirrhosis.[11,12]

This review article will provide a comprehensive overview of the rationale behind current HCC surveillance guidelines, their utilisation, effectiveness, benefits, and harms as well as methods to improve the outcome of HCC surveillance.

RATIONALE FOR HCC SURVEILLANCE

The stage at cancer diagnosis is the most important factor determining overall survival in patients with HCC.[13] Patients with small, localized tumors are amenable to curative treatments such as resection, ablation, or liver transplantation, and their long-term survival can be excellent.[14] On the other hand, patients with large, multifocal tumors, macrovascular invasion, or extrahepatic metastasis are only amenable to palliative treatments and have significantly poorer survival.[15] Therefore, the cornerstone of a surveillance program for HCC is diagnosis of HCC at early stages in high-risk individuals so that they can receive curative treatments and achieve improved long-term survival, translating into a decrease in liver cancer mortality.[16]

This rationale is backed by clear-cut data, early diagnosis rendering a 5-year survival exceeding 70%, compared to intermediate and advanced stage diagnosis which leads to a dismal, less than 20%, survival.[17] More explicitly, new data has shown that patients diagnosed and treated in the earliest Barcelona Clinic Liver Cancer (BCLC) 0 stage had an 86.2% 5-year survival, with a significant decrease in survival with upstaging 69.0% for BCLC A and 49.9% for BCLC B.[18] These figures dramatically drop when analysing survival for late stage, BCLC C and D HCC, where survival is rarely above 12 months and 3 months, respectively.[19]

RCTs are the best study design to evaluate the effectiveness of medical intervention. However, there has been a paucity of properly conducted, universally generalizable RCTs on the benefits of HCC surveillance. Only two RCTs have been reported, both of which were single-centre studies from China in patients with chronic viral hepatitis.[20,11] While one of the studies showed a significantly reduced mortality rate in the screening group compared to the control group,[11] the other study did not show a difference in mortality.[20]

In 2011, Poustchi *et al.*[21] tested the feasibility of conducting an RCT of HCC surveillance in patients with cirrhosis and concluded that an RCT of HCC surveillance is not feasible, as most patients decline randomization and prefer to receive surveillance when provided with informed consent.

A meta-analysis by Singal *et al.*[12] reported that HCC surveillance was still associated with a significant improvement in survival after adjusting for lead-time bias. No randomized trials have been conducted in populations with other aetiologies, including chronic hepatitis C virus (HCV) or steatohepatitis; thus, controversy remains regarding whether surveillance truly leads to a reduction in mortality in these populations, especially in Western countries where HBV infection is not common.

INDICATIONS FOR HCC SURVEILLANCE

The HCC surveillance recommendations from the American Association for the AASLD,[8] European Association for the EASL,[9] and APASL[10] are summarized in Table 1.

All major guidelines recommend surveillance of high-risk groups. These groups include most patients with cirrhosis but not those with advanced liver failure unless they are on the transplant waiting list. Patients with non-cirrhotic HBV infection and patients with HCV infection and advanced fibrosis are also recommended to have surveillance due to high incidence of HCC in these groups.[8–10]

TARGET POPULATIONS FOR HCC SURVEILLANCE

The target population for HCC surveillance differs between guidelines. The target populations of each guideline are summarised in Table 2.

In all guidelines, patients with cirrhosis of any cause are the target population, except for the Asian Pacific Association for the Study of the Liver (APASL) guideline, in which the targets are limited to cirrhosis

Table 1: Indications for HCC surveillance

AASLD	EASL	APASL
1. All adults with cirrhosis, except for Child-Pugh class C patients ineligible for liver transplant 2. High risk patients with HBV - Asian men age > 40 - Asian women age > 50 - African ancestry - Family history of HCC	1. Cirrhotic patients, Child-Pugh stage A & B 2. Cirrhotic patients, Child-Pugh stage C awaiting LT 3. Non-cirrhotic HBV patients at intermediate or high risk of HCC according to PAGE-B* classes for Caucasians 4. Non-cirrhotic F3 patients based on individual risk assessment	1. All adults with cirrhosis, except for Child-Pugh class C patients ineligible for liver transplant 2. High risk patients with HBV - Asian men age > 40 - Asian women age > 50 - African ancestry age > 20 - Family history of HCC

AGA: In addition to above recommendations, patients with non-alcoholic fatty liver disease with non-invasive markers showing evidence of advanced liver fibrosis or cirrhosis should be considered for HCC screening

Chinese clinical guidelines: All patients with cirrhosis, HBV, and HCV

*PAGE-B (platelet, age, gender, hepatitis B) score is calculated using age (16–29 = 0, 30–39 = 2, 40–49 = 4, 50–59 = 6, 60–69 = 8, ≥ 70 = 10), sex (male = 6, female = 0), and platelet count (≥ 200,000/μL= 0, 100,000–199,999/μL = 1, < 100,000/μL = 2). AASLD: American Association for the Study of the Liver Diseases; APASL: Asian Pacific Association for the Study of the Liver; EASL: European Association for the Study of the Liver; HBV: hepatitis B virus; HCC: hepatocellular carcinoma.

Table 2: Target population for HCC surveillance guidelines of various professional organizations

Organization	Target population
AASLD	Cirrhotic patients, non-cirrhotic HBV carriers with a family history of HCC, non-cirrhotic Africans and African Americans with HBV, non-cirrhotic Asian male HBV carriers past the age of 40 years, non-cirrhotic Asian female HBV carriers past the age of 50 years
EASL	Cirrhotic patients, non-cirrhotic HBV carriers with a family history of HCC, non-cirrhotic HBV carriers with active hepatitis, non-cirrhotic patients with chronic HCV and advanced liver fibrosis (F3)
APASL	Cirrhotic patients with HBV or HCV infection
JSH	Cirrhotic patients, non-cirrhotic patients with chronic HBV infection, non-cirrhotic patients with chronic HCV infection

AASLD: American Association for the Study of Liver Diseases; AFP: alpha-fetoprotein; AFP-L3%: Lens culinaris agglutinin A-reactive fraction of AFP; APASL: Asian Pacific Association for the Study of the Liver; DCP: serum des-carboxy prothrombin; EASL: European Association for the Study of the Liver; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; JSH: Japan Society of Hepatology

with HBV or HCV. HBV patients without cirrhosis are recommended for surveillance in most guidelines, except for the APASL guideline, because of their high risk for HCC.[10] In the Japanese Society of Hepatology (JSH) guideline,[22] patients with cirrhosis and HBV or HCV are further stratified into an extremely high-risk population for HCC.

HCC SURVEILLANCE IN CIRRHOTIC PATIENTS

Most HCC cases are attributable to chronic HBV and/or HCV infection, especially in the setting of advanced fibrosis and established cirrhosis.[23] There is regional variation in the importance of different risk factors for cirrhosis.[24] HBV cirrhosis is more strongly associated with HCC in Asia and Africa compared to Western Europe and America, with 5%–50% developing HCC in Asia and Africa compared to 3%–10% developing HCC in Western Europe and America.[25]

In Japan, around 70% of cases diagnosed with HCC over the last 10 years were HCV antibody (HCV-Ab)-positive.[26] A retrospective epidemiological study from Egypt on 1313 patients, found that HCV Ab was detected in 91.32% of the studied patients.[27] Although only a minority of patients with non-alcoholic fatty liver disease (NAFLD) progress to cirrhosis, NAFLD has become the commonest cause of cirrhosis in western nations.[28]

In Northern England, the number of HCC cases referred to the tertiary centre in Newcastle upon Tyne has increased over tenfold with NAFLD accounting for 35% of cases.[29] Other less common causes of cirrhosis such as primary biliary cholangitis, hemochromatosis, and autoimmune hepatitis, have been recommended for HCC surveillance by APASL guidelines.[10]

HCC SURVEILLANCE IN NON-CIRRHOTIC PATIENTS

Advanced fibrosis without cirrhosis is one of the debatable issues for HCC screening. Because it is difficult to define the transition from advanced fibrosis to cirrhosis, those patients of advanced fibrosis have been recommended for HCC screening by European guidelines.[9] On the other hand, this population has not been considered for screening by American guidelines.[8] While HCC can develop in HCV infected patients in the

absence of cirrhosis, the odds decrease to one fifth when elastography shows a lack of advanced fibrosis (< 10 kPa).[30] Currently, HCC surveillance is not recommended in patients with chronic hepatitis C without cirrhosis.[8]

Patients with chronic HBV represent a unique population who require HCC surveillance outside of the setting of cirrhosis. Table 1 shows the specific recommendations for surveillance in patients with chronic hepatitis B without cirrhosis among different guidelines. High levels of HBV DNA are associated with a higher risk of developing HCC and worse prognosis in those with HCC.[31] It is thought that active HBV viral proliferation promotes carcinogenesis through both direct and indirect mechanisms and therefore antiviral treatment can lower the risk for HCC occurrence in these patients.[32]

The incidence of HCC in patients with non-cirrhotic NAFLD is very low. Hence, no guidelines recommend screening of HCC in patients with NAFLD without cirrhosis.[8–10]

CURRENT TOOLS FOR HCC SURVEILLANCE

All international societies agree that US is the cornerstone of HCC screening, due to its widespread availability, low costs, lack of ionizing radiation, repeatability, and well-tolerability by patients.[8–10]

Liver ultrasonography every 6 months with or without serum AFP level is widely recommended as the standard modality for HCC surveillance as shown in Table 3.[8–10]

There is no universal agreement about adding AFP to ultrasound (US) in HCC screening. EASL guidelines[9] do not recommend AFP in addition to US given its insufficient sensitivity and specificity. AASLD[8] states that is not possible to establish whether US should be coupled with AFP for HCC surveillance. On the other hand, the combination of AFP and B-mode US is endorsed by Eastern countries.[10,22]

In 2018, a meta-analysis[33] comparing sensitivity for HCC with or without AFP, showed that the pooled sensitivity of US alone was poor (63%) for early HCC and even worse in the subgroup of prospective studies (42%). By combining AFP and US, 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%).

Contrast-enhanced ultrasound (CEUS) utilizing microbubble-based contrast materials such as perfluorobutane (Sonazoid) is expected to further increase the efficacy of ultrasound-based HCC surveillance. CEUS improves the assessment of tumor boundaries, tumor vascularity, and tumor characterization compared to B-mode ultrasound[34]. In a prospective, multicentre study of 23 institutions, the average size of HCCs detected by CEUS was significantly smaller than the size of HCCs detected by B-mode ultrasound, suggesting that CEUS is superior to B-mode ultrasound for early detection and the study recommended that CEUS should be considered as first-line screening tool for HCC in patients with liver cirrhosis, especially those with very coarse liver parenchyma[35].

Multiphase, contrast-enhanced, cross-sectional imaging modalities such as computerized tomography (CT) or magnetic resonance imaging (MRI) are not recommended as first-line surveillance methods due to their lower availability, higher cost, exposure to radiation (CT) and contrast material (CT and MRI), and poor patient tolerance (MRI).[36]

A prospective surveillance study at a tertiary care centre compared the HCC detection rate of US and MRI in patients with cirrhosis who are at high risk for HCC. The study concluded that screening using MRI with liver-specific contrast resulted in a higher HCC detection rate and lower false-positive findings compared with US. With MRI screening, most of the cancers detected were at very early stage, which was associated with a high chance of curative treatments and favourable survival of patients.[37]

SURVEILLANCE INTERVAL

Most guidelines recommend ultrasonographic screening every 6 months.[9,10,22] This interval was initially recommended based on tumor doubling time but has been supported by Italian Liver Cancer (ITA.LI.CA) Group who compared semi-annual versus annual surveillance and found that semi-annual surveillance increases the detection rate of very early hepatocellular carcinomas and reduces the number of advanced tumors as compared to the annual program.[38]

A large multicentre randomized controlled trial from France, compared the effectiveness of US surveillance between 3- and 6-month periodicities. The study results showed that US surveillance, performed every 3 months, detected more small focal lesions than US every 6 months, but did not improve detection of small HCC, probably because of limitations in recall procedures. There was no difference in survival between both groups. Most of the patients (> 83%) included in this European study were HCV and alcohol-related liver

Table 3: Recommended HCC surveillance methods

AASLD	EASL	APASL
1. Biannual abdominal ultrasonography with or without AFP 2. CT and MRI may be utilized in select patients with a high likelihood of having an inadequate ultrasound or if ultrasound is attempted but inadequate	1. Biannual abdominal ultrasonography 2. AFP not recommended particularly in patients with active liver inflammation 3. MRI/CT can be used for patients on the waiting list for liver transplant 4. MRI/CT can be used for patients who have had inadequate ultrasonography, but their risk and cost make their use in long-term surveillance highly debatable	1. Biannual abdominal ultrasonography with or without AFP 2. Cut-off value of AFP should be set at 200ng/mL when used in combination with ultrasonography 3. Cut-off value of AFP can be set lower with hepatitis virus suppression or eradication

Chinese clinical guidelines: Biannual abdominal ultrasonography with AFP

AASLD: American Association for the Study of the Liver Diseases; AFP: alpha-fetoprotein; APASL: Asian Pacific Association for the Study of the Liver; CT: computerized tomography; EASL: European Association for the Study of the Liver; HCC: hepatocellular carcinoma; MRI: magnetic resonance imaging.

disease.[39]

CURRENT PROVISION OF HCC SURVEILLANCE

Reports of HCC surveillance in patients with cirrhosis consistently show poor uptake and adherence to the published guidance. The Hepatocellular Carcinoma UK (UK HCC) Study Group conducted a questionnaire survey regarding the provision of ultrasound sonography (USS) for detection of HCC in 156 units from all parts of the UK. The survey showed that provision of surveillance was poor overall. Provision was ad hoc and there were not standardized recall policies for follow-up of abnormal findings. Sixty per cent (60%) of patients presenting to specialist multi-disciplinary team meetings have radiologically incurable disease.

This survey highlighted many barriers to the implementation of 6-monthly USS; difficulty accessing radiology services, cost, doubts over effectiveness, not considered a priority in their hospital. Other reasons cited included: logistical problems, lack of an accurate liver database, time to organise the system, ultrasound capacity, poor patient adherence, and pressure from other sources.[40]

In a large, real-life cohort of patients with chronic hepatitis C cirrhosis, only 24% underwent HCC surveillance every 6 months and only 44% had surveillance at least every 12 months. The study showed that adherence to HCC surveillance guidelines has remained poor over time. In this large cohort study of patients with CHC cirrhosis (considered high-risk for HCC), adherence to the AASLD and EASL surveillance guidelines was seen in less than half of the patients. Adherence was poor over the course of the fifteen years of the study, with no significant improvement over time, not even after the 2011 AASLD guideline. The study recommended that more work is necessary to determine effective methods of improving knowledge of the guidelines and to overcome barriers to care.[41]

SURVEILLANCE UTILIZATION

The effectiveness of HCC surveillance at improving outcomes in high-risk patients relies not only on the accuracy of surveillance tests but also on the real-life implementation of surveillance. Both provider and patient-related factors can lead to suboptimal adherence to surveillance recommendations.[42]

HCC surveillance implementation can be affected by either provider or patient-related factors; patients must be engaged in healthcare and have a clinic visit, providers must accurately identify at-risk patients, providers must order appropriate surveillance tests; surveillance tests must be scheduled, and the patient must adhere with the surveillance recommendations. There appears to be breakdowns at each of these steps in clinical practice, although the most common issues are lack of engagement in healthcare/clinic visits and lack of provider recommendation for surveillance testing in patients with known cirrhosis. Patients' nonadherence to surveillance testing can occur but appears to be relatively rare.[43]

A recent systematic review and meta-analysis included was conducted to assess utilization of hepatocellular carcinoma surveillance in patients with cirrhosis. A total of 118,799 patients, met inclusion criteria, with a pooled estimate for surveillance utilization of 24.0%. In subgroup analyses, the highest surveillance receipt was reported in studies with patients enrolled from subspecialty Gastroenterology/Hepatology clinics and lowest in studies characterizing surveillance in population-based cohorts (73.7% *vs.* 8.8%, $P < 0.001$).

This systematic review and meta-analysis highlighted that HCC surveillance continued to be underutilized, with only 1 in 4 patients with cirrhosis receiving surveillance. HCC surveillance underuse appears particularly problematic among patients with non-viral liver disease and those followed by primary care providers or outside academic centres. They recommended that clear interventions are needed to increase HCC surveillance.[44]

A retrospective multicentre cohort study from 5 centres in the USA found underuse of HCC surveillance, with significant site-level variation. They found only 1 in 7 patients receiving semi-annual surveillance and 1 in 4 patients receiving annual surveillance. Surveillance underuse in the study was attributed to multiple failures; patients having unrecognized cirrhosis prior to HCC diagnosis, and lack of surveillance orders by clinicians or patients failing to complete surveillance after being ordered.

The findings of this study point to several gaps in cirrhosis care and the need for interventions to improve recognition of cirrhosis, as well as more convenient, accurate surveillance tests to improve adherence.[45]

Another retrospective cohort study aimed to characterize reasons for failure in the HCC surveillance process among a cohort of cirrhotic patients with HCC. They classified reasons for failure into four categories: failure to recognize liver disease, failure to recognize cirrhosis, failure to order surveillance, and failure to complete surveillance despite orders. Their data showed underutilization of HCC surveillance with only one in five patients received surveillance prior to HCC diagnosis. There were multiple points of failure in the surveillance process, with the most common being failure to order surveillance in patients with known cirrhosis (38%).[43]

Similar results were shown in a multi-centre cross-sectional study of patients at-risk for HCC in Argentina. The study evaluated HCC surveillance throughout the entire process: risk assessment, implementation of surveillance, and performance of surveillance to detect HCC at an early stage. The study illustrated several pitfalls in the HCC surveillance process: 25% of patients are unaware of their risk for HCC, only 43% of at-risk patients are under surveillance at time of HCC diagnosis, and surveillance fails to detect HCC at an early stage in 25% of patients.[46]

HCC surveillance failure was also addressed in a large retrospective cohort study from USA. The study included 1,014 patients with cirrhosis with HCC. The authors categorized reasons for screening underuse as a potential failure at each of the following steps required for HCC screening: receipt of regular outpatient care, recognition of liver disease, recognition of cirrhosis, screening orders in patients with cirrhosis, and adherence to screening ultrasound appointments.

The study concluded that the most common reasons for HCC screening underuse in patients with cirrhosis are lack of regular outpatient care and lack of screening orders in those with known cirrhosis. Remarkably from the findings of the study that nearly two thirds of patients failed to have regular outpatient care before HCC diagnosis, with over one third not having any prior PCP or gastroenterology visits.[47]

EFFECTIVENESS OF HCC SURVEILLANCE

The World Health Organization and American College of Physicians emphasize that "screening is not a single test but a comprehensive intervention with a cascade of subsequent events of either benefit or harm".[48,49]

Proper screening for HCC is a continuum of services, extending from initial patient screening, diagnosis, treatment and ultimately surveillance. As one may expect, there are numerous chances for failure in the delivery of cancer screening care.[50]

BENEFITS OF HCC SURVEILLANCE

The intended benefits of entering a patient into a surveillance programme are clear. The aim is to detect early cancers in at-risk groups and enable potentially curative treatments for this group of patients. More specifically, the aim is to detect cancers which are less than 2–2.5 cm which can be treated with ablative strategies, as treatment in this group has demonstrated significant survival benefit.[51]

One meta-analysis, published by Singal *et al.* in 2014, was the systematic review to quantitatively evaluate the benefits of HCC screening. It included 47 observational studies that compared the proportion of early HCC and 3-year survival rate between HCC screening and no screening groups in cirrhosis patients. They concluded that HCC surveillance is associated with significant improvements in early tumour detection, receipt of curative therapy, and overall survival in patients with cirrhosis.[12]

In addition, another meta-analysis published by Singal *et al.* in 2021 was an update of the meta-analysis published in 2014, which evaluated the benefits and harms of HCC screening in patients with cirrhosis from cohort studies. In terms of benefit outcomes, it reported HCC surveillance is associated with improved early detection, curative treatment receipt, and survival in patients with cirrhosis, although there was heterogeneity in pooled estimates.[52]

Recently, comparable results were recorded by a recent meta-analysis that included 67 studies (including four RCTs and 63 cohort studies). The meta-analysis of RCTs showed HCC screening was significantly associated with reduced HCC mortality, prolonged overall survival rates, increased the proportion of early HCC detection. Similarly, meta-analysis of cohort studies indicated HCC screening was more effective than non-

screening. However, pooled proportion of physiological harms was 16.30% and most harms were of a mild to moderate severity.[53]

A retrospective cohort study from USA assessed the effectiveness of surveillance for HCC in clinical practice. The study showed that patients who received surveillance were significantly more likely to have early-stage disease HCC and receive potentially curative (20.9% *vs.* 11.6%) or palliative (59.2% *vs.* 45.5%) treatments compared to those without HCC surveillance. Receipt of HCC surveillance was associated with 38% reduction in overall mortality risk that declined to 20% after adjusting for HCC stage and treatment, compared to those without HCC surveillance.[54]

A large cohort of 1074 cases in the Netherlands revealed that Surveillance for hepatocellular carcinoma was associated with smaller tumor size, earlier tumor stage, with an impact on therapeutic strategy and was an independent predictor of survival.[55]

HARMS OF HCC SURVEILLANCE

When considering the risk versus benefits of HCC surveillance we must consider the possible harm to the patient. Such concerns include false-positive testing resulting in unnecessary and risk-associated procedures such as liver biopsy, overdiagnosis of HCC among patients with cirrhosis, as well as false-negative investigations resulting in delayed diagnosis of HCC.[56]

There are many types of harms that should be considered when evaluating a cancer surveillance program, including the potential for physical, financial, and psychological harms. Physical harms can result from surveillance or follow-up testing and extend beyond medical complications to include discomfort. Financial harms can include anticipated or actual costs of surveillance and diagnostic evaluation, plus indirect costs such as missed work. Psychological harms can occur at any step of the surveillance process and include anticipation or fear of abnormal results; reactions of depression, anxiety, or cancer-specific worry after positive results; and psychological effects of being labelled with a diagnosis.[56]

The different types of harms are shown in Table 4 adapted from Rich *et al.* and Korenstein *et al.*[57,58]

Physical harms

Potential physical harms may result from initial screening tests as well as subsequent diagnostic testing for positive results, both invasive and non-invasive. These harms may range from relatively minor in severity (*i.e.*, patient discomfort with venipuncture) to moderate (*i.e.*, radiation exposure, minor bleeding) to more severe (*i.e.*, requiring hospitalization or resulting in permanent disability or death).[59] A retrospective cohort study of 680 patients with cirrhosis showed that over 25% of patients with cirrhosis experience physical harm for false positive or indeterminate surveillance tests—more often related to ultrasound than AFP.[60]

In another single-centre study which included 999 patients undergoing HCC surveillance, they studied the benefits and harms of HCC surveillance. In view of benefits of an HCC Surveillance Program, the study achieved serial surveillance at 46%, which is higher than those reported in literature. Further 78% of patients diagnosed with HCC were diagnosed at an early stage within Milan criteria. The study found that surveillance can also create harms, with indeterminate nodules IN (any lesion more than 1 cm in diameter that could not be categorized as definitely benign or definite HCC on cross-sectional imaging) being identified in 26% of patient's undergoing surveillance, and with 73% of those did not result in a diagnosis of HCC. This study addressed only the physical harms and did not assess the psychological or financial harms.[61]

Psychosocial harms

Cancer screening may result in psychological harms at any point along the screening "cascade" and have deleterious effects on patients' quality of life. For instance, a patient may experience harm prior to the screening test (due to anxiety about a potential positive result), while awaiting test results, after a positive screening test result while awaiting diagnostic testing, after a diagnosis of cancer is made, during cancer treatment, and following cancer cure (due to concern about recurrence). These harms may range in severity from mild anxiety to severe depression, or even suicide.[62]

Receiving a cancer diagnosis is a stressful event, and patients may experience adverse psychological consequences from being labelled as a "cancer patient". A systematic review of 35 quantitative studies concluded that labelling is a potential psychological harm of screening. It is a real phenomenon that has been underappreciated and understudied.[63]

Patients with false-negative screening tests may experience significant psychological distress after an eventual (delayed) cancer diagnosis is made. Further, patients with false-positive screening tests may be less likely to participate in subsequent cancer screening.[64]

Financial harms

The cost effectiveness of surveillance programmes in a

Table 4: Different types of harms of screening for HCC adapted from Rich *et al*. and Korenstein *et al*.[57,58]

Domain	Description	Examples
Physical	Temporary or permanent pain, injury, illness, or impairment	Pain from venipuncture Contrast-induced nephropathy following CT Bleeding after liver biopsy from false positive ultrasound
Psychosocial	Negative emotions, mood symptoms, or psychiatric disorder Disruption of relationships, altered social identity or status owing to a medical condition	Fear that screening test will be positive Anxiety following positive ultrasound while awaiting CT/MRI results Depression about cancer diagnosis and "labeling" as a cancer patient
Financial	Patient-level: Monetary costs, including treatment expenses, nonmedical expenses incurred while obtaining treatment and indirect costs due to loss of productivity Society-level: Costs to healthcare system	Direct cost of screening test and downstream testing after a positive test Opportunity cost related to missed work during follow-up testing
Overdiagnosis	Detection of pre-malignant lesion Detection of indolent cancer Detection of cancer in patient with high competing mortality risk	Biopsy of lesion detected by screening reveals dysplastic nodule Small HCC detected with slow tumor doubling time in a patient that eventually dies with, not from HCC HCC detected in a patient with decompensated cirrhosis that is not a candidate for locoregional therapy due to poor liver function; patient dies of sepsis

healthcare system should be considered as the health system is already underfunded and under-resourced at present. The potential financial harms of cancer screening include not only the direct costs of screening tests and downstream diagnostic testing, but also travel costs and costs related to missed work for undergoing investigations or follow-up clinic appointments.

Data from a study presented by Singal *et al*.[65] found that patients with cirrhosis in the United States have substantial financial burden and this is associated with underuse of surveillance for HCC. The patients included in the study reported many barriers which included testing costs and difficulties with the scheduling process. 11.8% reported they needed to borrow money or go into debt to pay for care, 24.4% said they were unable to afford copays or deductibles, and 42.8% expressed worry about being able to pay their medical bills.

In the recently published NICE guidance a new health economic evaluation was undertaken. It did not support surveillance at the £20,000 per quality-adjusted life year (QALY) threshold that is typically used by NICE but the recommendation for surveillance use was justified on the basis that implementation was already widespread.[66]

OVERDIAGNOSIS IN CANCER SCREENING

Overdiagnosis can have serious negative consequences including overtreatment and associated complications, financial toxicity, and psychological harms related to being labelled with a cancer diagnosis. Overdiagnosis can occur for several different reasons including inaccurate diagnostic criteria, detection of premalignant or very early malignant lesions, detection of indolent tumors, and competing risks of mortality. The risk of overdiagnosis is partly mitigated, albeit not eliminated by several guideline recommendations, including definitions for the at-risk population in whom surveillance should be performed, surveillance modalities, surveillance interval, recall procedures, and HCC diagnostic criteria.[67]

Many HCC tumors are diagnosed at an asymptomatic stage; however, treatment for a small, screen-detected HCC can result in significant morbidity and mortality. Curative and palliative treatments can result in prolonged survival in well-selected patients but may result in complications and debility, resulting in poorer QOL without a concomitant increase in survival, in poorly selected patients and those with overdiagnosed tumor. Overdiagnosis leads to misleading and incorrect information about screening tests. For instance, overdiagnosis not only overestimates disease incidence and inflates survival statistics, but also the sensitivity, specificity, and positive predictive value of a particular screening test.[57]

EMERGING HCC SURVEILLANCE METHODS

Emerging imaging techniques

Contrast-enhanced ultrasound: CEUS is a real-time dynamic imaging technique, which enables the use of US to assess the contrast-enhancement patterns of FLLs in real time, without ionizing radiation and with a much higher temporal resolution than is possible with CT and MRI.[68] In a prospective, multicentre, randomized, controlled study of 23 institutions, the average size of HCCs detected by CEUS was significantly smaller than the size of HCCs detected by B-mode ultrasound, suggesting that CEUS is superior to B-mode ultrasound for early detection. The study recommended CEUS as first-line screening tool for HCC in patients with liver cirrhosis, especially those with very coarse liver

parenchyma.[35]

Another prospective multicentre diagnostic study has reported that the use of CEUS for HCC surveillance reduced the false referral rate without a significant improvement in the detection rate of early-stage hepatocellular carcinoma for surveillance.[69]

Contrast-enhanced CT and MRI: Overall, MRI has a sensitivity of 77%–100% for detecting nodular HCC while CT has a sensitivity of 68%–91%. However, the sensitivity is only 45%–80% with MRI and 40%–75% with CT for lesions measuring 1–2 cm and it is close to 100% for lesions larger than 2 cm.[70]

Multiphase, contrast-enhanced, cross-sectional imaging modalities such as CT or magnetic resonance imaging (MRI) are not recommended as first-line surveillance methods due to their lower availability, higher cost, exposure to radiation (CT) and contrast material (CT and MRI), and poor patient tolerance (MRI).[36]

AASLD recommends utilizing CT or MRI for HCC surveillance in select patients with inadequate ultrasound or those with a high likelihood of having an inadequate ultrasound,[8] while EASL recommends using CT or MRI for HCC surveillance in high-risk patients on the liver transplant waiting list.[9]

(18F) fluoro-2-deoxy-D-galactose positron emission tomography/computed tomography (FDGal PET/CT): The use of FDGal PET/CT was first demonstrated in a small study of 39 patients. The study revealed that it has great clinical potential as a PET tracer for detection of extra- but also intra-hepatic HCC. The specificity of FDGal PET/CT was 100% with known or suspected HCC and demonstrated high specificity (100%).[71]

FDGal PET/CT has limited value in the diagnosis of HCC since most HCCs are not highly metabolically active. For this reason, PET can miss 30%–50% of HCC lesions.[9]

Novel serum HCC biomarkers: Serum HCC biomarkers can be classified into 3 categories: tumor proteins, micro-RNA markers and immune markers.

Tumor proteins biomarkers: Because the specificity of AFP is relatively low, as it can be elevated in non-HCC malignancies and other chronic inflammatory conditions of the liver. This limitation has partially been overcome by the identification of the biomarker AFP-L3, lens culinaris agglutinin-reactive fraction of AFP. Choi and colleagues[72] showed that AFP and AFP-L3 combination, adopting cut-off values (5 ng/mL and 4%, respectively), significantly improved the sensitivity for detecting HCC at a very early stage.

Des-gamma-carboxyprothrombin (DCP), also known as prothrombin induced by vitamin K absence II (PIVKA II), is an abnormal prothrombin molecule which is upregulated in HCC. In a study of 90 patients with cirrhosis with US evidence of liver nodules, 40 were diagnosed to have HCC at very early/early stages. PIVKA-II had 60% sensitivity, 88% specificity, 80% positive predictive value (PPV), and 73% negative predictive value (NPV), whereas AFP had 67% sensitivity, 68% specificity, 63% PPV, and 72% NPV. The study concluded that PIVKA-II is a useful tool for the diagnostic definition of US-detected liver nodules in cirrhotic patients, and it provides high diagnostic accuracy for HCC when combined with AFP.[73]

A randomized controlled trial evaluating HCC surveillance through ultrasound with or without AFP, AFP-L3 and DCP has demonstrated that the association of these biomarkers with ultrasound increases sensitivity while decreasing specificity.[74] Johnson and his colleagues developed a score which includes these biomarkers is the GALAD score, an acronym for gender, age, AFP-L3, AFP and DCP.[75]

A single centre cohort study of 111 HCC and 180 controls with cirrhosis, assessed the performance of the GALAD score in comparison to liver ultrasound for detection of HCC. the GALAD score had a sensitivity of 91% and a specificity of 85% for HCC detection. The performance of the GALAD score was superior to ultrasound for HCC detection. The combination of GALAD and ultrasound (GALADUS score) further improved the performance of the GALAD score.[76]

Glypican-3 (GPC3), a member of the glypican family that attaches to the cell surface by a glycosylphosphatidylinositol anchor, is overexpressed in HCC cases and is elevated in the serum of a large proportion of patients with HCC. GPC3 is specifically expressed in HCCs and can be found in HCC patient serum. Increased GPC3 can be considered as a sign of HCC progression. GPC3 can be used as a serum and histochemical marker for diagnosis of early-stage of HCC.[77]

MicroRNA Biomarkers: Micro RNAs (miRNAs) are small non-coding RNA molecules of approximately 22–24 nucleotides in length that regulate gene expression and are critically involved in the processes of liver development during embryogenesis, liver homeostasis and liver pathophysiology.[78] miRNAs can be measured by molecular biology methods, like quantitative polymerase chain reaction (PCR), microarray or RNAseq analysis. Moreover, because miRNAs are small molecules, have a high sequence homology among family members and low abundance, new methods, such as those based on nanomaterials, are being developed

for highly sensitive detection of miRNAs.[79]

A recent study evaluated the use of circulating miRNAs to identify HCC by analysing serum samples from 345 patients with HCC, 46 patients with chronic hepatitis (CH), 93 patients with liver cirrhosis (LC), and 1,033 healthy individuals. The study concluded that circulating miRNAs could serve as biomarkers for the accurate detection of HCC (area under the curve, 0.99; sensitivity, 97.7%; specificity, 94.7%). Because diagnostic accuracy was maintained even in stage I, this may represent an accurate detection method even for early-stage HCC.[80]

Immune biomarkers: Transforming growth factor β (TGF-β1) acts as a growth inhibitor in normal cells, whereas in tumor cells, it loses the ability to mediate growth inhibition and instead promotes tumor progression by enhancing migration, invasion, and survival of tumor cells.[81]

An Egyptian study[82] aimed to evaluate the association of serum levels of TGF-β1 with HCC disease severity. Serum levels of TGF-β1 were significantly higher in patients with HCC (1,687.47 ± 1,462.81 pg/mL) than cirrhotics (487.98 ± 344.23 pg/mL, $P < 0.001$) and controls (250.16 ± 284.61 pg/mL, $P < 0.001$). The study concluded that TGF-β1 may have a role in tumor growth and progression.

Other studies have addressed TGF-β role as a biomarker in HCC in combination with the expression of other proteins or mRNA and not as a stand-alone biomarker.[83]

Osteopntin (OPN) is highly expressed in tumor tissues and is present in the serum of many patients with malignant tumors (including liver cancer).[84] In a meta-analysis, the area under ROC curve of serum OPN in diagnosis of HCC was higher than that of alpha-fetoprotein (AFP).[85]

Evaluation of osteopontin as a biomarker in Hepato-cellular Carcinomas in Egyptian Patients with Chronic HCV Cirrhosis revealed that the serum OPN levels were significantly higher in the HCC group compared to normal group ($P = 0.009$), with a strong positive correlation with AFP expression. However, there was no significant difference between OPN expression in tumor and non-tumor liver tissue. The study concluded that serum OPN is highly suggested to be a professional candidate for HCC early diagnosis, with a diagnostic ability and accuracy equal or higher than for AFP.[86]

Recently, serum pentraxin 3 also has been suggested as a candidate biomarker of HBV-induced HCC in a study from China. Evaluating the serum pentraxin 3 levels in 107 patients with HCC in comparison to 159 chronic HBV and 99 cirrhotic patients demonstrated that pentraxin 3 was highly discriminative of AFP-negative and early-stage HCC, and the diagnostic performance of pentraxin 3 was superior to AFP.[87]

The concept of liquid biopsy refers to the release and molecular analysis of tumor components, mostly nucleic acids, circulating tumor cells (CTCs) and extracellular vesicles (EVs), which are released by tumors to the bloodstream or other body fluids.[88]

Liquid biopsy represents a novel, minimally invasive, powerful tool for biomarker discovery in HCC, with the potential to significantly change decision-making in the short term.[89] Liquid biopsy seems to be a very promising instrument and, in the near future, some of these new non-invasive tools will probably change the clinical management of HCC patients.[90]

LIMITATIONS OF HCC SURVEILLANCE

HCC surveillance process should be considered as an integrated whole system, rather than just screening tests. There should be a process that includes identification of the at-risk group(s), application of the test, appropriate recall procedures and a process in place to manage diseases discovered by screening. Thus, failure of HCC screening can be looked at from the point of view of the program, or from the point of view of the individual who suffered a failure of screening.[91]

The surveillance program failure was discussed in detail under the section of surveillance utilization.

From an individual's perspective, surveillance failure can occur at different steps; failure to detect HCC at an early stage where curative options are available, failure of recall strategies or failure to deliver a suitable treatment at timely manner after detection.[91]

Studies of resection and local ablation suggest that the likelihood of cure starts to diminish once the HCC is between 2 and 2.5 cm in diameter.[92,93]

A population-based study to determine the relationship between tumor size at diagnosis and pathological grade, surveillance, epidemiology, and treatment selection. Multivariable Cox regression analysis identified tumor size at diagnosis as an independent predictor of survival risk (tumor size of 0.1–2.0 *vs.* 2.1–5.0 and 5.1–10.0 *vs.* 10.1–20.0 cm, respectively, with HR of 1.00 *vs.* 1.66 *vs.* 2.92 *vs.* 3.67, respectively).The study concluded that tumor size at diagnosis could be used as an independent risk predictor associated with histological grade, stage, selection of surgery, and survival in HCC.[94]

AFP is the most used surveillance marker but is the least sensitive. A test that indicates advanced disease cannot also be a marker of early-stage disease. Many authors have evaluated the relation between AFP levels and HCC size. Saffroy *et al.* discovered that larger tumors presented with higher AFP levels, while a wide proportion of small HCCs (80%) had normal AFP. The sensitivity of this marker was higher when nodules exceeded 3 cm in diameter (52% compared to 25% in tumors below 3 cm).[95]

The recommended screening tool for HCC surveillance is the ultrasound. Surveillance ultrasound detected most tumors before they presented clinically, with a pooled sensitivity of 94%. However, ultrasound was less effective for detecting early HCC with a sensitivity of 63%. Alpha-fetoprotein provided no additional benefit to ultrasound.[96]

Another study evaluated the ultrasound quality for hepatocellular carcinoma surveillance. The study revealed that one in 5 ultrasound exams in the cohort of patients with cirrhosis were of inadequate quality for HCC surveillance. The most common reasons for inadequate quality were rib shadowing and inadequate ultrasound beam penetration. Obesity, Child Pugh B or C cirrhosis, and alcohol or NASH-related cirrhosis are associated with inadequate ultrasound quality, with these patients having inadequate exams in over one-third of cases.[97]

A matched case-control study within the US Veterans Affairs (VA) health care system found that screening patients with cirrhosis for HCC by abdominal ultrasonography (USS), measurement of serum level of AFP, either test, or both tests was not associated with decreased HCC-related mortality.[98]

IMPROVING HCC SURVEILLANCE OUTCOMES

It is important to consider surveillance as a program rather than the provision of surveillance tests alone. This should include identification of the at-risk population, determining the optimal tests(s) and surveillance interval, and establishing the optimal recall strategy. The recall strategy includes when and how to investigate abnormal surveillance test results and to come to an appropriate diagnosis. Improvements in any of these components could eventually enhance the outcomes achieved with surveillance programs.[99]

Failure to identify at-risk patients is strongly associated with advanced HCC stage at diagnosis and may be related to patient evaluation by non-specialist care providers.[100]

To overcome the failure in identification of high-risk groups, a couple of measures should be implemented. The use of electronic medical records to facilitate the recognition of patients with abnormal liver functions, positive viral markers and the assessment of non-invasive laboratory markers of liver disease.

Abnormal tests must be recognised, and appropriate investigations initiated. There is evidence that many steps along this pathway are carried out poorly. In one study only about 2% of patients with cirrhosis underwent bi-annual surveillance.[101]

Cirrhosis is essentially silent until liver failure supervenes. Nonetheless, there are clues such as elevated alanine aminotransferase (ALT), a falling platelet count, coarse appearance of the liver on ultrasound and abnormal albumin or international normalised ratio that should lead to further investigation.[99]

Reduce under-recognition of HCV-positive cases should be avoided. Centres for Disease Control and Prevention 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.[102]

Primary care providers (PCPs) have misconceptions about tests to detect HCC that contribute to ineffective surveillance. Reported barriers to surveillance include suboptimal knowledge about guidelines, indicating a need for interventions, including provider education, to increase HCC surveillance effectiveness.[103]

Failure to access care and patients' adherence is not considered a major barrier to HCC screening. To overcome this difficulty, there is a great role for the health care systems. The government health care authorities should cover patient expenses and offer more screening tests and shorter screening intervals. This eventually will end up with a higher compliance to HCC surveillance.

Failure of detection of HCC is another issue in surveillance. To overcome the limitations of US as a screening tool, CT or MRI-based surveillance has been proposed. MRI proved the best method of surveillance for early HCC (sensitivity of 83.7%) but high costs, long scan times and low availability prevent the widespread use of MRI as an imaging technique for screening.[37]

After detection of an abnormality there is the recall procedure. This includes a definition of what severity or type of abnormality constitutes a result warranting further intervention, and what the intervention should be. In order to avoid pitfalls of the recall procedure, much research have been conducted to improve the tools of HCC surveillance.

An abbreviated MRI protocol (AMRI) which comprises two sequences performed approximately 20 mins after the intravenous injection of gadoxetate disodium can be performed at a lower cost in a shorter time than a complete examination, thus making it more suitable for routine HCC surveillance.[104] In a recent mathematical model, biannual 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.[105]

To improve the reporting of imaging of liver nodules, the American Radiological Society devised a set of reporting guidelines that classified the risk of a lesion being HCC from Li-RADS® (Liver Imaging Data and Reporting System) 1 (benign) to Li-RADS 5 (definitely HCC).[106]

FUTURE DIRECTIONS AND HCC SURVEILLANCE

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.[107]

Several risk scores have been developed for hepatitis B. Among them the risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B)[108] and the platelets, age, gender in chronic hepatitis B (PAGE-B).[109] A risk score for HCV patients has been developed using the hepatitis C antiviral long-term treatment against cirrhosis (HALT-C) cohort.[110]

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).[75]

Development of artificial intelligence (AI) provides a unique set of novel tools to aimed at solving the problems within HCC surveillance and improve HCC detection, characterisation, prediction of survival and treatment outcomes. AI will revolutionise the way we detect and characterise HCC, as well as predict the course of its development, however, it is still experimental.[111]

Health care professionals must learn the true usefulness of AI and accept the need for its coexistence with the indispensable need for human evaluation, accepting that AI is here to support human intelligence, never to replace it.[112]

CONCLUSION

Surveillance in high-risk patients is critical for early detection of HCC, which leads to higher chances of curative treatment and prolonged survival. Biannual ultrasound with or without AFP remains the standard surveillance method endorsed by major societies. Although there is evidence of the benefits of HCC surveillance in terms of improved cancer mortality, The current HCC surveillance strategy has its own limitations, harms and is underutilised. The significant under-utilization of HCC surveillance is a major problem. Widespread patient/provider education and outreach efforts are necessary to make sure the at-risk patients receive the benefits of HCC surveillance while minimizing the potential physical, financial, and psychological harms. In addition, the rapid developments in AI technology may greatly improve individualized HCC risk prediction and interpretation of imaging studies. More studies are still needed to implement new modalities for surveillance and to improve its quality to cope with future scenarios where the aetiology of cirrhosis is changing and the population at risk is becoming larger.

DECLARATIONS

Author contributions

Both authors created the paper's design. Omar Khalifa Elsayed M wrote the paper. Talkhan MG revised the paper and wrote the abstract.

Conflicts of interest

There is no conflict of interest among the authors.

Data sharing statement

No additional data is available.

REFERENCES

1. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of Hepatocellular Carcinoma. Hepatology 2021; 73 Suppl 1: 4-13.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.
3. Petrick JL, Florio AA, Znaor A, Ruggieri D, Laversanne M, Alvarez CS, Ferlay J, Valery PC, Bray F, McGlynn KA. International trends in hepatocellular carcinoma incidence, 1978-2012. Int J Cancer 2020; 147: 317-330.
4. Ferlay J, Ervik M, Lam F, *et al.* Cancer Today 2020. Global cancer observatory: international agency for research on cancer. [Accessed July 15, 2021] Available from: https://gco.iarc.fr/today/ home.
5. Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: New trends. J Hepatol 2020; 72: 250-261.
6. Liu Z, Suo C, Mao X, Jiang Y, Jin L, Zhang T, *et al.* Global incidence trends in primary liver cancer by age at diagnosis, sex, region, and etiology, 1990-2017. Cancer 2020; 126: 2267-2278.

7. Dasgupta P, Henshaw C, Youlden DR, Clark PJ, Aitken JF, Baade PD. Global trends in incidence rates of primary adult liver cancers: a systematic review and meta-analysis. Front Oncol 2020; 10: 171.
8. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, *et al.* Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2018; 68: 723-750.
9. European Association for the Study of the Liver. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018; 69: 182-236.
10. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, *et al.* Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017; 11: 317-370.
11. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004; 130: 417-422.
12. Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. PLoS Med 2014; 11: e1001624.
13. Cillo U, Vitale A, Grigoletto F, Farinati F, Brolese A, Zanus G, *et al.* Prospective validation of the Barcelona clinic liver cancer staging system. J Hepatol 2006; 44: 723-731.
14. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018; 391: 1301-1314.
15. Finn RS, Zhu AX, Farah W, Almasri J, Zaiem F, Prokop LJ, *et al.* Therapies for advanced stage hepatocellular carcinoma with macrovascular invasion or metastatic disease: A systematic review and meta-analysis. Hepatology 2018; 67: 422-435.
16. Yang JD, Heimbach JK. New advances in the diagnosis and management of hepatocellular carcinoma. BMJ 2020; 371: m3544.
17. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 2009; 27: 1485-1491.
18. Tsilimigras DI, Bagante F, Sahara K, Moris D, Hyer JM, Wu L, *et al.* Prognosis After Resection of Barcelona Clinic Liver Cancer (BCLC) Stage 0, A, and B Hepatocellular Carcinoma: A Comprehensive Assessment of the Current BCLC Classification. Ann Surg Oncol 2019; 26: 3693-3700.
19. Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, *et al.* Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol 2012; 57: 821-829.
20. Chen JG, Parkin DM, Chen QG, Lu JH, Shen QJ, Zhang BC, *et al.* J Med Screen 2003; 10: 204-209.
21. Poustchi H, Farrell GC, Strasser SI, Lee AU, McCaughan GW, George J. Feasibility of conducting a randomized control trial for liver cancer screening: is a randomized controlled trial for liver cancer screening feasible or still needed? Hepatology 2011; 54: 1998-2004.
22. Kokudo N, Takemura N, Hasegawa K, Takayama T, Kubo S, Shimada M, *et al.* Clinical practice guidelines for hepatocellular carcinoma: The Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update. Hepatol Res 2019; 49: 1109-1113.
23. Yang JD, Roberts LR. Hepatocellular carcinoma: A global view. Nat Rev Gastroenterol Hepatol 2010; 7: 448-458.
24. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012; 142: 1264-1273.e1.
25. McGlynn KA, London WT. The global epidemiology of hepatocellular carcinoma: present and future. Clin Liver Dis 2011; 15: 223-243, vii-vix.
26. Fasani P, Sangiovanni A, De Fazio C, Borzio M, Bruno S, Ronchi G, *et al.* High prevalence of multinodular hepatocellular carcinoma in patients with cirrhosis attributable to multiple risk factors. Hepatology 1999; 29: 1704-1707.
27. Shaker MK, Abdella HM, Khalifa MO, El Dorry AK. Epidemiological characteristics of hepatocellular carcinoma in Egypt: a retrospective analysis of 1313 cases. Liver Int 2013; 33: 1601-1606.
28. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, *et al.* Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018; 15: 11-20.
29. Dyson J, Jaques B, Chattopadyhay D, Lochan R, Graham J, Das D, *et al.* Hepatocellular cancer: the impact of obesity, type 2 diabetes and a multidisciplinary team. J Hepatol 2014; 60: 110-117.
30. Masuzaki R, Tateishi R, Yoshida H, Goto E, Sato T, Ohki T, *et al.* Prospective risk assessment for hepatocellular carcinoma development in patients with chronic hepatitis C by transient elastography. Hepatology 2009; 49: 1954-1961.
31. Chen CJ, Yang HI, Iloeje UH; REVEAL-HBV Study Group. Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. Hepatology 2009; 49: S72-S84.
32. Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, *et al.* Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004; 351: 1521-1531.
33. Tzartzeva K, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, *et al.* Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis. Gastroenterology 2018; 154: 1706-1718.e1.
34. Maruyama H, Sekimoto T, Yokosuka O. Role of contrast-enhanced ultrasonography with Sonazoid for hepatocellular carcinoma: evidence from a 10-year experience. J Gastroenterol 2016; 51: 421-433.
35. Kudo M, Ueshima K, Osaki Y, Hirooka M, Imai Y, Aso K, *et al.* B-Mode Ultrasonography versus Contrast-Enhanced Ultrasonography for Surveillance of Hepatocellular Carcinoma: A Prospective Multicenter Randomized Controlled Trial. Liver Cancer 2019; 8: 271-280.
36. Yang JD, Heimbach JK. New advances in the diagnosis and management of hepatocellular carcinoma. BMJ 2020; 371: m3544.
37. Kim SY, An J, Lim YS, Han S, Lee JY, Byun JH, *et al.* MRI with liver-specific contrast for surveillance of patients with cirrhosis at high risk of hepatocellular carcinoma. JAMA Oncol 2017; 3: 456-463.
38. Santi V, Trevisani F, Gramenzi A, Grignaschi A, Mirici-Cappa F, Del Poggio P, *et al.* Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. J Hepatol 2010; 53: 291-297.
39. Trinchet JC, Chaffaut C, Bourcier V, Degos F, Henrion J, Fontaine H, *et al.* Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: a randomized trial comparing 3- and 6-month periodicities. Hepatology 2011; 54: 1987-1997.
40. Cross TJS, Villanueva A, Shetty S, Wilkes E, Collins P, Adair A, *et al.* A national survey of the provision of ultrasound surveillance for the detection of hepatocellular carcinoma. Frontline Gastroenterol 2016; 7: 82-89.
41. Tran SA, Le A, Zhao C, Hoang J, Yasukawa LA, Weber S, *et al.* Rate of hepatocellular carcinoma surveillance remains low for a large, real-life cohort of patients with hepatitis C cirrhosis. BMJ Open Gastroenterol 2018; 5: e000192.
42. Ahn JC, Lee YT, Agopian VG, Zhu Y, You S, Tseng HR, *et al.* Hepatocellular carcinoma surveillance: current practice and future directions. Hepatoma Res 2022; 8.
43. Singal AG, Yopp AC, Gupta S, Skinner CS, Halm EA, Okolo E, *et al.* Failure rates in the hepatocellular carcinoma surveillance process. Cancer Prev Res (Phila) 2012; 5: 1124-1130.
44. Wolf E, Rich NE, Marrero JA, Parikh ND, Singal AG. Use of hepatocellular carcinoma surveillance in patients with cirrhosis: a systematic review and meta-analysis. Hepatology 2021; 73: 713-725.
45. Parikh ND, Tayob N, Al-Jarrah T, Kramer J, Melcher J, Smith D, *et al.* Barriers to surveillance for hepatocellular carcinoma in a multicenter cohort. JAMA Netw Open 2022; 5: e2223504.

46. Dirchwolf M, Marciano S, Ruf AE, Singal AG, D'Ercole V, Coisson P, *et al.* Failure in all steps of hepatocellular carcinoma surveillance process is frequent in daily practice. Ann Hepatol 2021; 25: 100344.
47. Marquardt P, Liu PH, Immergluck J, Olivares J, Arroyo A, Rich NE, *et al.* Hepatocellular Carcinoma Screening Process Failures in Patients with Cirrhosis. Hepatol Commun 2021; 5: 1481-1489.
48. Harris RP, Wilt TJ, Qaseem A; High Value Care Task Force of the American College of Physicians. A value framework for cancer screening: advice for high-value care from the American College of Physicians. Ann Intern Med 2015; 162: 712-717.
49. WHO. National cancer control programmes: policies and managerial guidelines - Second edition. 2002.
50. Harris PS, Hansen RM, Gray ME, Massoud OI, McGuire BM, Shoreibah MG. Hepatocellular carcinoma surveillance: An evidence-based approach. World J Gastroenterol 2019; 25: 1550-1559.
51. Roskilly A, Rowe IA. Surveillance for hepatocellular cancer. Clin Med (Lond) 2018; 18: s66-s69.
52. Singal AG, Zhang E, Narasimman M, Rich NE, Waljee AK, Hoshida Y, *et al.* HCC surveillance improves early detection, curative treatment receipt, and survival in patients with cirrhosis: A meta-analysis. J Hepatol 2022; 77: 128-139.
53. J. Yang, Z. Yang, X. Zeng et al., Benefits and harms of screening for hepatocellular carcinoma in high-risk populations: systematic review and meta-analysis, Journal of the National Cancer Center, https://doi.org/10.1016/j.jncc.2023.02.001
54. Mittal S, Kanwal F, Ying J, Chung R, Sada YH, Temple S, *et al.* Effectiveness of surveillance for hepatocellular carcinoma in clinical practice: A United States cohort. J Hepatol 2016; 65: 1148-1154.
55. van Meer S, de Man RA, Coenraad MJ, Sprengers D, van Nieuwkerk KM, Klümpen HJ, *et al.* Surveillance for hepatocellular carcinoma is associated with increased survival: Results from a large cohort in the Netherlands. J Hepatol 2015; 63: 1156-1163.
56. Heleno B, Thomsen MF, Rodrigues DS, Jørgensen KJ, Brodersen J. Quantification of harms in cancer screening trials: literature review. BMJ 2013; 347: f5334.
57. Rich NE, Parikh ND, Singal AG. Overdiagnosis: An Understudied Issue in Hepatocellular Carcinoma Surveillance. Semin Liver Dis 2017; 37: 296-304.
58. Korenstein D, Chimonas S, Barrow B, Keyhani S, Troy A, Lipitz-Snyderman A. Development of a Conceptual Map of Negative Consequences for Patients of Overuse of Medical Tests and Treatments. JAMA Intern Med 2018; 178: 1401-1407.
59. Petrasek J, Singal AG, Rich NE. Harms of hepatocellular carcinoma surveillance. Curr Hepatol Rep 2019; 18: 383-389.
60. Atiq O, Tiro J, Yopp AC, Muffler A, Marrero JA, Parikh ND, *et al.* An assessment of benefits and harms of hepatocellular carcinoma surveillance in patients with cirrhosis. Hepatology 2017; 65: 1196-1205.
61. Verma A, Konerman MA, Zhao B. Impact of a Structured Hepatocellular Carcinoma Surveillance Program in Patients with Cirrhosis: Frequency, Evaluation and Subsequent Clinical Outcomes of Patients with Abnormal Imaging Findings. Presented at: AASLD: The Liver Meeting 2017, October 20–24, 2017, Washington, DC.
62. McGovern PM, Gross CR, Krueger RA, Engelhard DA, Cordes JE, Church TR. False-positive cancer screens and health-related quality of life. Cancer Nurs 2004;27:347-352.
63. Cotter AR, Vuong K, Mustelin L, Yang Y, Rakhmankulova M, Barclay CJ, *et al.* Do psychological harms result from being labelled with an unexpected diagnosis of abdominal aortic aneurysm or prostate cancer through screening? A systematic review. BMJ Open 2017; 7: e017565.
64. Alamo-Junquera D, Murta-Nascimento C, Macià F, Baré M, Galcerán J, Ascunce N, *et al.* Effect of false-positive results on reattendance at breast cancer screening programmes in Spain. Eur J Public Health 2012; 22: 404-408.
65. Singal AG MK, Ortiz C, Kramer J, et al. Financial burden is common in U.S. patients with cirrhosis and associated with lower HCC surveillance receipt. In: American Association for the Study of Liver Diseases Annual Meeting; 2019; Boston, MA; 2019.
66. National Institute for Health and Care Excellence. Clinical Guideline 50: Cirrhosis in over 16s: Assessment and management. NICE, 2016. [Accessed 12 July 2016] Available from: https://www.nice.org.uk/guidance/ng50/evidence/full-guideline-2546537581
67. Rich NE, Singal AG. Overdiagnosis of hepatocellular carcinoma: Prevented by guidelines? Hepatology 2022; 75: 740-753.
68. Bartolotta TV, Vernuccio F, Taibbi A, Lagalla R. Contrast-Enhanced Ultrasound in Focal Liver Lesions: Where Do We Stand? Semin Ultrasound CT MR 2016; 37: 573-586.
69. Park JH, Park MS, Lee SJ, Jeong WK, Lee JY, Park MJ, *et al.* Contrast-enhanced US with Perfluorobutane for Hepatocellular Carcinoma Surveillance: A Multicenter Diagnostic Trial (SCAN). Radiology 2019; 292: 638-646.
70. Hennedige T, Venkatesh SK. Advances in computed tomography and magnetic resonance imaging of hepatocellular carcinoma. World J Gastroenterol 2016; 22: 205-220.
71. Sørensen M, Frisch K, Bender D, Keiding S. The potential use of 2-[^{18}F]fluoro-2-deoxy-D-galactose as a PET/CT tracer for detection of hepatocellular carcinoma. Eur J Nucl Med Mol Imaging 2011; 38: 1723-1731.
72. Choi J, Kim GA, Han S, Lee W, Chun S, Lim YS. Longitudinal Assessment of Three Serum Biomarkers to Detect Very Early-Stage Hepatocellular Carcinoma. Hepatology 2019; 69: 1983-1994.
73. Saitta C, Raffa G, Alibrandi A, Brancatelli S, Lombardo D, Tripodi G, *et al.* PIVKA-II is a useful tool for diagnostic characterization of ultrasound-detected liver nodules in cirrhotic patients. Medicine (Baltimore) 2017; 96: e7266.
74. Sherman M, Feld J, Yamada H, Mori Y, Janssen H. A randomized controlled trial of US vs US + biomarkers for the diagnosis of hepatocellular carcinoma: an interim report. J Hepatol 2017;66(Suppl.):S13.
75. Johnson PJ, Pirrie SJ, Cox TF, Berhane S, Teng M, Palmer D, *et al.* The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. Cancer Epidemiol Biomarkers Prev 2014; 23: 144-153.
76. Yang JD, Addissie BD, Mara KC, Harmsen WS, Dai J, Zhang N, *et al.* GALAD Score for Hepatocellular Carcinoma Detection in Comparison with Liver Ultrasound and Proposal of GALADUS Score. Cancer Epidemiol Biomarkers Prev 2019; 28: 531-538.
77. Shih TC, Wang L, Wang HC, Wan YY. Glypican-3: A molecular marker for the detection and treatment of hepatocellular carcinoma. Liver Res 2020; 4: 168-172.
78. Niveditha D, Jasoria M, Narayan J, Majumder S, Mukherjee S, Chowdhury R, *et al.* Common and unique micrornas in multiple carcinomas regulate similar network of pathways to mediate cancer progression. Sci Rep 2020;10:2331 (2020)
79. Ye J, Xu M, Tian X, Cai S, Zeng S. Research advances in the detection of miRNA. J Pharm Anal 2019; 9: 217-226.
80. Yamamoto Y, Kondo S, Matsuzaki J, Esaki M, Okusaka T, Shimada K, *et al.* Highly sensitive circulating microrna panel for accurate detection of hepatocellular carcinoma in patients with liver disease. Hepatol Commun 2020; 4: 284-297.
81. Oh S, Kim E, Kang D, Kim M, Kim JH, Song JJ. Transforming growth factor-β gene silencing using adenovirus expressing TGF-β1 or TGF-β2 shRNA. Cancer Gene Ther 2013; 20: 94-100.
82. Kohla, MAS, Attia A, Darwesh N, Obada M, Taha H, Youssef MF. Association of serum levels of transforming growth factor β1 with disease severity in patients with hepatocellular carcinoma. Hepatoma Res 2017;3:294-301.
83. Ibrahim GH, Mahmoud MA, Aly NM. Evaluation of circulating Transforming growth factor-beta1, Glypican-3 and Golgi protein-73 mRNAs expression as predictive markers for hepatocellular carcinoma

in Egyptian patients. Mol Biol Rep 2013; 40: 7069-7075.
84. Zhao H, Chen Q, Alam A, Cui J, Suen KC, Soo AP, *et al.* The role of osteopontin in the progression of solid organ tumour. Cell Death Dis 2018; 9: 356.
85. Sun T, Li P, Sun D, Bu Q, Li G. Prognostic value of osteopontin in patients with hepatocellular carcinoma: A systematic review and meta-analysis. Medicine (Baltimore) 2018; 97: e12954.
86. Abdel-Hafiz SM, Hamdy HE, Khorshed FM, Aboushousha TS, Safwat G, Saber MA, *et al.* Evaluation of osteopontin as a biomarker in hepatocellular carcinomas in egyptian patients with chronic HCV cirrhosis. Asian Pac J Cancer Prev 2018; 19: 1021-1027.
87. Deng H, Fan X, Wang X, Zeng L, Zhang K, Zhang X, *et al.* Serum pentraxin 3 as a biomarker of hepatocellular carcinoma in chronic hepatitis B virus infection. Sci Rep 2020; 10: 20276.
88. Labgaa I, Villanueva A. Liquid biopsy in liver cancer. Discov Med 2015; 19: 263-273.
89. von Felden J, Garcia-Lezana T, Schulze K, Losic B, Villanueva A. Liquid biopsy in the clinical management of hepatocellular carcinoma. Gut 2020; 69: 2025-2034.
90. Pelizzaro F, Cardin R, Penzo B, Pinto E, Vitale A, Cillo U, *et al.* Liquid Biopsy in Hepatocellular Carcinoma: Where Are We Now? Cancers (Basel) 2021; 13.
91. Sherman M. Limitations of screening for hepatocellular carcinoma. Hepat Oncol 2014; 1: 161-163.
92. Shah SA, Cleary SP, Wei AC, Yang I, Taylor BR, Hemming AW, *et al.* Recurrence after liver resection for hepatocellular carcinoma: risk factors, treatment, and outcomes. Surgery 2007; 141: 330-339.
93. Sala M, Llovet JM, Vilana R, Bianchi L, Solé M, Ayuso C, *et al.* Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. Hepatology 2004; 40: 1352-1360.
94. Wu G, Wu J, Wang B, Zhu X, Shi X, Ding Y. Importance of tumor size at diagnosis as a prognostic factor for hepatocellular carcinoma survival: a population-based study. Cancer Manag Res 2018; 10: 4401-4410.
95. Saffroy R, Pham P, Reffas M, *et al.* New perspectives and strategy research biomarkers for hepatocellular carcinoma. Clin Chem Lab Med. 2007; 45:1169-1179.
96. Singal A, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, *et al.* Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther 2009; 30: 37-47.
97. Simmons O, Fetzer DT, Yokoo T, Marrero JA, Yopp A, Kono Y, *et al.* Predictors of adequate ultrasound quality for hepatocellular carcinoma surveillance in patients with cirrhosis. Aliment Pharmacol Ther 2017; 45: 169-177.
98. Moon AM, Weiss NS, Beste LA, Su F, Ho SB, Jin GY, *et al.* No Association Between Screening for Hepatocellular Carcinoma and Reduced Cancer-Related Mortality in Patients With Cirrhosis. Gastroenterology 2018; 155: 1128-1139.e6.
99. Sherman M. How to improve HCC surveillance outcomes. JHEP Rep 2019; 1: 460-467.
100. Walker M, El-Serag HB, Sada Y, Mittal S, Ying J, Duan Z, *et al.* Cirrhosis is under-recognised in patients subsequently diagnosed with hepatocellular cancer. Aliment Pharmacol Ther 2016; 43: 621-630.
101. Singal AG, Tiro J, Li X, Adams-Huet B, Chubak J. Hepatocellular Carcinoma Surveillance Among Patients With Cirrhosis in a Population-based Integrated Health Care Delivery System. J Clin Gastroenterol 2017; 51: 650-655.
102. Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Ward JW. Hepatitis C virus testing of persons born during 1945-1965: recommendations from the Centers for Disease Control and Prevention. Ann Intern Med 2012; 157: 817-822.
103. Dalton-Fitzgerald E, Tiro J, Kandunoori P, Halm EA, Yopp A, Singal AG. Practice patterns and attitudes of primary care providers and barriers to surveillance of hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol 2015; 13: 791-8.e1.
104. Marks RM, Ryan A, Heba ER, Tang A, Wolfson TJ, Gamst AC, Sirlin CB, Bashir MR. Diagnostic per-patient accuracy of an abbreviated hepatobiliary phase gadoxetic acid-enhanced MRI for hepatocellular carcinoma surveillance. AJR Am J Roentgenol 2015; 204: 527-535.
105. Goossens N, Singal AG, King LY, Andersson KL, Fuchs BC, Besa C, *et al.* Cost-effectiveness of risk score-stratified hepatocellular carcinoma screening in patients with cirrhosis. Clin Transl Gastroenterol 2017; 8: e101.
106. Mitchell DG, Bruix J, Sherman M, Sirlin CB. LI-RADS (Liver Imaging Reporting and Data System): summary, discussion, and consensus of the LI-RADS Management Working Group and future directions. Hepatology 2015; 61: 1056-1065.
107. Francica G, Borzio M. Status of, and strategies for improving, adherence to HCC screening and surveillance. J Hepatocell Carcinoma 2019; 6: 131-141.
108. Yang HI, Yuen MF, Chan HL, Han KH, Chen PJ, Kim DY, *et al.* Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. Lancet Oncol 2011; 12: 568-574.
109. Papatheodoridis G, Dalekos G, Sypsa V, Yurdaydin C, Buti M, Goulis J, *et al.* PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol 2016; 64: 800-806.
110. Lok AS, Seeff LB, Morgan TR, di Bisceglie AM, Sterling RK, Curto TM, *et al.* Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. Gastroenterology 2009; 136: 138-148.
111. Kawka M, Dawidziuk A, Jiao LR, Gall TMH. Artificial intelligence in the detection, characterisation and prediction of hepatocellular carcinoma: a narrative review. Transl Gastroenterol Hepatol 2022; 7: 41.
112. Jiménez Pérez M, Grande RG. Application of artificial intelligence in the diagnosis and treatment of hepatocellular carcinoma: A review. World J Gastroenterol 2020; 26: 5617-5628.