Thematic Miniseries

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HCC surveillance after SVR in patients with F3/F4 fibrosis

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Summary

HCV eradication by antiviral treatment reduces but does not eliminate HCC risk. Patients with established cirrhosis require HCC surveillance "indefinitely" after sustained virologic response (SVR) because they appear to have a high risk of HCC even many years after SVR. Patients without established or known cirrhosis may still require surveillance after SVR if they have a sufficiently high HCC risk. In all patients who achieve SVR, the key question is how we can reliably estimate HCC risk, and the change in HCC risk over time, to determine whether the patient might benefit from HCC surveillance. HCC risk is one of the most important factors that should inform decisions of whether and how to screen for HCC. Promising strategies for estimating HCC risk include simplified scoring systems (such as fibrosis-4), liver elastography and multivariable HCC risk calculators. Such tools may enable risk stratification and individualised, risk-based surveillance strategies ("precision HCC screening") in the future.

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Introduction

Eradication of HCV by antiviral treatment reduces but does not eliminate the risk of hepatocellular carcinoma (HCC). In particular, patients with advanced fibrosis (F3) or cirrhosis (F4), have a substantial residual risk of HCC that remains after viral eradication. In patients with cirrhosis, the residual HCC risk after sustained virologic response (SVR) is high enough that there is currently universal agreement that these patients need to continue HCC surveillance. Patients with F3 fibrosis are difficult to stage reliably in a non-invasive manner and have a lower HCC risk than those with cirrhosis, making HCC surveillance decisions harder. In all patients who achieve SVR, the key question is how we can reliably estimate HCC risk, since HCC risk is the key determinant of the cost-effectiveness of screening. Exciting frontiers for current and future research are how HCC risk might decline (or not) as years accrue after HCV eradication, how to estimate HCC risk in individual patients and how to incorporate estimates of HCC risk into risk-based, individualised surveillance strategies. Patients, providers and healthcare systems also desperately need guidance as to whether HCC surveillance can ever be safely discontinued after HCV eradication in patients with cirrhosis, or whether these patients are committed to lifelong surveillance.

SVR reduces HCC risk, but a substantial risk persists

Randomised controlled trials of antiviral treatment assessing long-term outcomes, such as HCC risk reduction, have never been performed for ethical reasons. However, well-conducted observational studies accounting for confounders, selection bias and immortal time bias overwhelmingly demonstrate that HCV eradication by antiviral treatment reduces HCC risk dramatically (by up to 70%[1–5]). Patients who achieved SVR have lower HCC risk than those who fail to achieve SVR or remain untreated. In fact, HCV antiviral treatment can be regarded as one of the best forms of HCC "chemoprevention" currently available.

Why does HCV eradication reduce HCC risk?

It is likely that multiple mechanisms are at play (Fig. 1). First, persistent HCV infection causes progression of fibrosis and cirrhosis, which is ultimately the strongest risk factor for HCC. Eradication of HCV may stop progression or even cause regression of fibrosis and even early cirrhosis, thereby reducing HCC risk. Second, HCV-induced inflammatory responses drive hepatocarcinogenesis indirectly; these responses are eliminated after SVR.[6] Third, HCV drives hepatocarcinogenesis directly via its proteins or transcripts (even though it is an RNA virus without a DNA intermediate and does not integrate into the host genome, in contrast to HBV). The HCV core protein plays a role in the downregulation of tumour suppressor genes, promoter activation of oncogenes, dysregulation of apoptosis, reactive oxidation species formation and immune modulation.[7] HCV also induces epigenetic changes that promote HCC, such as hypermethylation of tumour suppressor genes and alteration of micro-RNA profiles implicated in HCC.[8] In fact, patients with HCV-related cirrhosis have 2–3× greater risk of HCC than patients with alcohol-related or non-alcoholic fatty liver disease-related cirrhosis, even after adjusting for other predictors

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Key point

HCV eradication (SVR) reduces but does not eliminate HCC risk.

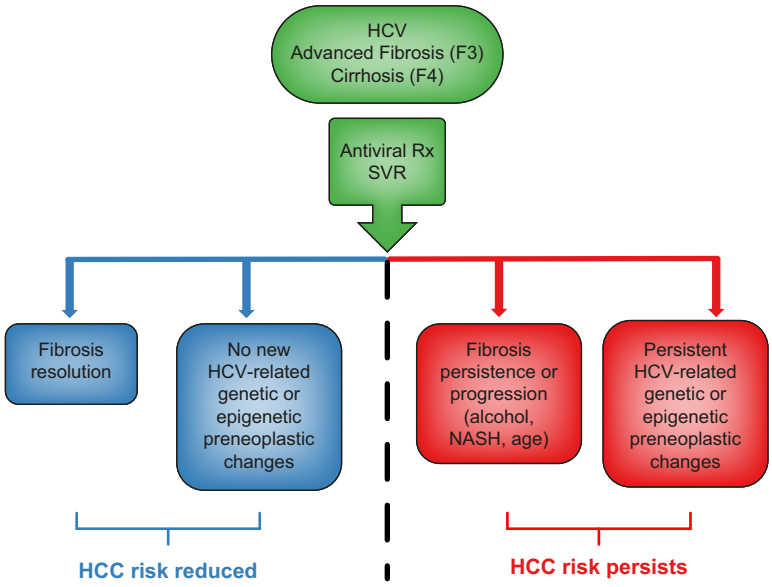

Fig. 1. Schematic representation of how SVR reduces HCC risk while a residual risk persists. HCC, hepatocellular carcinoma; SVR, sustained virological response.

Key point

Patients with established cirrhosis require HCC surveillance "indefinitely" after SVR.

of HCC,[9] which may reflect the direct carcinogenic effects of the virus. Therefore, HCV eradication reduces HCC risk by eliminating the direct carcinogenic effects of the virus.

Why does some residual HCC risk persist after HCV eradication?

Two analogous mechanisms may be at play (Fig. 1). First, advanced fibrosis or cirrhosis may take a long time to resolve after HCV eradication, during which time patients will continue to have a residual HCC risk. Furthermore, in some patients with advanced cirrhosis, the liver may be incapable of remodelling, while in other patients, fibrosis may progress due to other concomitant hepatotoxic injuries (*e.g.* alcohol, or non-alcoholic steatohepatitis) despite HCV eradication. Second, HCV-related preneoplastic genetic and epigenetic changes and monoclonal micronodules that occurred before SVR may persist "indefinitely" after SVR,[10] predisposing a patient to develop HCC many years after SVR.

It is a critical and clinically relevant fact that while many complications of portal hypertension are largely eliminated after SVR, HCC remains a considerable risk.

Controversy about HCC surveillance after SVR in patients with cirrhosis (F4) *vs.* pre-cirrhotic advanced fibrosis (F3)

There is general consensus that patients with cirrhosis should continue HCC surveillance after SVR. However, there are discrepant recommendations among professional societies for patients with advanced fibrosis (F3). EASL recommends ongoing surveillance in patients with advanced fibrosis (F3)[11] whereas AASLD does not[12] (Table 1). This discrepancy arises partly from the difficulty in accurately determining patients with F3 fibrosis and the fact that they represent a heterogeneous group with some patients having F3-F4 fibrosis and higher HCC risk and others having F2-F3 fibrosis with lower HCC risk. In addition, there is potential for misclassification of cirrhosis; some patients are understaged by biopsy or non-invasive markers of fibrosis and therefore their risk of HCC is underestimated.[13,14] Overall, the EASL guideline took the more conservative approach of recommending HCC surveillance in F3 fibrosis, whereas the AASLD guidance did not.

It is inevitable that a small proportion of HCC cases occur after SVR in patients with pre-cirrhotic liver disease. These HCC cases often present at advanced stages due to a low index of suspicion and lack of screening. This represents a great gap in clinical care and, currently, a frustrating conundrum. On the one hand, we know that a certain proportion of HCC cases will arise in non-cirrhotic livers, but on the other we do not currently have proven, reliable tools to identify those patients who are at high HCC risk despite not having cirrhosis. However, some strategies are emerging to help us identify patients with pre-cirrhotic liver disease who have a high enough HCC risk such that they may benefit from HCC screening.

It is tempting to consider less frequent screening (*i.e.* annual instead of biannual) in patients at lower risk of HCC, such as F3 fibrosis. Indeed, cost-effectiveness studies suggest that annual screening is more cost-effective than biannual screening (*i.e.* has a lower incremental cost-effectiveness ratio [ICER]).[15,16] However, annual screening is less effective and given the median doubling time of HCC, which is approximately 6 months (112–204 days),[17,18] annual screening carries an inherent risk of identifying HCCs at later stage than biannual screening, and has not been recommended by professional societies.

Another difference between EASL and AASLD guidelines is that EASL recommends screening by ultrasonography every 6 months in both HCV[11] and HCC guidelines,[19] whereas AASLD recommends screening by ultrasonography ± serum alpha-fetoprotein (AFP) in HCV[12] and HCC[20] guidelines. This is an important distinction, but formally evaluating the performance characteristics of these screening tests is beyond the scope of this mini-review. A recent meta-analysis showed that the sensitivity of US for detecting T1 or T2 HCC was only 47% (95% CI 33%–61%) with a specificity of 91% (86%–94%).[21] The sensitivity of ultrasonography combined with serum AFP was higher at 63% (95% CI 48%–75%) but the specificity also decreased to 84% (95% CI 77%–89%).

Table 1. Differences between EASL and AASLD recommendations on HCC surveillance after SVR.

	EASL: Recommendations on treatment of hepatitis C 2018[11]	AASLD: Hepatitis C Guidance 2019[12]
Advanced fibrosis (F3)		
Definition of F3	• Histological • FibroScan® 10–13 kPa • Aixplorer® 9–13 kPa • ARFI (VTQ®) 1.6–2.17 m/s (FIB-4 and APRI cut-offs not provided)	n.a.
HCC surveillance recommended after SVR?	YES Ultrasound every 6 months "indefinitely"	NO
Cirrhosis (F4)		
Definition of cirrhosis (F4)	• Clinical • Histological • FibroScan® >13 kPa • Aixplorer® >13 kPa • ARFI (VTQ®) >2.17 m/s • FIB-4 >3.25 • APRI >2	• Clinical • Histological • FibroScan® >12.5 kPa • Other elastography test indicating cirrhosis • FIB-4 >3.25 • FibroSure, ELF* above "threshold"
HCC surveillance recommended after SVR?	YES Ultrasound every 6 months "indefinitely"	YES Ultrasound ± AFP every 6 months "Indefinitely"

AFP, alpha-fetoprotein; APRI, aspartate aminotransferase-to-platelet ratio index; ARFI, acoustic radiation force impulse; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; SVR, sustained virological response.
*ELF, Enhanced liver fibrosis test.

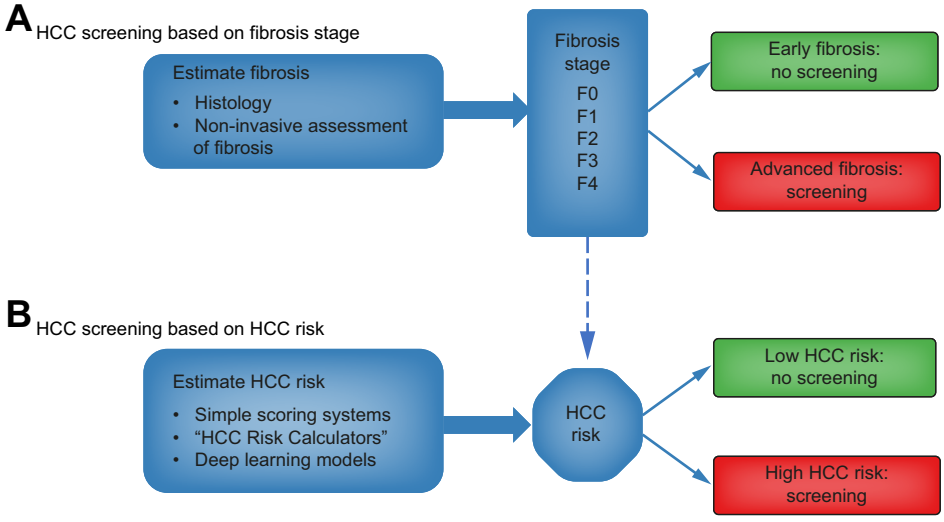

Fig. 2. Estimating HCC risk directly is a better strategy for determining the need for HCC screening than categorising patients solely based on fibrosis stage. HCC, hepatocellular carcinoma.

Estimating HCC risk directly is a better strategy than categorising patients based on fibrosis stage

Our current strategy for determining the need for HCC surveillance depends almost entirely on histological stage. This is problematic for several reasons. First, histological stage is not the only predictor of HCC (hence patients with pre-cirrhotic liver disease occasionally develop HCC). This is particularly important after SVR when fibrosis regression may occur but not correlate perfectly with HCC risk reduction because of preneoplastic changes that occurred before SVR. Second, histological stage falls into distinct categories (F0-F4) whereas HCC risk is a continuous variable (hence the "controversy" about whether F3 fibrosis is closer to F4 or F2). Third, histological stage is nowadays rarely ascertained by the "gold standard" test of liver biopsy and almost never serially after SVR. Instead, non-invasive measures of fibrosis are used to estimate histological stage, which, in turn, is used as a surrogate for HCC risk.

A better and more accurate approach is to estimate HCC risk directly (rather than indirectly by extrapolating from fibrosis stage) and use this estimate of HCC risk to make decisions about HCC surveillance, as shown in Fig. 2. Tools for estimating HCC risk have been developed and are summarised in subsequent sections.

Risk after SVR is the most important factor driving HCC surveillance decisions

It is imperative to estimate HCC risk after SVR because it is the most important factor in

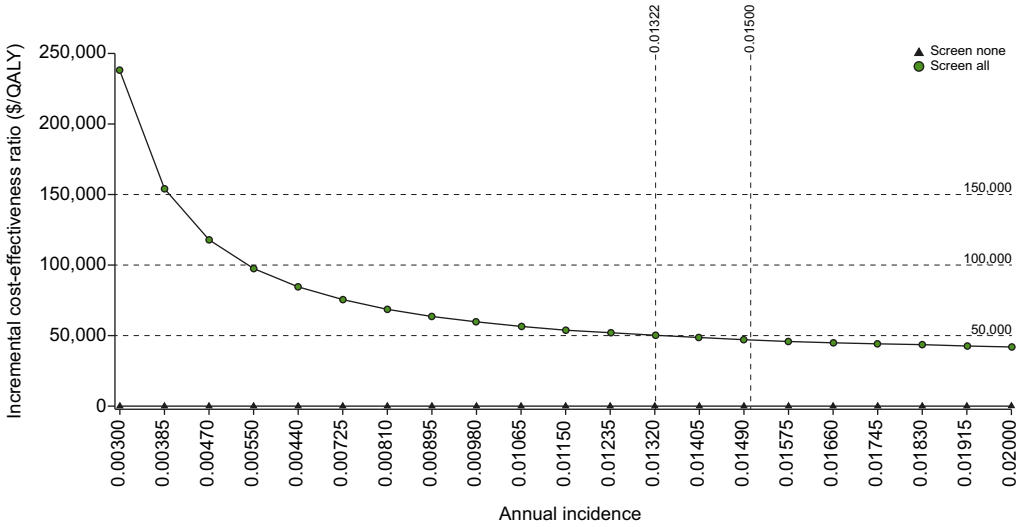

Fig. 3. ICER decreases almost exponentially with increasing HCC incidence in patients who achieved SVR.[15] Reproduced with permissions from reference.[15] The plot shows ICER plotted against HCC annual incidence. The ICER drops below the $50,000 per QALY willingness-to-pay threshold at approximately 1.32% per year. HCC, hepatocellular carcinoma; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted liver year; SVR, sustained virological response.

determining the cost-effectiveness of an HCC surveillance programme. Only patients who are destined to develop HCC can possibly benefit from HCC surveillance. All other patients can only experience the costs and potential harms of HCC surveillance including financial costs as well as the potential harms of screening anxiety, incidental findings, subsequent confirmatory imaging studies and invasive tests such as liver biopsy.[22]

Assuming that HCC surveillance is effective in reducing HCC-related mortality, it has been shown that the cost of screening per quality-adjusted life year (QALY) decreases almost exponentially with increasing HCC risk (incidence) (Fig. 3).

Key point

Patients without established/known cirrhosis may still require surveillance after SVR if they have a sufficiently high HCC risk, such as patients with FIB-4 ≥3.25.

Therefore, although the question of whether to screen or not is usually framed in terms of the underlying stage of fibrosis (*i.e.* does the patient have cirrhosis or advanced fibrosis or not), it is more appropriate to make HCC surveillance decisions in terms of a specific patient's individualised HCC risk at that point in time, recognising that multiple factors may affect that risk besides fibrosis stage.

What is the HCC risk above which HCC surveillance after SVR may be cost-effective?

Professional society guidelines have frequently quoted an annual HCC risk threshold >1.5% above which HCC screening is "recommended" because screening was considered cost-effective in patients with cirrhosis or advanced fibrosis if HCC risk was >1.5%.[16,23–26] However, these cost-effectiveness analyses were based on projections from decision analytic modelling studies rather than prospective HCC surveillance studies. Furthermore, HCC treatments and their success rates have improved substantially since the publication of these studies, which would be expected to improve the cost-effectiveness of screening.

More recently, a cost-effectiveness analysis was performed specifically in HCV-infected patients who achieved SVR. This analysis estimated that the annual incidence of HCC has to be greater than 1.32% in order to achieve an ICER of <$50,000/QALY (a frequently quoted willingness-to-pay threshold).[15] It is important to emphasise that there are no prospective studies of HCC surveillance with HCC-related mortality as an outcome. Therefore, estimates of the sensitivity and specificity of screening, the effectiveness of curative treatments and the impact of surveillance on HCC-related mortality that are used as inputs in cost-effectiveness analyses are derived instead from retrospective studies. These estimates can have a great impact on cost-effectiveness analyses, which, therefore, have potentially large margins of error. Therefore, it is perhaps more appropriate to use a lower, more conservative threshold of annual HCC risk (>1%) at which HCC surveillance might be considered cost-effective.

The aforementioned cost-effectiveness analysis assumed an annual HCC incidence of ~1.8% in patients with cirrhosis following SVR, resulting in a low estimated ICER of $43,229 per QALY for HCC surveillance. In contrast, for advanced fibrosis (F3) they assumed an annual HCC incidence of only 0.3–0.4% resulting in a much higher estimated ICER of $188,157 per QALY, which is considered prohibitively high. Ultimately, what is important in these calculations is the estimation of HCC risk rather than stage of fibrosis. It is likely that some patients

Table 2. Tools for estimating HCC risk after SVR to inform HCC screening strategies.

Tools for HCC risk estimation	Examples	Predictor variables	Advantages	Disadvantages
Simplified HCC scoring systems	FIB-4 score cirrhosis[3,9,27–29]	Age, AST, ALT, platelet count	Readily available; easy to use.	Not specifically developed for HCC prediction; less accurate
Elastography	Fibroscan-derived elastography[31]	Liver stiffness (kPa)	Increasingly common; additionally, provides estimate of fibrosis	Not specifically developed for HCC prediction; less accurate. expensive
Multivariable regression models ("HCC risk calculators")	VA HCC model at hccrisk.com[35] and aMAP[36]	VA model: SVR, age, sex, BMI, race/ethnicity, HCV genotype, platelet count, AST, ALT, albumin, INR and haemoglobin. aMAP: age, male sex, albumin-bilirubin and platelet count	More accurate than simple scores or elastography	Require special tools to calculate (*e.g.* web-based or app-based calculators)
Deep learning HCC risk prediction models	Recurrent Neural Network (RNN) HCC model[37]	Age, sex, race, HCV genotype and 24 laboratory tests	More accurate than regression models	Hard to implement in clinical practice currently

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; INR, international normalised ratio; SVR, sustained virological response; VA, Veterans Affairs.

with pre-cirrhotic chronic liver disease have an estimated annual HCC risk >1% and may also benefit from HCC screening. How can we estimate HCC risk following SVR in patients with or without clear evidence of cirrhosis in order to identify those who may benefit from screening?

Tools for estimating HCC risk after SVR to identify patients who may benefit from HCC screening

Tools for estimating HCC risk are summarised and compared in Table 2.

Simplified HCC scoring systems: FIB-4

The fibrosis-4 (FIB-4) score provides a simplified method to estimate HCC risk after SVR. The FIB-4 score, calculated using a simple formula based on aspartate aminotransferase (AST), alanine aminotransferase (ALT), age and platelet count ([AST x age]/[platelet count x √ALT]) was originally developed as a non-invasive biomarker panel of fibrosis stage. However, a high FIB-4 score ≥3.25 also appears to be a particularly strong predictor of HCC risk, both in patients with and without cirrhosis.[3,9,27–29] Specifically, among HCV-infected patients who achieved SVR after antiviral treatment, a FIB-4 score of ≥3.25 *vs.* <3.25 could accurately identify high-risk and low-risk patients, respectively.[30] Patients without cirrhosis but with FIB-4 score ≥3.25 had an annual HCC risk of 1.22% during long-term follow-up after SVR, which would suggest that they need to continue HCC surveillance. In contrast, patients without cirrhosis with a FIB-4 score <3.25 had a much lower annual HCC risk of 0.24% after SVR, suggesting no need for ongoing surveillance.

Furthermore, the change in FIB-4 score after SVR could be used to further fine tune HCC risk prediction (Fig. 4).[30] Specifically, patients whose FIB-4 was ≥3.25 both before and after SVR had a very high risk (~2%/year) whereas patients whose FIB-4 dropped from ≥3.25 before SVR to <3.25 after SVR had a much lower HCC risk. Taken together, these findings suggest that the subgroup of non-cirrhotic patients who continue to have a FIB-4 score ≥3.25 both before and after SVR have an annual HCC risk that well exceeds 1% and need to continue HCC surveillance, even if they do not carry a diagnosis of cirrhosis.

Liver elastography (liver stiffness)

Fibroscan-derived liver stiffness correlates well with fibrosis stage. In addition, multiple studies show that liver stiffness is independently associated with HCC risk, both in patients with known cirrhosis and in patients with pre-cirrhotic liver disease. For example, in a prospective study of HCV-infected patients, annual HCC risk was 0.11% in patients with liver stiffness ≤10 kPa, 2.9% in patients with liver stiffness 10–15 kPa, 5% in patients with liver stiffness 15–20 kPa, 8.3% in patients with liver stiffness 20–25 kPa and 14.4% in patients with liver stiffness >25 kPa.[31] Although fibroscan, which measures vibration-controlled transient elastography, is currently the most commonly used method of hepatic elastography, many other methods are also available including shear-wave elastography and magnetic resonance elastography. Exactly how elastography should be combined with other even more readily available measures (such as FIB-4 or multivariable risk calculators) to improve HCC risk estimation remains to be determined.

Multivariable "HCC risk calculators"

Multivariable "HCC risk calculators" have been developed to estimate HCC risk in individual patients with cirrhosis or chronic liver disease,[32–34] including specifically HCV-infected patients following antiviral treatment.[35] This prediction tool uses 12 routinely available predictors to estimate 3-year HCC risk after antiviral treatment using a multivariable Cox proportional hazards model in both patients with and without cirrhosis.[35] These predictors are SVR (Yes/No), age, gender, BMI, race/ethnicity, HCV genotype, platelet count, AST, ALT, albumin, international normalised ratio and haemoglobin. This model shows that many patients

Key point

HCC risk is one of the most important factors that should inform decisions on whether and how to screen for HCC.

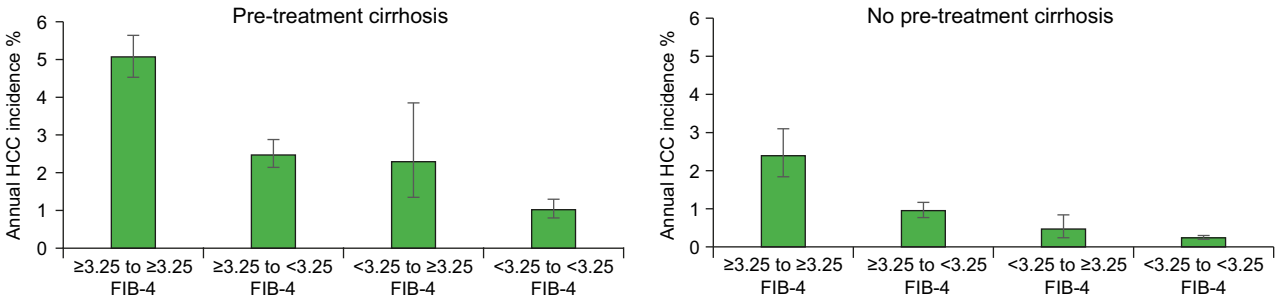

Fig. 4. HCC risk according to pre and post-treatment FIB-4 score in patients who achieved SVR. Adapted from.[30] FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; SVR, sustained virological response.

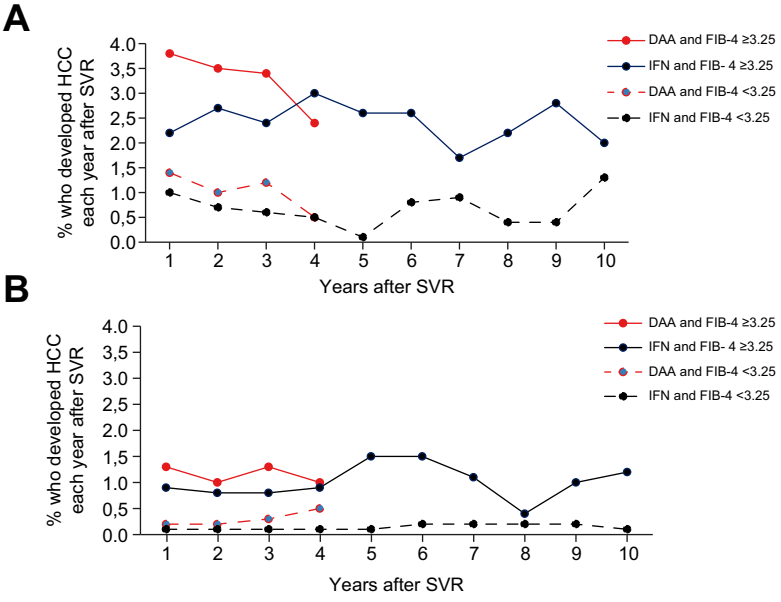

Fig. 5. Annual HCC incidence after SVR according to treatment type (IFN *vs.* DAA) and FIB-4 score. (A) Patients with pre-treatment cirrhosis and (B) patients without pre-treatment cirrhosis.[30] Reproduced with permission from.[30] DAA, direct-acting antiviral; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; IFN, interferon; SVR, sustained virological response.

without cirrhosis who fail to achieve SVR can have a very high annual HCC risk (well above 1%) and need to continue HCC surveillance. Given the very high SVR rates of current direct-acting antiviral (DAA) regimens, this, fortunately represents only a small absolute number of patients. The model also shows that among non-cirrhotic patients who achieve SVR, a small proportion can have an annual HCC risk >1%, *e.g.* if they have a number of HCC risk factors such as low platelet count, low albumin, high AST/ALT ratio, male sex, advanced age or genotype 3 HCV infection prior to eradication. These HCC risk calculators are available as web-based tools at www.hccrisk.com and can be used to calculate HCC risk in individual patients in order to determine whether HCC surveillance is warranted or not. These tools were derived using large populations of patients undergoing antiviral treatment in the Veterans Affairs (VA) healthcare system and have not yet been externally validated in non-VA populations.

Key point

"HCC risk calculators" that estimate HCC risk may allow for risk stratification and individualized, risk-based surveillance strategies ("precision HCC screening") in the future.

Recently the aMAP risk score was developed to estimate HCC risk in patients with chronic hepatitis, including patients with HCV with/without cirrhosis who achieved SVR.[36] aMAP uses only age, male sex, albumin-bilirubin and platelet count as predictors and was derived and externally validated using 11 international, prospective observational cohorts or randomised controlled trials. aMAP performed remarkably well, especially considering that patients from multiple countries, with/without cirrhosis, and with both HBV and HCV were used in model development.

"Deep learning" HCC prediction models

Deep machine learning models, such as neural network or complex tree-based models, are generally expected to outperform conventional linear models in accuracy of prediction. However, this usually occurs at the expense of sacrificing interpretability or risking substantial overfitting. Also, most electronic health record systems do not support real-time implementation of deep learning algorithms or do not have the necessary computational power. However, incorporation of deep learning prediction and diagnostic algorithms into clinical practice is currently an area of tremendous growth and it is likely that many such algorithms will become available in routine clinical practice in the next 10 years. A deep learning, recurrent neural network model predicting HCC in patients with HCV was recently published.[37]

Future strategies for HCC risk estimation

The aforementioned strategies are based on routine, "generic" clinical features. It is possible that in the future more patient-specific genetic, epigenetic transcriptomic or molecular profiling may identify individual patients at particularly high risk of HCC development.[38,39] It is important, however, to distinguish biomarkers and biomarker panels such as GALAD,[40,41] which are being developed as HCC screening tools (*i.e.* to be performed at regular intervals for early detection), from HCC risk estimation/stratification tools.

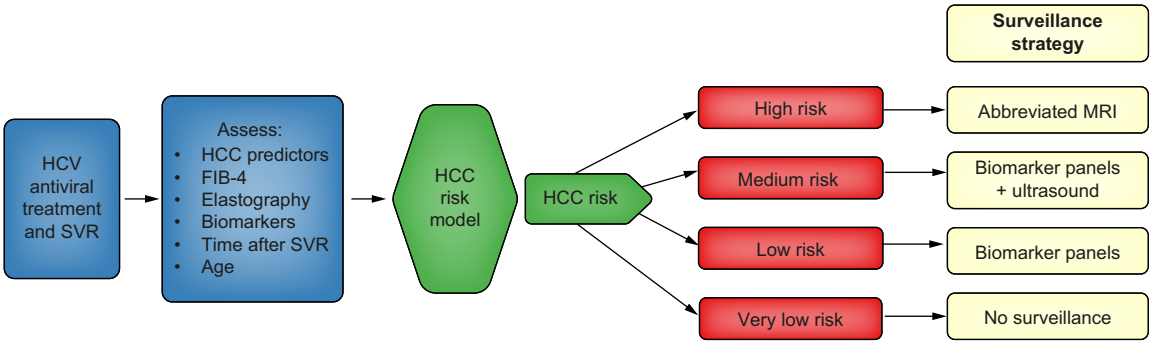

Fig. 6. Future directions in HCC risk stratification and risk-based surveillance in patients who achieve SVR: A hypothetical schematic.* *The schematic is hypothetical and asssumes increasing cost in screening strategy as we go from biomarker panels to biomarker panels ± ultrasound to abbreviated MRI, but also increase in effectiveness (*i.e.* quality-adjusted life expectancy). HCC, hepatocellular carcinoma; SVR, sustained virological response.

Does HCC risk decline over time after SVR and can we ever safely discontinue HCC surveillance?

It is tempting to assume that HCC risk would gradually decline after SVR in patients with cirrhosis or advanced fibrosis as the liver remodels, eventually reaching a low enough level that HCC surveillance would no longer be warranted. Unfortunately, studies have demonstrated that annual HCC risk continues to be >2% for up to 10 years after SVR in patients with cirrhosis and a FIB-4 score ≥3.25[30,42] (Fig. 5). Even patients without pre-treatment cirrhosis continue to have a substantial annual HCC risk >1% if their FIB-4 score is >3.25.[30] Therefore, based on current data, patients with pre-treatment cirrhosis or those without cirrhosis but with FIB-4 >3.25 before and after treatment should continue to undergo HCC surveillance "indefinitely". This is a great strain on healthcare systems that already have relatively low rates of HCC surveillance. There is a great need to develop dynamic tools that incorporate changes over time in age, liver stiffness, FIB-4 score or blood-based biomarkers to calculate changes in HCC risk in order to identify those patients who have attained a sufficiently low HCC risk at a certain time point after SVR and can safely discontinue HCC surveillance.

Future directions: Risk stratification and risk-based surveillance strategies

We currently we have a "one-size-fits-all" HCC surveillance strategy, whereby surveillance is recommended based on the presumed stage of fibrosis and all patients are recommended to undergo surveillance by the same relatively ineffective strategy (ultrasonography +/− serum AFP) irrespective of their underlying risk of HCC. An alternative, risk-based surveillance strategy would involve 2 steps. First estimating an individual patient's HCC risk using their risk factor profile and appropriate models. Second, using the HCC risk estimation to determine whether to recommend surveillance or not and whether to recommend an appropriate surveillance strategy according to the patient's risk. The principle is that the comparative effectiveness or cost effectiveness of a surveillance strategy depends on the patient's HCC risk. More effective strategies that are also more expensive (such as screening by abbreviated MRI) or more invasive/harmful, could be more cost-effective if they focus on the high-risk groups.[16] Conversely, patients at lower risk of HCC, may undergo screening using only serum/plasma biomarker panels without any ultrasonography, while patients at intermediate risk may undergo screening with both ultrasound and biomarkers.

For risk-based surveillance to become a reality, HCC risk calculators and prediction models need to be improved and validated in diverse populations so that we can reliably estimate HCC risk. Furthermore, the performance characteristics of different screening modalities (including novel imaging tests and biomarker panels) need to be described so that they can be applied according to HCC risk, as shown in a hypothetical example in Fig. 6.

Abbreviations

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAA, direct-acting antiviral; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SVR, sustained virologic response; VA, Veterans Affairs.

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Conflict of interest

The author declares no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

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