Hepatocellular Carcinoma Risk, Outcomes, and Screening After Hepatitis C Eradication

It is now generally accepted that hepatitis C virus (HCV) eradication substantially reduces the risk of hepatocellular carcinoma (HCC), whether achieved by direct-acting antivirals (DAAs) available since 2014, or prior, interferon-based treatments.[1,2] It is also well established that HCC does occur even after sustained virologic response (SVR), especially in patients who had developed cirrhosis of advanced fibrosis before SVR. Critical questions that remain and are informed by the study by Toyoda et al.[3] are:

a Is the natural history, biology, and response to treatment of HCC that occurs in the setting of cured HCV different from HCC that occurs in the setting of active HCV? and
b What is the optimal HCC surveillance strategy after SVR?

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; APASL, Asian Pacific Association for the Study of the Liver; DAA, direct-acting antiviral; EASL, European Association for the Study of the Liver; ESLD, end-stage liver disease; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virologic response.

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ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

George N. Ioannou, B.M.B.Ch., M.S.
Research and Development
Veterans Affairs Puget Sound Healthcare System
1660 S. Columbian Way
Seattle, WA 98108, USA
E-mail: georgei@medicine.washington.edu
Tel.: +1-206-277-3136

Differences in HCC That Occurs in Cured HCV Versus HCC That Occurs in Active HCV

Early, uncontrolled studies suggested that DAA-induced SVR may be linked to increased risk of HCC recurrence[4,5] and more aggressive HCC pattern,[6,7] while subsequent studies did not confirm these findings. In their retrospective study, Toyoda et al. compared features of *de novo* HCC that occurred in patients with cured HCV following DAA treatments between 2014 and 2020 (n = 181) versus HCC that occurred in patients with active HCV between 2011 and 2015 (n = 127).[3] A very important feature of the study design is that all patients were in a 6-monthly U.S. surveillance program, regardless of the stage of liver fibrosis. In fact, absence of cirrhosis was demonstrated at baseline in 36% of treated versus 32% of untreated patients. At HCC development, rates of cirrhosis (P = 0.54) and co-factors of liver damage, such as diabetes (P = 0.61) or alcohol intake (P = 0.29), were similar. In patients with cured HCV, HCC was smaller (P = 0.0002) and mostly single (P = 0.0008), although without differences in rates of extrahepatic spread (P = 1.00) or neoplastic portal vein invasion (P = 0.15) when compared to patients with active HCV. Nevertheless, curative treatments were equally offered in both groups. The main conclusions of the study were:

a HCC that occurred in the setting of DAA-cured HCV did not appear to be more aggressive or have a higher recurrence rate than HCC that occurred in active HCV; and
b Survival after HCC diagnosis was better in patients with cured HCV than in patients with active HCV, which the authors attributed to improved liver function, although causes of death (i.e., HCC progression vs. end-stage liver disease [ESLD] versus non-liver-related) were not reported.

Benefits of DAA-Induced SVR on Liver Function, Patient Survival, and HCC Risk and Outcomes

Beyond the reduced risk of HCC *itself*, the achievement of SVR translates into benefits in terms of residual liver function, ranging from prevention of decompensation to improvement in Child-Pugh-Turcotte scores in most patients. Taken together, these aspects finally account for an overall reduction in liver-related mortality, which includes both HCC and ESLD-related deaths. Of note, preserved liver function not only reduces ESLD-associated mortality, but also enables HCC treatments with higher curative intent. The demonstration by Toyoda et al. that HCC that occurs following DAA-induced SVR is not more aggressive and may have better survival than HCC that occurs in active HCC, further supports large-scale HCV eradication efforts. Unfortunately, the authors did not report any data on HCC treatment strategies, with the exception of resection, which was similarly offered to patients with cured HCV and active HCV, despite significant differences in albumin-bilirubin scores. Other studies also reported increased survival in patients with HCC who undergo antiviral treatment after HCC treatment compared to those who remain untreated, thus providing support for also offering antiviral treatment after successful treatment of HCC.

Role of Pre-SVR and Post-SVR Fibrosis on HCC Risk

About one-third of the patients in the two study cohorts (cured HCV vs. active HCV) were not considered as having cirrhosis, although the authors did not clarify how cirrhosis or advanced (F3) fibrosis were ascertained. In addition, only mild fibrosis (F0-F2) surrounded HCC in some patients who underwent resection (15% of active HCV and 28% of cured HCV). These findings suggest that a substantial proportion of HCCs may occur in the absence of cirrhosis, which has already been reported. However, it is important to emphasize that the risk of HCC is considered to be low in patients with mild fibrosis, and even lower following viral eradication—especially in the absence of cofactors such as diabetes and advanced age. The higher-than-expected prevalence of precirrhotic liver disease reported in the study needs to be interpreted in the context of the following potential limitations and confounding factors:

1. Retrospective design of the study, including lack of data on the total number of patients without cirrhosis being treated with DAAs;
2. Limitations of noninvasive tests of fibrosis;
3. Presence of comorbidities increasing the risk of HCC in the absence of cirrhosis (i.e., metabolic-associated liver disease); and
4. The possibility of cirrhosis regression (i.e., improvement of fibrosis) potentially occurring after viral eradication.

Further complicating this issue is whether the most clinically meaningful parameter with respect to HCC risk is the fibrosis stage that was present before SVR versus the fibrosis stage after SVR. In fact, the inclusion in specific surveillance algorithms currently relies on criteria that include pre-SVR fibrosis stage (Table 1), which potentially influences the residual risk of post-SVR HCC. Whether post-SVR fibrosis, which may be influenced by remodeling processes occurring following SVR, would further influence HCC risk is controversial.

What Is the Appropriate HCC Surveillance Strategy After SVR?

There is general consensus that patients with cirrhosis should continue HCC surveillance with 6-monthly ultrasound ± alpha-fetoprotein (AFP) after SVR, given that HCC risk persists in these patients long after viral eradication.[1] However, there are discrepant recommendations among professional societies for patients

TABLE 1. DIFFERENCES AMONG APASL, EASL, AND AASLD RECOMMENDATIONS ON HCC SURVEILLANCE AFTER SVR

	APASL[10]	EASL[8]	AASLD[9]
No/early fibrosis (F0-F2)			
Definition of F0-F2	Not reported	N/A	N/A
HCC surveillance recommended after SVR?	Yes US ± tumor markers every 6 months for 2 years after EOT; thereafter every 12 months (US ± AFP)	No	No
Advanced fibrosis (F3)			
Definition of F3	Not reported	• Histological • FibroScan 10-13 kPa • Aixplorer* 9-13 kPa • ARFI (VTQ) 1.6-2.17 m/s	N/A
HCC surveillance recommended after SVR?	Yes US with tumor markers (AFP, AFP-L3, DCP) every 6 months indefinitely	Yes US every 6 months indefinitely	No
Cirrhosis (F4)			
Definition of cirrhosis (F4)	Not reported	• 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 US with tumor markers (AFP, AFP-L3, DCP) every 6 months indefinitely	Yes US every 6 months indefinitely	Yes US ± AFP every 6 months indefinitely

*Supersonic Imagine, Aix-en-Provence, France.
Abbreviations: AFP-L3, lens culinaris agglutinin–reactive AFP isoform; APRI, aspartate aminotransferase–to-platelet ratio index test; ARFI, acoustic radiation force impulse; DCP, des-γ-carboxy prothrombin; ELF, Enhanced Liver Fibrosis test; EOT, end of treatment; FIB-4, Fibrosis-4 index; N/A, not available; US, ultrasound.

with advanced fibrosis (F3) or even early fibrosis (F0-F2) (Table 1). The European Association for the Study of the Liver (EASL) recommends ongoing surveillance in patients with advanced fibrosis (F3),[8] whereas the American Association for the Study of Liver Diseases (AASLD) does not.[9] Also, it should be noted that both the EASL and AASLD broadly define "cirrhosis" as radiographic, clinical and histological evidence, as well as either liver stiffness measurement (LSM) or serological noninvasive tests (NITs) above pre-identified cutoffs for cirrhosis (Table 1). The Asian Pacific Association for the Study of the Liver (APASL) has the most aggressive recommendations, supporting 6-monthly surveillance in all patients with chronic hepatitis C (CHC) before treatment and up to 2 years after SVR, regardless of fibrosis stage. Thereafter, APASL recommends 6-monthly surveillance of F3-F4 and annual surveillance of F0-F2. Moreover, patients with CHC with alcohol abuse and/or diabetes are warranted to remain under ultrasound surveillance.[10]

In the study by Toyoda et al., all patients with cured HCV underwent HCC surveillance in accordance with APASL recommendations. Indeed, 64 of 178 (36%) patients with cured HCV who developed HCC were reported not to have cirrhosis, including 22 of 50 (44%) who underwent resection. Does this mean that all patients should undergo HCC surveillance after SVR, regardless of their fibrosis stage? Unfortunately, the study does not provide the necessary data to address this question for two reasons. First, the study does not report the incidence of HCC among the 5,248 patients who achieved SVR according to their baseline fibrosis stage, or at least according to absence/presence of cirrhosis or advanced fibrosis. Therefore, we cannot determine whether the incidence of HCC in patients with precirrhotic HCC was high enough to merit surveillance. Second, the study does not report whether any of the patients who were reported as not having cirrhosis at the time of HCC diagnosis had cirrhosis before antiviral treatment and HCV eradication.

In the future, optimization of HCC surveillance after SVR might be focused on the identification of two subgroups of patients:

1. Those in whom surveillance could be safely discontinued. We would need to be able to identify patients with a very low risk of HCC with very high sensitivity, considering changes (before/after) in LSM or other NITs, as well as comorbidities and other factors that influence HCC risk; and
2. Those in whom surveillance should be continued, due to the presence of unfavorable risk factors for HCC development (e.g., established cirrhosis, portal hypertension, presence of undefined nodules, comorbidities).

Although the role of clinical features such as pretreatment fibrosis stage, directly or indirectly assessed, age, gender, and presence of comorbidities has been well recognized, some open questions still remain regarding the optimal way they should be combined, and whether other factors may further improve prediction accuracy. In addition, physiological changes in most of these clinical factors over time, mostly related to aging population, should be taken into consideration when striving for individualized, dynamic surveillance programs.

Roberta D'Ambrosio [1]
George N. Ioannou [2,3]
[1]**Division of Gastroenterology and Hepatology**
Foundation IRCCS Ca' Granda Ospedale
Maggiore Policlinico
Milan, Italy
[2]**Division of Gastroenterology**
Department of Medicine Veterans Affairs Puget
Sound Healthcare System
University of Washington
Seattle, WA, USA
[3]**Research and Development**
Veterans Affairs Puget Sound Healthcare System
Seattle, WA, USA

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