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Surveillance for patients at risk of hepatocellular carcinoma: how to improve its cost-effectiveness and expand the role of multidisciplinary tumor board?

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Abstract

Surveillance for hepatocellular carcinoma (HCC) improves early tumor detection, increases access to curative therapies, and reduces mortality by about 40%. Early diagnosis through surveillance is essential and should be extended to as many at-risk patients as possible to maximize the benefits of multidisciplinary tumor board evaluations. Current guidelines recommend semi-annual abdominal ultrasonography (US), with/without serum alpha-fetoprotein measurement, for patients with cirrhosis and certain subgroups of individuals with pre-cirrhotic chronic liver disease. However, the populations eligible for surveillance include subsets with varying degrees of HCC risk, which may change over time in some individuals. As risk level is a key determinant of cost-effectiveness, the rigid, "one-size-fits-all" strategy appears inadequate. Moreover, certain non-cirrhotic patients - particularly those with advanced liver fibrosis - are currently excluded from surveillance but may benefit from risk stratification to identify those for whom surveillance would be cost-effective. Surveillance strategies must also consider potential harms, and the limitations of US as a screening test. In response, alternative approaches such as biomarkers-based tests and abbreviated magnetic resonance imaging are under investigation. This article reviews the literature advocating for a transition from the current "one-size-fits-all" approach to programs tailored to

individual oncological risk (risk-stratified surveillance) or those that also consider the main factors (sex, etiology, phenotype) that influence screening test performance (precision surveillance). Additionally, it presents a seminal proposal for a risk-stratified algorithm designed to optimize cost-effectiveness and the risk-benefit balance by integrating variable screening intervals and modality selection.

Keywords: Surveillance, hepatocellular carcinoma, precision surveillance, DAA, HBV, HCV, HCC risk

CURRENT SCENARIO

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related mortality worldwide and the primary cause of death among patients with compensated cirrhosis, which represents the main predisposing condition for this tumor[1]. The major etiologies of HCC include hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-associated liver disease (ALD), and metabolic dysfunction-associated steatotic liver disease (MASLD). HCC is frequently diagnosed at an advanced stage, where only palliative therapies with limited efficacy are available. To address this issue, national and international guidelines recommend routine surveillance for patients at risk of developing HCC, primarily through semi-annual abdominal ultrasonography (US), with or without serum alpha-fetoprotein (AFP) measurement. Although most supporting evidence comes from non-randomized studies - due to ethical concerns and patient reluctance to be assigned to a no-surveillance arm[2] - a meta-analysis of 59 reports involving over 145,000 patients consistently supported this recommendation. The findings demonstrate that surveillance increases the rate of early diagnosis, improves access to curative treatments, and significantly reduces mortality (HR: 0.67, 95%CI: 0.61-0.72) compared to patients diagnosed outside of surveillance programs[3].

The growing complexity of HCC management, driven by continuous advancements in diagnostic and therapeutic tools, underscores the critical role of multidisciplinary tumor board (MTB) involvement. Despite the lack of randomized studies and possible interference by referral bias, accumulating evidence suggests that multidisciplinary management enhances early-stage HCC detection and improves patient survival, especially in complex cases[4-6]. By anticipating the diagnosis of tumors at an asymptomatic stage, surveillance further amplifies the benefits of multidisciplinary management by broadening the therapeutic scenario available for MTB evaluation[7]. Additionally, determining the most appropriate post-treatment surveillance strategy for HCC recurrence remains an important issue requiring further research and, in the meantime, should be established by MTB.

Current international guidelines recommend "conventional" surveillance (US ± AFP) for all patients with cirrhosis, regardless of etiology, except for non-transplantable Child-Pugh C patients (for whom surveillance is deemed futile[8]). Surveillance is also advised for selected populations with non-cirrhotic viral hepatitis or MASLD, albeit with some differences in the selection criteria[9-15] [Table 1]. The European Association for the Study of the Liver (EASL)[7] advocates surveillance for HBV patients with a PAGE-B score of ≥ 10, and suggests considering surveillance for HCV patients with advanced (F3) fibrosis as per the METAVIR score. This approach is also endorsed by the American Association for the Study of Liver Diseases (AASLD) guidelines[10]. These recommendations are informed by cost-effectiveness analyses and risk-benefit assessments, which are fundamentally determined by three factors: (1) the performance of the adopted surveillance test(s); (2) the survival gain achievable with available tumor therapies; (3) the magnitude of HCC risk[16,17].

However, patient groups deemed eligible for surveillance under current guidelines consist of subgroups with varying risks of HCC development. For instance, among patients with cirrhosis, the Toronto HCC risk

Table 1. Recommendations of Western and Eastern guidelines for the surveillance of patients at risk of developing hepatocellular carcinoma

Condition	AASLD guidelines	EASL guidelines	APASL guidelines	Chinese guidelines	JSH-HCC guidelines	KLCA-NCC guidelines	CASL guidelines
Cirrhosis	Surveillance recommended for patients with Child-Pugh A or B cirrhosis; for patients with Child-Pugh C cirrhosis only if they are candidates for liver transplantation	Surveillance recommended for patients with Child-Pugh A or B cirrhosis; for patients with Child-Pugh C cirrhosis only if they are awaiting liver transplantation	Surveillance recommended	Surveillance recommended	Surveillance recommended	Surveillance recommended	Surveillance recommended for patients with Child-Pugh A or B cirrhosis; for patients with Child-Pugh C cirrhosis only if they are awaiting liver transplantation
Chronic hepatitis B without cirrhosis	Surveillance recommended for men over 40 years of age from endemic areas, women over 50 years of age from endemic areas, individuals from Africa, individuals with a family history of HCC, and individuals with a PAGE-B score ≥ 10	Surveillance recommended for patients at intermediate or high risk of HCC (PAGE-B score ≥ 10)	Surveillance recommended for Asian men over 40 years of age, Asian women over 50 years of age, African American individuals over 20 years old, and individuals with a family history of HCC	Surveillance recommended	Surveillance recommended	Surveillance recommended	Surveillance recommended for Asian men over 40 years of age, Asian women over 50 years of age, African American individuals over 20 years old, and individuals with a family history of HCC
Chronic hepatitis C without cirrhosis	Routine surveillance not recommended	Surveillance may be considered for individuals with F3 fibrosis	Surveillance recommended for patients with cured HCV infection regardless of the fibrosis stage	Surveillance recommended	Surveillance recommended	Surveillance recommended	No specific recommendations
MASLD without cirrhosis	Routine surveillance not recommended	Surveillance may be considered for patients with F3 fibrosis	No specific recommendations	Surveillance may be considered for patients with FIB-4 score > 1.30 (moderate or advanced fibrosis)	Surveillance should be considered in male NAFLD with F2 or F3 fibrosis, and female NAFLD with F3 fibrosis	No specific recommendations	No specific recommendations

AASLD: American Association for the Study of Liver Diseases; EASL: European Association for the Study of the Liver; APASL: Asia-Pacific Association for the Study of the Liver; CASL: Canadian Association for the Study of the Liver; DAA: directly acting antivirals; JSH: Japan Society of Hepatology; KLCA-NCC: Korean Liver Cancer Association- National Cancer Center Korea; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; MASLD: metabolic dysfunction-associated steatotic liver disease; NAFLD: non-alcoholic fatty liver disease.

index calculator - validated in European and Chinese patients - stratifies individuals into three risk categories: low, intermediate, and high, based on age, sex, etiology, and platelet count. The cumulative 10-year incidence of HCC in these subgroups is 2.7% (approximately 0.3% per year), 9.8% (approximately 1.0% per year), and 32.1% (approximately 3.2% per year), respectively[18]. Similarly, in a cohort of more than 18,000 patients with chronic HBV infection, HCC progression rates - estimated using the AASLD criteria based on age, sex, and disease activity - varied widely. The annual incidence of HCC ranged from 0.40% to 8.83% in patients with cirrhosis, and from 0.04% to 2.19% in those without cirrhosis[19]. In virus-suppressed HBV patients beyond the threshold for cost-effective surveillance indicated by EASL guidelines (PAGE-B score > 10), the probability of developing HCC greatly increases beyond score 18 (from 0.60% to 3.40% per year)[20]. Furthermore, a study testing the predictive power of elastography in 866 HCV patients found that annual HCC incidence ranged from 0%

to 11% in patients with liver stiffness values ≤ 10 kPa and rose to 14.4% in those with values > 25 kPa[21]. This considerable intra-group variability raises the question of whether the "one-size-fits-all" strategy recommended by some guidelines and ordinarily adopted in clinical practice is indeed the best option available.

The decision to implement surveillance must consider that the "functional cure" of HBV infection (undetectable viremia) achieved with nucleos(t)ide agents and the eradication of HCV infection with direct-acting antivirals (both attainable in almost all treated subjects) substantially reduce - albeit do not eliminate - the risk of HCC compared to untreated or treatment-resistant cases[22-25]. Moreover, studies have shown a time-dependent decrease in HCC risk after the cure of viral infections. In HBV-infected patients with pre-treatment cirrhosis undergoing antiviral therapy, the annual incidence of HCC was 3.2% during the first 5 years, and 1.6% in the subsequent quinquennia[22]. In HCV-infected patients with cirrhosis, the annual incidence of HCC gradually declined from 3.8% to 1.4% over the 7 years following the infection cure[26]. Therefore, it can be inferred that patients with cirrhosis should be kept under surveillance for at least 10 years after the infection cure. Conversely, in non-cirrhotic patients with chronic HBV or HCV infection, the annual incidence of HCC is low, and the risk is reduced by approximately 70% following effective antiviral therapy. Consequently, the cost-effectiveness threshold for surveillance is generally not met (or is missed after infection cure) for most of these patients[27]. In high-income countries, where nearly all known cases of chronic HBV or HCV infection are currently treated with antiviral therapy, the proportion of cured or virologically suppressed patients will soon exceed that of patients with active infection. In the United States, for example, the number of individuals cured of HCV is projected to increase from 106,000 in 2012 to 649,000 by 2030, with the percentage of these cases among surveillance candidates rising from 8.5% to 64.6%[28]. Given this evolving landscape of viral liver disease and the fact that the HCC risk is a key determinant in cost-effective surveillance, it is appropriate to evaluate whether, how, and for how long patients should be monitored following the cure or suppression of their infection.

Patients with alcohol-related cirrhosis have a lower risk of HCC development (2.9%) compared to those with viral hepatitis[29]. This risk decreases by 6%-7% per year following alcohol withdrawal; however, it takes more than 20 years for their risk to match that of non-drinkers[30].

Patients with non-cirrhotic MASLD pose an even greater dilemma due to the widespread prevalence and heterogeneity of this condition. In this context, two key considerations arise. First, over one-fourth of HCC cases occur in the pre-cirrhotic stage, and approximately one-fourth of patients without cirrhosis have a low FIB-4 score[31]. This suggests that metabolic factors (such as obesity, diabetes, metabolic syndrome, and insulin resistance) and genetic factors (including single nucleotide polymorphisms in *PNPLA3*, *TM6SF2*, *GCKR*, and *MBOAT7*) contribute to HCC pathogenesis independently of fibrosis progression. Second, the incidence of HCC in the MASLD population is relatively low (ranging from 0.08 to 0.63 per 1,000 person-years), making universal surveillance in this group not cost-effective[32]. Nonetheless, given the established association between annual HCC incidence and fibrosis stage, non-invasive methods for assessing baseline liver fibrosis (or its progression over time) through FIB-4 score calculation or liver stiffness measurement with transient elastography may help stratify the HCC risk, which achieves a figure of 1%-1.5% per year in MASLD-related cirrhosis[33-35]. Although significant differences in risk exist even among cirrhotic patients (which are overlooked when these patients are aggregated into a single group), the most urgent unmet need is the availability of validated risk calculators for patients with pre-cirrhotic MASLD, who constitute the vast majority of the MASLD population.

Although there is general agreement that surveillance should continue in patients with cirrhosis after the cure/control of viral infection or alcohol withdrawal, the indications for pre-cirrhotic patients are rather vague and somewhat discordant. Therefore, non-cirrhotic patients with eradicated or suppressed infections and those with MASLD - particularly those with advanced fibrosis - would benefit from risk stratification to identify those at the highest risk for whom surveillance would be cost-effective. In the meantime, decisions regarding surveillance in patients with advanced fibrosis should be decided on a *case-by-case* basis[9,36], considering additional factors such as age, sex, obesity, type 2 diabetes, ethnicity, family history of HCC, detectable viremia, alcohol intake, HBV/HCV coinfections, human immunodeficiency virus coinfection, the presence of hyperplastic liver nodules, and exposure to environmental carcinogens[37], as well as in patients with MASLD, genetic polymorphisms in *PNPLA3*, *TM6SF2*, and *GCKR*, which are involved in determining the risk of HCC[32,36,38].

COST AND HARMS OF SURVEILLANCE

Other important factors to consider are the negative aspects of surveillance, such as costs and potential harms. These include: (1) organizational costs to the healthcare system, and costs to the patient (absence from work, travel expenses for accessing diagnostic centers); (2) the risk of overdiagnosis, i.e., the detection of a subclinical disease that will not significantly affect survival); (3) false-positive results, leading to unnecessary costs and exposure to confirmatory tests such as computed tomography (CT), magnetic resonance imaging (MRI), and liver biopsy; (4) false-negative results, leading to a delayed diagnosis; (5) adverse psychological effects (apprehension, anxiety, stress, and depression) stemming from the patient's cognizance of being at high risk for cancer development and from false-positive or indeterminate surveillance results. False-positive results occur in 27% of cirrhotic patients over a 3-year period, and physical harms are reported in 9%-27% of surveyed patients, with most being mild in severity[3,16,39]. Only two recent studies have addressed the financial and psychological harms, showing that patients' financial distress is exacerbated by both true- and false-positive results, and false-positive and indeterminate results induce a mild increase in depressive symptoms[40,41]. In general, the risk/benefit ratio of surveillance is less favorable in patients with a low risk of developing HCC than in those at high risk[42]. Strengthening clinical guidance and developing more refined strategies addressing these issues will help reduce unnecessary tests and treatments. In view of these negative aspects, the British Guidelines recommend discussing the risks of HCC and the potential harms of surveillance prior to enrolling a person in this procedure[43].

PERFORMANCE OF ROUTINE SURVEILLANCE TESTS

The performance of US is highly dependent on the operator's expertise and scrupulousness, as well as several patient-related factors that can reduce its sensitivity. In particular, US performs worse in patients with steatotic livers or obesity[44,45], and this drawback is particularly alarming given the increasing prevalence of these conditions. A meta-analysis has shown that the overall sensitivity of US for detecting HCC in cirrhotic livers is > 80%, but it drops to approximately 50% for tiny lesions (< 2 cm), which represents the optimal target for surveillance[46]. This study also found that adding AFP to US increases the sensitivity of surveillance to 63%, at the expense of an 8% reduction in specificity. It is also worth noting that more than 50% of tiny tumors (≤ 2 cm) are associated with low AFP levels (< 20 ng/mL)[47]. However, AFP demonstrates higher specificity in non-viral diseases or in cases where the necroinflammation flares of viral diseases are blunted by antiviral therapy[48-51], making it possible to adopt AFP cut-offs lower than the traditional 20 ng/mL to improve its performance in non-viral patients and those treated with antiviral treatment[52]. Furthermore, monitoring changes in biomarker values over time can enhance their performance compared to a standalone measurement[53,54].

Despite the drawbacks of US-based surveillance, its adoption is supported due to the unfeasible routine use of CT and MRI as screening tests because of their high costs, less accessibility, and concerns about associated risks (radiation exposure, adverse reactions to contrast agents).

IMPLEMENTATION OF SURVEILLANCE AND PATIENT COMPLIANCE IN CLINICAL PRACTICE

The success of HCC surveillance also depends on the systematic implementation of the procedure for all at-risk patients, and their adherence to the recommended program. Unfortunately, these factors are still suboptimal. A multicenter cohort study revealed that, in the United States, merely 14% of at-risk patients underwent semi-annual surveillance, with about two-thirds of the cohort not participating in any surveillance program before HCC diagnosis[55].

Regarding patient adherence to recommended programs, a meta-analysis of 22 studies involving 19,511 patients reported an overall adherence rate of 52%, with lower rates observed in non-cirrhotic patients compared to cirrhotic patients[56]. Costs, difficulties associated with scheduling US, and transportation issues are reported by patients as the main barriers to adhering to US-based surveillance[17]. Indeed, the requested access to qualified (and sometimes distant) services for instrumental assessments significantly reduces adherence, particularly among cured or non-viremic patients, conditions that greatly reassure patients (and physicians) regarding disease progression and oncologic risk. This issue is in the decreasing percentage of patients who continue follow-up after the cure of HCV infection[57]. To optimize the benefits of surveillance in real-world settings, strategies aimed at improving patient adherence, such as the implementation of policies to raise awareness about the value of surveillance and the incorporation of scheduled mail/telephone message reminders, should be included in future risk-based programs.

Maintaining the patient under proper surveillance is indeed a key determinant of its benefit (and cost-effectiveness), and this should be considered alongside the risk of HCC when designing personalized surveillance plans. The risk of failure due to poor compliance may be mitigated by tailoring the interval between tests (6 months *vs.* 12 months) and selecting the appropriate test type (imaging *vs.* biomarkers) for some "difficult" patients, adhering to the principle that "something is better than nothing".

Lastly, it must be acknowledged that malfunctions in downstream procedures, such as diagnostic and therapeutic delays, and underutilization of curative treatments, decrease the overall benefits of surveillance[58,59] [Figure 1].

POTENTIAL INNOVATIVE SURVEILLANCE TESTS

Two complementary strategies are being explored to surmount or mitigate the aforementioned limitations of conventional surveillance:

(1) The use of serum biomarker panels, which obviates the need for access to centers with qualified US services (which represents a major barrier to maintaining appropriate adherence to imaging-based surveillance) and the subjectivity of US results. Biomarker-based surveillance becomes particularly appealing in areas with limited imaging facilities. Potentially useful biomarkers include: GALAD (Gender, Age, Lectin-bound AFP, AFP, Des-carboxy prothrombin), its derivative BALAD-2[60], PAaM (age, sex, albumin, bilirubin, platelet count, AFP)[61], microRNAs, extracellular vesicles, methylation markers, and cell-free DNA[10]. However, with the exception of AFP, no other biomarker has completed all five phases required for the validation of cancer screening biomarkers[62]. Only PAaM and GALAD have successfully reached phase III[61,63], and GALAD is currently under evaluation in a phase IV trial in which US is the

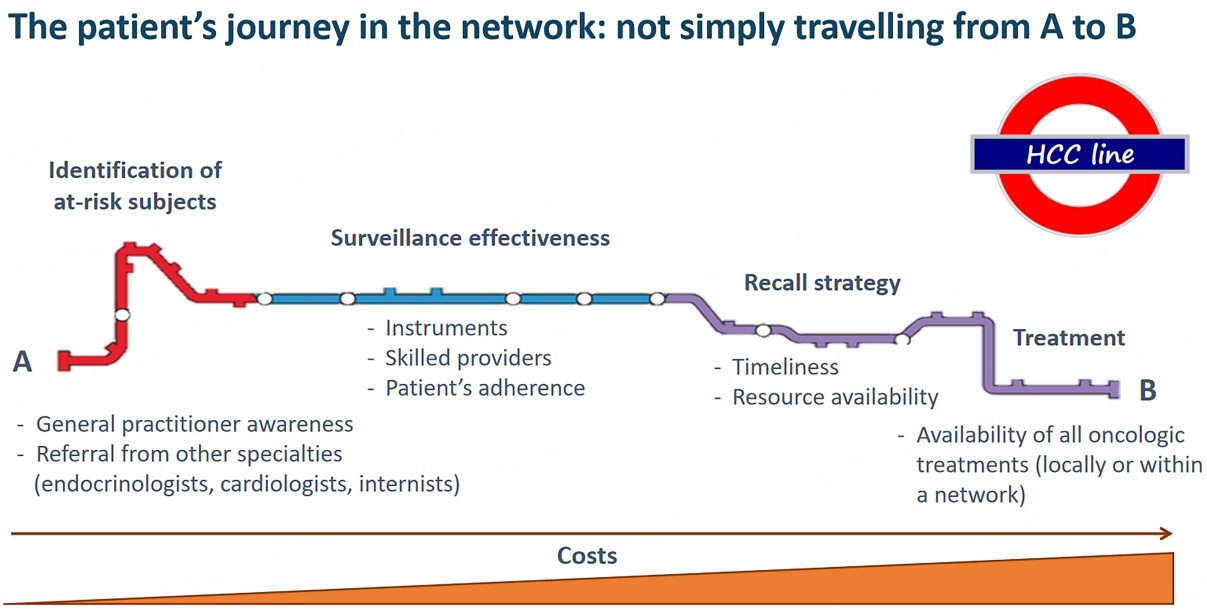


Figure 1. The patient's journey in the surveillance network: not simply traveling from A to B.

comparator[64]. Nevertheless, the era when blood-based biomarkers will replace US is approaching[65].

(2) The use of non-contrast "abbreviated" MRI (AMRI) in patients at the highest risk of HCC, which reduces acquisition time from approximately 45 to 12-15 min while maintaining excellent diagnostic accuracy for small lesions[66-68]. A retrospective study indicates that AMRI is cost-effective for patients with compensated cirrhosis and an annual HCC risk > 3%[69]. If ongoing phase IV trials comparing AMRI to US validate AMRI as a cost-effective surveillance tool, it could be routinely employed as a "niche" solution for patients at the highest risk of HCC, outperforming conventional procedures in terms of cost-effectiveness[70].

THRESHOLDS FOR COST-EFFECTIVENESS SURVEILLANCE

The cost-effectiveness of any procedure can be calculated with statistical models that provide a useful framework for choosing strategies aligned with local economic resources.

Based on an Incremental Cost-Effectiveness Ratio (ICER) of $50,000/year of quality-adjusted life year (QALY), the minimum annual incidence of HCC required for cost-effective surveillance is set at 1.3%; this threshold drops to 0.82% if the procedure is performed annually[71]. Notably, a review of available studies revealed that a significant proportion (up to 70%) of patients cured of HCV or functionally cured of HBV do not reach these thresholds[72]. However, increasing the willingness-to-pay up to $100,000/QALY or $150,000/QALY would make surveillance cost-effective at annual HCC incidences of 0.70% and 0.40%, respectively[73]. In line with a more permissive viewpoint, the AASLD has recently proposed a risk threshold of 0.8%[10]. These "lowered" thresholds would result in a significantly greater percentage of virologically cured or suppressed patients being eligible for surveillance, albeit with a considerably higher cost per QALY gained.

Other factors to consider include the economic resources of national health systems and the cost of surveillance tests, which vary significantly between countries. For example, the cost of liver US is about five times higher in the United States than in Asia, and the costs of CT and MRI also vary across countries.

Therefore, it is unrealistic to expect a universal agreement on a given cost-effectiveness threshold. Moreover, within the same country, rich people may demand a lower cost-effectiveness threshold than poorer people. To achieve an ethical policy, efforts should be made to reduce the cost of surveillance tests as much as possible.

Lastly, the cumulative cost of surveillance tests increases with the duration of the procedure. This issue is one of the factors supporting the design of risk-stratified surveillance (see below), as the higher the risk, the shorter the surveillance period needed to detect tumor occurrence.

FUTURE ADVANCEMENTS

The implementation of widespread surveillance programs relies more on general practitioners and physicians than on HCC specialists, and, as stated above, diagnostic and therapeutic delays, along with the underutilization of curative treatments, diminish the benefits of surveillance[58,59]. To further improve the benefits of timely HCC management, an ideal collaboration between non-HCC specialists and MTB should allow general practitioners to access MTB meetings online to discuss patients with suspected or proven HCC, bypassing the need for preliminary evaluation by a HCC specialist.

From a cost-effectiveness and risk/benefit perspective, surveillance programs should evolve from a "one-size-fits-all" strategy to more "personalized" solutions. Future programs should be based on individual oncological risk (risk-stratified surveillance) and, in addition, consider the main factors (sex, etiology of liver disease, phenotype) that influence the performance of screening tests (precision surveillance) [Figure 2].

The goals of personalized surveillance are to:

- reduce the use of low-utility resources and exposure to procedural risks in low-risk patients;
- improve the rate of early tumor detection;
- maintain (or even improve) sustainable cost-effectiveness ratios.

In line with this position, the EASL recently released a policy statement endorsing the implementation of "risk-stratified" surveillance[74], which has been shown to improve QALY and cost-effectiveness in other neoplasms, such as breast cancer[75]. The EASL document states that MRI should be used for the 5%-10% of patients considered at highest risk, while intermediate-risk patients should receive conventional surveillance, and low-risk individuals - presumably including up to 20% of patients with cirrhosis - may not need surveillance at all[74]. Some key indications for a risk-based strategy have already been proposed by others[76]. For example, the Japanese nationwide program of risk-stratified surveillance detected 60%-65% of HCCs at an early stage (BCLC A), compared to just 10%-30% globally, further supporting this approach[77]. Additionally, a recent prospective study compared risk-stratified surveillance based on the GES score with conventional surveillance in two large cohorts of HCV patients with advanced liver disease who achieved sustained viral response[78]. In the risk-stratified procedure, low-risk patients were monitored with US and AFP annually, intermediate-risk patients every 6 months, and high-risk patients every 2-3 months. This strategy improved early-stage detection and the amenability to curative treatment compared to the conventional procedure.

The updated Chinese guidelines for the surveillance of patients at risk of HCC have recently endorsed risk-stratified surveillance[37], proposing the following schedule: (1) patients at low risk (estimated annual incidence of HCC < 1%): conventional surveillance (US plus AFP) once every 1 year or more; (2) patients at

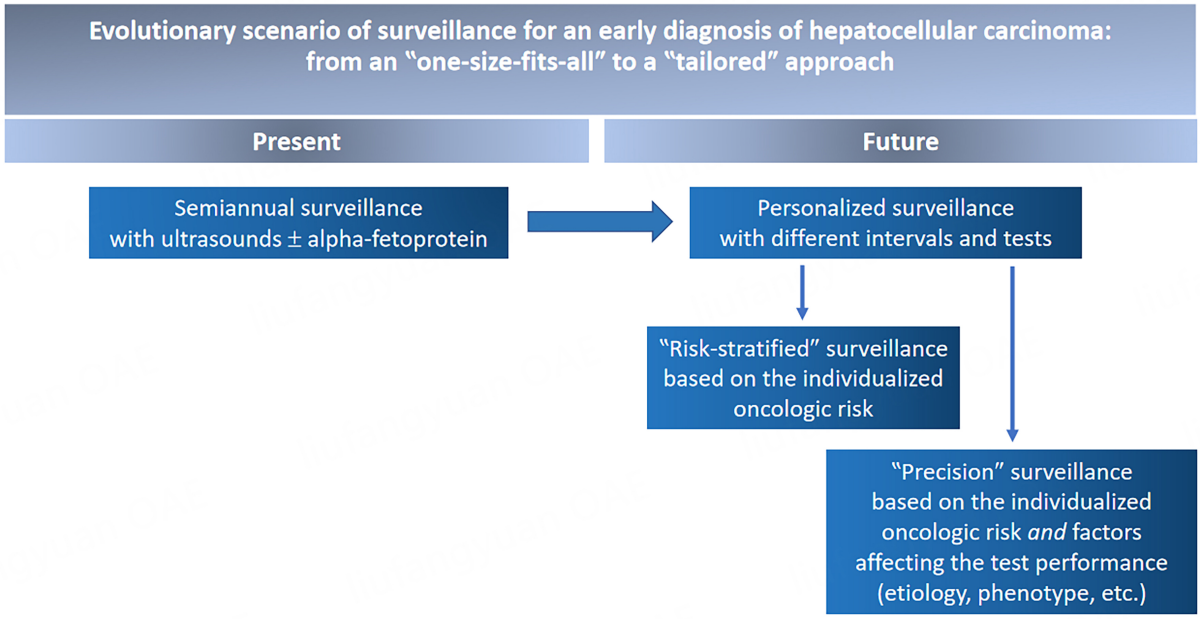


Figure 2. Evolutionary scenario of surveillance for an early diagnosis of hepatocellular carcinoma: transition from a "one-size-fits-all" strategy to a patient-tailored approach.

intermediate risk (estimated annual incidence of HCC 1%-3%): conventional surveillance once a year; (3) patients at high risk (estimated annual incidence of HCC 3.1%-6%): conventional surveillance every 6 months; (4) patients at extremely high risk (estimated annual incidence of HC > 6%): conventional surveillance every 3 months, plus CT and MRI every 6-12 months. In this proposal, risk class attribution is based on several demographic and clinical factors, combined with the results of some risk calculators, rendering the categorization into the appropriate risk class rather complex. Additionally, the authors exclude patients defined as "risk-free" from surveillance, without specifying the risk threshold below which exclusion should take place.

The 2021 Japanese guidelines also propose a model of risk-stratified surveillance. Patients eligible for this procedure are those with at least one of the following conditions: cirrhosis, chronic hepatitis B, or chronic hepatitis C[13]. The surveillance protocol includes abdominal US and tumor marker measurements. Among high-risk patients, those with viral cirrhosis are considered at extremely high risk. Recommended surveillance intervals are: 6 months for the high-risk group and 3 to 4 months for the extremely high-risk group. For the latter group, the surveillance protocol may be supplemented with CT/MRI. Unlike the Chinese guidelines, this proposal does not include a low-risk group, and, as discussed above, the two risk classes encompass patients with very different annual incidences of HCC, which can be evaluated with specific risk calculators.

RISK CALCULATORS

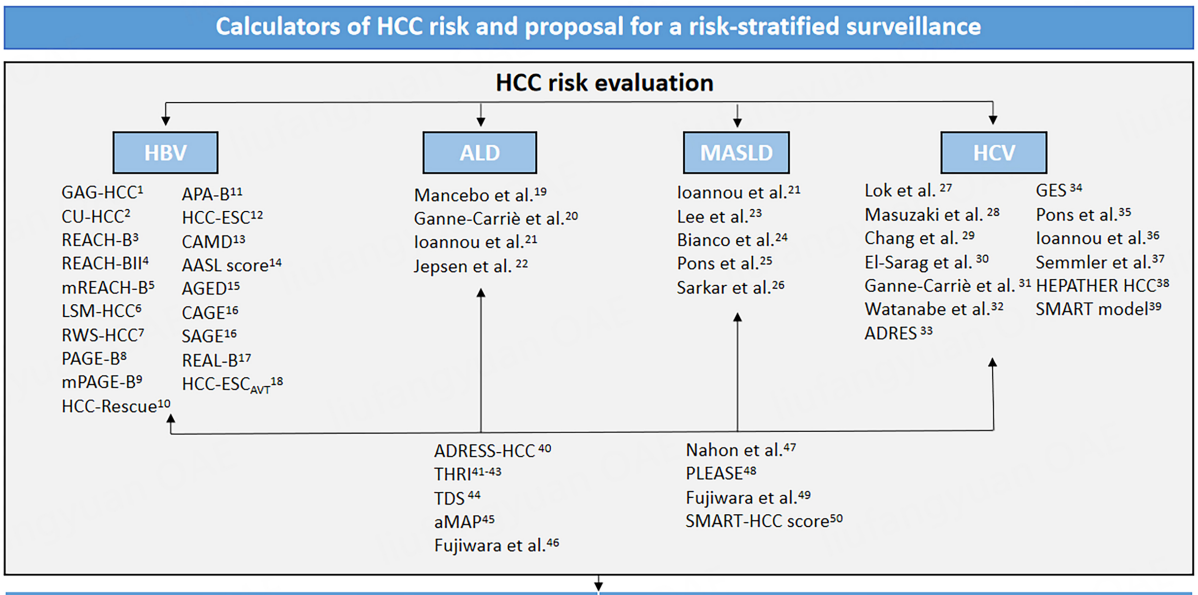
Risk-stratified surveillance means that the decision to screen, the type of screening test, and the interval between tests are dictated by the individual's oncological risk that should be assessed by reliable "calculators". An ideal risk calculator should be simple yet comprehensive, incorporating routinely measured parameters and developed using a large patient cohort with internal and external validation, possibly including prospective data. Numerous validated calculators are currently available, with some being "generalists" that do not account for the etiology of liver disease, while others are "etiology-specific" (also

including patients after the cure or control of the infection) [Figure 3]. These calculators typically rely on demographic characteristics, virologic factors, liver function tests, liver stiffness measurements, fibrosis scores, and signs of portal hypertension. Some also include secretome signatures. They categorize patients into low-, moderate-, or high-risk groups for HCC. A detailed description of these calculators and their performance is beyond the scope of this article but can be found in dedicated reviews[72,78,79,80]. It is important to note that although metabolic disorders (such as obesity and diabetes) are recognized risk factors for HCC in viral and alcohol-related diseases, and social drinking impacts MASLD and viral diseases[81,82], only three risk calculators[83,84,85] incorporate a metabolic parameter. Additionally, only one[86] accounts for active alcohol intake, and another includes both variables[87]. The omission of these variables could have decreased the accuracy of the available calculators, suggesting that room for future improvement in their performance exists. Another hot point is the variation in risk group prevalence obtained with different calculators in the same population[78], indicating that, although several validated calculators enable risk stratification, the optimal approach remains uncertain. Further studies, possibly based on large-scale prospective cohorts, will help scientific associations determine the most appropriate risk calculator(s) for clinical practice in different patient populations.

The implementation of "precision" surveillance is inherently complex, as several factors influencing the efficacy of surveillance tests must be considered, potentially hindering its application in clinical practice. Nevertheless, we anticipate that Artificial Intelligence will provide substantial assistance in navigating this complexity, thus facilitating the implementation of such an innovative periodic screening. Appropriately, a recent review highlights the transformative potential of Artificial Intelligence in refining oncology care and maintaining the efficacy of MTB amid increasing clinical demands[88].

Since personalized surveillance strategies targeting different risk groups outperform the current standard of care in terms of cost-effectiveness[89], Figure 3 presents a proposed personalized, "risk-stratified" surveillance model, which is based on available cost-effectiveness data from various screening methods, with the following assumptions: (1) an annual incidence of HCC < 0.6%-0.8% does not justify the procedure in terms of cost-effectiveness and risk/benefit; (2) more frequent screening intervals (transitioning from annual to semi-annual) and the use of more expensive but more efficient tests may be acceptable for patients at higher oncological risk, as the number of individuals needing surveillance to detect one tumor ("number needed to survey") decreases as risk levels increase. According to available evidence, up to 70% of patients with controlled or cured viral disease would not enter this surveillance program, sparing them from the physical and psychological burden of screening while reallocating economic resources to more fruitful healthcare initiatives[72]. However, the proposed stratification thresholds should be adjusted according to local sustainable willingness-to-pay, which differs significantly across geopolitical areas. Furthermore, as some risk factors inevitably worsen over time (e.g., aging), while others may improve with antiviral therapy, lifestyle changes, and alcohol abstinence (e.g., liver disease activity, liver stiffness, and portal hypertension), HCC risk should be retested systematically every 1-2 years.

Two final considerations are essential: first, before personalized surveillance can be implemented in clinical practice, its cost-effectiveness and risk/benefit ratio should be tested in randomized controlled trials or large cohort studies comparing it with conventional surveillance; second, risk stratification is only one aspect of improving surveillance, and a collaborative effort among stakeholders, including policy-makers, scientific organizations, healthcare practitioners, and patient caregivers, is crucial to improving patient adherence and maximizing the benefits of any surveillance program.



HCC risk per 100 patients/year	Surveillance strategy
<0.60/0.80	No surveillance
0.61/0.81- 1.30	Annual ultrasounds *
1.31 – 2.00	Semi-annual ultrasounds ± alpha-fetoprotein *
2.01-3.00	Semi-annual ultrasounds + alpha-fetoprotein *
>3	AMRI

Figure 3. *If ongoing studies confirm the equivalence or superiority of biomarkers (i.e., GALAD) over US, they could replace US in surveillance. Risk calculators of hepatocellular carcinoma and proposal for risk-stratified surveillance. Pertinent references are provided in the Supplementary Materials. ALD: Alcoholic liver disease; HBV: hepatitis B virus; HCV: hepatitis C virus; HCC: hepatocellular carcinoma; MAFLD: metabolic-associated steatotic liver disease; GALAD: gender, age, lectin-bound AFP, AFP, des-carboxy prothrombin.

In conclusion, while surveillance for HCC in at-risk patients is universally accepted as a tool to improve prognosis once cancer develops, the current challenge lies in generating sufficiently robust evidence to support the clinical adoption of personalized surveillance, which can enhance the cost-effectiveness of the current standard of care and, at the time of HCC detection, provide the broadest possible therapeutic options for MTB decision making.

DECLARATIONS

Authors' contributions

Contributed to the conception and design of the study: Lani L, Trevisani F
Contributed to the final version of the study: Giannini EG, Zaccherini G

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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