Meeting the challenges of HCC post SVR in the Post-DAA Era: A Path Forward

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Infection with chronic Hepatitis C virus (HCV) has been a major cause of hepatocellular carcinoma (HCC) worldwide. In patients with active viral cirrhosis there is a 2-5% annual incidence of HCC\(^1\). The development of direct-acting antiviral (DAA) therapies has led to cure of HCV with sustained virologic response (SVR) in >95% of those treated. Cohort studies have demonstrated up to 70% reduction in risk of development of HCC compared to those who remain viremic\(^2\). Nevertheless, the risk of HCC post-SVR persists leading to a growing proportion of HCC cases in the post-DAA era. In this issue of *Clinical and Molecular Hepatology*, Huang et al. discuss risk factors, pathophysiology, and screening strategies for HCC development following HCV eradication\(^3\).
Recent data have helped refine our understanding of the molecular profiles of HCC and how they contribute to the risk of HCC that persists in HCV-infected individuals after SVR. These include genomic factors, changes in epigenetics and gene expression, and changes in innate and adaptive immunity. Identification of individuals who carry these risk factors is important to ensure they are appropriately enrolled in surveillance programs and allows tailoring of surveillance to risk. HCCs demonstrate a remarkable degree of genetic heterogeneity, though next-generation sequencing technologies are expanding our knowledge of the molecular landscape of HCC\(^4\). Our understanding of molecular changes in post-SVR HCCs is at an early stage. One important observation is that a reduction in mutated ARID2 genes is observed in HCV - SVR HCCs compared to HCV-positive HCC patients which has prognostic importance. Other observed somatic mutations in HCV-SVR HCCs include increases in KEAP1, which promotes carcinogenesis via accumulation of NRF2 protein conferring resistance to oxidative stress, and PREX2 mutations which promote cell migration\(^5,6\). There are also unique changes in TP53 suppressor genes in DAA-treated HCV patients compared to interferon-treated patients that could serve as future prognostic markers. Genome-wide association studies have allowed identification of risk alleles in a variety of diseases, and alleles for the development of HCC post-SVR are emerging which may allow additional risk stratification of patients post-SVR\(^7\).

An emerging area of investigation in the molecular mechanisms of HCC are the epigenetic modifications that occur during HCV infection and that persist after SVR, leaving an epigenetic scar that may contribute to progressive hepatic injury and HCC. Importantly, these findings appear to be more pronounced in DAA-treated individuals compared to those
treated with interferon, where reversion of epigenetic changes has been observed. A wide range of epigenetic changes over a broad range of intracellular pathways including cytoskeletal, WNT signal transduction, cell signaling oncogenes, and tumor suppressor genes have been identified and associated with increased risk of HCC, as have epigenetic changes in the innate immune system via TLR3, which play a crucial role in HCC progression and may serve as future prognostic biomarkers. Finally, the high rate of chronicity with acute HCV infection relates to the unique ability of HCV to escape the innate immune response, and these changes induced by HCV infection appear to persist post-SVR. Because of a reduction in interferon-stimulated genes and reduced type 1 interferon response that has been observed post-SVR with DAA therapy, a weakened state of immune surveillance for HCC exists that may contribute to carcinogenesis.

Certain populations are at more elevated risk of developing HCC after HCV cure, including those with cirrhosis, clinically significant portal hypertension (hepatic venous pressure gradient (HVPG) ≥10 mmHg), history of hepatic decompensation, or co-infection with hepatitis B virus. Older age, male sex, alcohol consumption, and diabetes mellitus are also risk factors. There is consensus amongst international Hepatology societies regarding the importance of ongoing HCC screening post-SVR in those with cirrhosis. However, there are discrepancies in guidelines regarding the need for screening in those with F0-F3 fibrosis or certain risk factors as above, and regarding optimal screening modality (Table 1). The American Association for the Study of Liver Diseases recommends against routine HCC surveillance in patients with advanced fibrosis but without cirrhosis. By contrast, the Asian Pacific Association for the Study of the Liver and the Taiwan Association for the Study of
the Liver recommend ongoing screening of all post-SVR patients regardless of fibrosis level, whilst the European Association for the Study of the Liver recommends ongoing screening for patients with ≥F3 fibrosis\textsuperscript{10-12}. Whilst all guidelines support the use of periodic ultrasonography for the detection of suspicious lesions, there is variance in routine use of blood tests such as alpha fetoprotein (AFP) or protein induced by vitamin K absence-II (PIVKA-II) and clearly better biomarkers are required to screen for HCC in the HCV-SVR population. Importantly, there has been poor adherence to routine HCC surveillance regardless of liver disease etiology\textsuperscript{8,13}, and this is an ongoing challenge in the HCV post-SVR population. Many patient and provider factors are thought to contribute to low adherence rates, including failure to recognize patients at risk, limited illness understanding, lack of resources, and burdensome surveillance requirements including cost. Further work is needed to address these gaps, such as tracking and follow-up of deferred/missed surveillance through the electronic medical record, and more robust patient/family illness education strategies.

Several surrogate markers have been identified to help predict risk for post-SVR HCC and are currently used in practice. Cirrhosis is by far the most important risk factor, though higher degrees of fibrosis and/or portal hypertension are also predictive. Liver stiffness and spleen stiffness measurements have been used for risk stratification post-SVR\textsuperscript{14}. Other surrogate markers of advanced fibrosis or portal hypertension include low albumin or platelets, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, AST to platelet ratio index (APRI), fibrosis-4 index (FIB-4), and high post-treatment ALT. Non-fibrosis-related surrogate markers include high pre- or post-treatment AFP level, high pre-
or post-treatment GGT level, higher risk demographics (i.e. age, male sex) or comorbid conditions (i.e. alcohol use, diabetes, previous HCC). In addition to AFP, other circulating protein biomarkers associated with post-SVR HCC include serum sphingolipids, vascular endothelial growth factor (VEGF) and angiopoietin-2 (ANGPT2). Circulating microRNA (miRNA) profiles have also been identified as potential prognostic markers. Various risk stratification models using combinations of these surrogate markers have been proposed, with incorporation into artificial intelligence models, with the aim of better tailoring HCC surveillance to those at highest risk and these are evolving.

As summarized by Huang et al. in this issue, the incidence of HCC after HCV eradication ranges from 0.6%-4.9%, with higher incidence in those with cirrhosis. One large meta-analysis estimated incidence among patients with F3 fibrosis to be 0.5 per 100 person-years, and in patients with cirrhosis to be 2.1 per 100 person-years. It has been generally accepted that the annual risk of HCC needed for surveillance to be cost-effective is ≥1.5% although this threshold is debated. In one study, a Markov model was used to evaluate cost-effectiveness of biannual surveillance, with subgroup analyses showing surveillance to be cost-effective in patients with cirrhosis (incremental cost-effectiveness ratio (ICER) of $48,729 per quality-adjusted life-year (QALY)), but not in patients with F3 fibrosis (ICER of $188,157 per QALY). The difference in ICER was primarily driven by lower HCC incidence in patients with F3 fibrosis versus those with cirrhosis. This may support further risk stratification of those with F3 fibrosis using surrogate markers or predictive models as previously described before committing these patients to a surveillance program. It is worth
noting that cost-effectiveness was based on a willingness-to-pay threshold ICER of \( \leq 50,000 \) per QALY, which will likely vary amongst different regional healthcare systems.

Several potential preventive strategies are being explored to reduce the risk of HCC. These range from lifestyle modifications such as smoking cessation and control of diabetes/metabolic syndrome through diet and exercise, to chemopreventive medications such as metformin, statins, GLP-RAs and aspirin; with the growing epidemic of metabolic syndrome worldwide, these and other agents should be explored in trials in appropriate HCV-SVR patients to further mitigate risk of HCC. Dietary supplementation with fish oil, vitamin E, coffee, and certain phytochemicals may also be associated with HCC risk reduction and should also be explored prospectively. In patients with HCC and HCV viremia, HCV eradication with DAAs improves long-term survival, possibly due to preservation/recompensation of liver function or due to significant reduction in the HVPG. It is thus recommended to treat HCV-viremic HCC patients with DAAs unless a short life expectancy is expected\(^{20}\).

Despite advances in HCV therapy, HCC is an ongoing problem in patients who have attained SVR due to persistence of fibrotic and inflammatory milieu with oncogenic potential, as well as host genetic and epigenetic factors. The importance of ongoing HCC surveillance in those with cirrhosis has been well-described, however, there is controversy in optimal surveillance strategies for patients without cirrhosis but with other risk factors for HCC, and regional differences in screening practices. Further research is needed to develop precision medicine models using individual patient demographics and biomarkers for improved risk
stratification, especially in patients with non-cirrhotic fibrosis or portal hypertension. The vast underutilization of HCC surveillance should be a prioritized area of improvement initiatives, as more precise and individualized surveillance plans will be of limited use with poor adherence rates.
References:


11. Wei Teng, Hung-Wei Wang, Shi-Ming Lin, On behalf of Diagnosis Group and Systemic Therapy Group of TLCA; Management Consensus Guidelines for Hepatocellular Carcinoma: 2023 Update on Surveillance, Diagnosis, Systemic


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