Viral-Mediated Hepatocellular Carcinoma: A Review on Mechanisms and Implications for Therapy

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common cancers in the United States. Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are major risk factors of HCC. This review article discusses the pathogenesis behind HBV- and HCV-induced HCC, examining the ways these viruses contribute to the development of liver cancer. Furthermore, we aim to explore the therapeutic implications of viral-mediated HCC, with an interest in preventing chronic infections and subsequent HCC development. By understanding the underlying pathogenesis and therapeutic targets, we aim to contribute to improved outcomes for hepatitis-related liver cancer.

Keywords: hepatitis, hepatocellular carcinoma, radiation

Introduction

Hepatocellular carcinoma (HCC) poses a significant global health challenge, accounting for about 90% of liver cancer cases and projected to affect over 1 million individuals annually by 2025.[1] HCC is the sixth most common cancer diagnosis and the fourth most common cause of cancer-related death worldwide.[1,2] It has a poor prognosis as well, as patients have a 5-year survival of 18%.[3] The risk factors of HCC include hepatitis B virus (HBV), hepatitis C virus (HCV), non-alcoholic steatohepatitis, chronic alcohol use, aflatoxins, liver flukes, and inherited metabolic disorders, including hemochromatosis and α1-antitrypsin deficiency.[1,2,4] HBV infection contributes to around 60% of HCC cases in Asia and Africa and 20% of cases in the West. Likewise, chronic HCV infection is seen among HCC patients in North America, Europe, and Japan.[1,5] Viral-mediated HCC poses a unique challenge as patients who have viral-mediated disease tend to have worse outcomes than patients with a nonviral etiology.

Treatment for viral-mediated HCC depends on the stage of the disease. The Barcelona Clinic Liver Cancer (BCLC) guidelines are commonly referenced and personalized to patients. For early stage HCC (BCLC-0 and BCLC-A), curative options include ablation, surgical resection, or liver transplantation (LT).[6] In intermediate stages (BCLC-B), treatments such as transarterial chemoembolization (TACE) or LT are considered to manage tumor burden. For advanced HCC, particularly in patients with viral-mediated disease, systemic therapies — primarily immunotherapy — are the mainstay.[6] These therapies aim to address the unique challenges posed by viral infections,

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including higher recurrence rates and an immunosuppressive tumor microenvironment.

Current treatment paradigms have limitations, such as the high recurrence rates after curative treatments, resistance to systemic therapies, and the immunosuppressive tumor microenvironment. These challenges drive interest in exploring combination strategies like radiation therapy (RT) with immune checkpoint inhibitors (ICIs), which could potentially overcome resistance mechanisms, enhance antigen presentation, and improve systemic responses by altering the tumor microenvironment in viral-mediated HCC.

Pathogenesis of HBV- and HCV-Induced HCC

HBV is a double-stranded DNA virus implicated in the onset of HCC. By integrating its DNA into the host's genome, HBV disrupts normal cellular function and leads to chromosomal instability, a precursor to cancer development.[3,6] The HBV X protein (HBx), central to this process, initiates a cascade of cellular events that promote oncogenesis. It activates key signaling pathways such as MAPK and PI3K/Akt, which leads to inflammation and cellular proliferation, while also suppressing the tumor-suppressive actions of proteins like p53 by sequestering them away from the nucleus.[3,6] This leads to uncontrolled cell growth and genomic instability.[6] Furthermore, HBx alters the epigenetic landscape, affecting gene expression patterns linked to cancer progression and silencing tumor suppression.[3]

While HBV-induced HCC is most prevalent in patients with cirrhosis, accounting for around 80% of all HBV-related HCC, HBV can induce HCC without the presence of cirrhosis, partly due to mutations in its genome.[3] Notably, mutations in the TERT, ARID2, and ARID1A genes are implicated in increasing cancer risk.[3] Besides these genomic alterations, HBV's interaction with the host's immune system plays a critical role in its oncogenic process. The inhibitory effect of HBV on innate and adaptive immune cells causes evasion of host defenses and creates an environment conducive to tumor development.[3] Emerging research points to the involvement of additional mechanisms in HBV's pathogenicity. The virus influences processes like exosome release and metabolic regulation, which can accelerate the progression from liver inflammation to HCC. For instance, the virus's influence on the body's metabolic pathways could lead to the creation of a tumor-friendly microenvironment. Lastly, the release of exosomes loaded with viral particles or oncogenic proteins can facilitate cell-to-cell communication that promotes cancer progression.[3,7] These intricate and interconnected pathways underscore the complexity of HBV's role in hepatocarcinogenesis and highlight the virus's ability to hijack multiple cellular processes to facilitate the development of HCC.

HCV is a small, enveloped virus with a single-stranded RNA genome that significantly increases the risk of HCC. Chronic HCV infection increases oxidative stress in hepatocytes, leading to DNA damage and mutations that can progress to cancerous changes.[8] Cirrhosis-induced carcinogenesis is one of the major contributors of HCV-induced HCC, and this can occur even with HCV clearance.[1] The annual incidence rate of HCC in cirrhotic patients is 1% to 7%. HCV infection often results in chronic liver inflammation, driven by continuous immune cell activation and cytokine production, leading to fibrosis and eventually cirrhosis.[8] HCV's core proteins influence cell cycle and apoptosis pathways, contributing to malignant transformation of hepatocytes. Furthermore, HCV is associated with downregulation of tumor-suppressor genes such as TP53, TP73, and RB1, leading to uncontrolled cellular proliferation.[8-10] This virus also disrupts normal metabolic processes, including glucose and lipid metabolism, which contributes to conditions like steatosis, which are risk factors for HCC.[8] Finally, HCV can impair the immune system's ability to detect and destroy infected cells by interfering with immune checkpoint pathways.[8] Chronic HCV infection can evolve over decades from mild liver inflammation to severe conditions such as cirrhosis and finally HCC, especially when combined with other risk factors like alcohol use or co-infection with other viruses. Given the complexity of HCV-induced hepatocarcinogenesis, consistent monitoring and treatment are required to decrease the burden of HCC in patients with HCV infection.

Prevention of Chronic Viral Infection-Induced HCC

HBV-related HCC has had a reduced incidence rate due to preventive measures such as HBV vaccination and antiviral therapies.[1] It is estimated that the initiation of neonatal HBV vaccination in the 1980s in East Asian countries has reduced the incidence of HBV infection by 70% to 80%. For example, after 30 years of universal neonatal vaccination, the HCC rates decreased by 80%.[4] Nucleoside/nucleotide analogs (NUCs) are the first-line antiviral treatments for patients with chronic HBV due to high efficacy in viral suppression, high barrier to viral resistance, and favorable safety profile. It is reported that HCC prevention is mostly seen in patients with complete

viral suppression.[11-13] Additionally, NUCs prevent HBV reactivation in immunocompromised patients.[12] Meanwhile, pegylated-interferon has shown sustained virological response (SVR) in about 20% of patients with short duration of treatment, but it has lower efficacy and safety compared with NUCs.[11-14] The antiviral treatment does not cure chronic hepatitis B infection; however, their main goals are to provide viral suppression, progression of liver disease, and even reverse cirrhosis.[14] Some clinical trials have shown that direct acting antivirals (DAA) based interferon-free therapy has SVR rates of above 90%.[15] Furthermore, DAA therapy has contributed to a decreased incidence rate of HCV-induced HCC, with data suggesting a 76% risk reduction of HCC in patients who achieved SVR with DAA therapy compared with those who did not achieve SVR.[1,16] However, the risk of HCC remains high in patients with HCV cirrhosis despite achieving SVR, emphasizing the importance of continued surveillance with imaging and alpha fetoprotein (AFP) testing.[15]

Immunotherapy

Given the multiple mechanisms contributing to chronic viral infection-induced tumorigenesis, such as alternation of immune pathways and invasion of the immune system, the use of targeted immunotherapy in advanced HCC has been a promising research area. In viral-mediated HCC, chronic infections with HBV or HCV cause persistent inflammation and immune evasion, which not only promotes the progression of liver disease but also contributes to the establishment of an immunosuppressive tumor microenvironment. This immune invasion is crucial for the survival and proliferation of HCC cells, particularly in the context of viral infections. The PD-1 pathway, involving the PD-1 receptor on T cells and the PD-L1 ligand on cancer cells, is a key target for many ICIs. By blocking the PD-1 receptor or the PD-L1 ligand, these therapies help prevent cancer cells from evading immune detection, enabling T cells to recognize and attack them.[17] Additionally, the CTLA-4 checkpoint protein, which further impairs T cell function, is another critical target for ICI therapy.[18]

A phase 3 trial compared combination of tremelimumab (an anti-CTLA-4 antibody) and durvalumab (an anti-PD-L1 antibody) with durvalumab alone and sorafenib in patients with unresectable HCC. The trial demonstrated that combination immunotherapy significantly improved overall survival (OS) compared with sorafenib (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.65-0.92; $P = .0035$), while durvalumab alone was found to be noninferior to sorafenib (HR, 0.86; 96% CI, 0.73-1.03). The incidence of grade 3/4 treatment-related adverse events was 25.8% for the combination, 12.9% for durvalumab, and 36.9% for sorafenib.[19]

Interestingly on subgroup analysis, HBV cirrhosis drove a strong survival benefit (HR, 0.64; 95% CI, 0.48-0.86). Similarly, the IMBRAVE-150 study evaluated the combination of atezolizumab (an anti-PD-L1 antibody) and bevacizumab (a VEGF inhibitor) compared with sorafenib alone in patients with unresectable HCC. The 12-month OS rates were 67.2% in combination arm compared with 54.6% for sorafenib alone. Median progression-free survival (PFS) was also significantly longer at 6.8 months for the combination group vs 4.3 months for sorafenib (HR, 0.59; 95% CI, 0.47-0.76; $P < .001$).[20] These ICIs work in synergy as inhibiting PD-L1 activated T-effector cells and VEGF inhibition allows T cells to enter the tumor microenvironment to prevent cancer growth.[20] Similar to durvalumab and tremelimumab on subgroup analysis, patients with HBV had improved OS with immunotherapy (HR, 0.47; 0.33-0.67), while nonviral and hepatitis C etiology did not. Similarly, tremelimumab treats HCC by blocking the CTLA-4 checkpoint on T cells, which enhances T cell activation and proliferation. This improves the immune system's ability to recognize and attack cancer cells.[21] Meanwhile, adoptive cell immunotherapy (ACI) requires specific tumor antigens and is hindered by the tumor microenvironment, and sorafenib targets specific kinases that do not boost the immune response. ICIs overcome these limitations, providing a more comprehensive and durable treatment for viral HCC compared with ACI and sorafenib.[22,23]

Radiation Therapy

Currently, the BCLC staging does not include RT as part of the treatment paradigm for HCC. However, RT is increasingly recognized as a viable locoregional treatment for inoperable HCC, now included in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines).[24] Technological improvements in RT, including the use of stereotactic body radiation therapy (SBRT), have enabled more precise targeting of tumors, minimizing damage to healthy liver tissue and improving treatment outcomes.[17] RT can turn cancer cells into a personalized vaccine by causing them to release tumor-specific antigens, antigen-presenting cells, and primes T cells that activate the immune system. During radiation, reactive oxygen species are generated, which modify proteins and DNA, increasing

antigenicity and making the cancer cells more recognizable.[18] This triggers the cGAS-STING pathway, leading to type I interferon production and enhanced T cell priming by antigen-presenting cells.[25] Additionally, radiation upregulates immune markers like major histocompatibility complex (MHC) class I and FAS on tumor cells, attracting immune cells into the tumor microenvironment and facilitating a robust anticancer response throughout the body.[26,27] Clinical use of SBRT for patients with HCC who are not eligible for other curative therapy has shown promising data with high local control (LC) rates of 68% to 95% 2-3 years following treatment.[17] The use of partial liver RT to a median dose of 40-66 Gy using standard fractionation regimen has shown response rates ranging from 57% to 92%.[17] Even with these promising data, it is important to remember that RT can reactivate hepatitis, and retrospective data on HBV show that patients on antivirals undergoing radiation treatment have lower rates of HBV reactivation compared with patients who are not on antiviral treatment (7.5% vs 33.3%, $P < .001$).[28]

A promising synergistic systemic therapy for use with radiation is chimeric antigen receptor T cell therapy (CAR-T). CAR-T works by taking T cells from a patient and then they are modified to express receptors that can target specific antigens and proteins. Studies with CAR-T therapy and T cell receptor T cells targeting HBV antigens are promising, and the specificity of the tumor-specific antigens it targets can be used synergistically with RT.[28] The use of such adoptive cell therapy is a new and emerging field that could improve the efficacy of RT in viral-mediated HCC. While no studies are available focusing on the combination of RT and adoptive cell therapies for viral HCC, it is an unexplored field with a promising future.

A recent randomized phase 3 trial, RTOG 1112, compared clinic outcomes of SBRT followed by sorafenib with sorafenib alone in patients with new or recurrent HCC, unsuitable for surgery, ablation or TACE. Out of all 193 patients, 41% had hepatitis C and 19% had hepatitis B or B/C. It was found that SBRT with sorafenib improved OS (15.8 months vs 12.3 months) and PFS (9.2 months vs 5.5 months) compared with sorafenib alone. There was no difference in adverse effects in both groups.[29] Whether subgroup analysis will predict a greater benefit among patients with viral-induced cirrhosis remains to be evaluated, pending the final publication of these data.

In a study from the Asian Liver Radiation Therapy Study Group, a retrospective evaluation was conducted on the efficacy of SBRT in treating HCV infection-induced HCC compared with other etiologies. Patients with HCV-related HCC had superior 2-year LC of 88% compared with 78% for other patients. This pattern persisted across different schedules and tumor sizes. HCV etiology was associated with approximately 50% relative risk reduction and 10% to 20% absolute risk reduction for local recurrence post SBRT.[30] This association is particularly notable as it is the first report to demonstrate such a link, suggesting that HCV status could be a critical factor in tailoring SBRT for patients with HCC. RT has been shown to be an effective alternative for inoperable patients with HCC, with many studies showing favorable outcomes. RT should be a part of multidisciplinary team recommendation for patients with HCC based on the clinical presentation.

Synergistic Effect of Radiation Therapy and Immune Checkpoint Inhibitors

RT causes tumor cells to release tumor-associated antigens that help stimulate tumor-specific immune responses, leading to the recognition and death of tumor cells. Additionally, radiation can lead to the destruction of tumor stroma and tumor microenvironment, allowing evasion by immune cells.[28,31] ICIs further boost this response by blocking immune evasion mechanisms, leading to increased antitumor activity. The combination of RT with ICIs such as ipilimumab, which blocks CTLA-4, has gained significant attention for enhancing T cell activation and improving the ratio of CD8+ T cells to Treg cells.[32] This boosts the in situ vaccination effect of RT, where the tumor itself becomes a source of antigens that "vaccinates" the immune system to attack cancer cells throughout the body.[25] This strategy has shown promising results in both mouse models and human studies, leading to Food and Drug Administration approval for treating metastatic melanoma. Additionally, hypofractionated RT can increase PD-L1 expression in tumors, contributing to RT resistance, which suggests that combining PD-1/PD-L1 blockade with RT could help overcome tumor immunosuppression.[33] Anti-PD-1/PD-L1 monoclonal antibodies have already shown positive outcomes in treating cancers such as non-small cell lung cancer (NSCLC), melanoma, and kidney cancer.[34]

The combination of RT and ICIs has demonstrated promising outcomes in various cancers, including colorectal, breast, melanoma, and lung cancers. Preclinical studies in mouse models of colorectal, breast, and melanoma tumors showed that administering

Table 1. Comparison of Adverse Effects in Studies of ICI + RT, RT Monotherapy, and ICI Monotherapy

STUDY	TREATMENT ARMS	ADVERSE EVENTS
NCT03857815[40]	SBRT + sintilimab	Grade 3: 12% Grade 4 or 5: 0
NCT03203304[41]	SBRT + nivolumab vs SBRT + nivolumab + ipilimumab	SBRT + nivolumab Any grade: 83.3% Grade 3: 50% Grade 4 or 5: 0 SBRT + nivolumab + ipilimumab Any grade: 100% Grade 3: 71.4% Grade 4 or 5: 0
NCT04611165[42]	EBRT + nivolumab	Grade 3 or 4 adverse event: 12% Grade 3 or 4 severe adverse event: 4%
NCT02576509[43] (CheckMate 459)	Nivolumab vs sorafenib	Nivolumab Grade 3: 18% Grade 4: 4% Grade 5: < 1% Sorafenib Grade 3: 47% Grade 4: 2% Grade 5: < 1%
NCT03298451[19] (HIMALAYA)	Tremelimumab + durvalumab (STRIDE) vs durvalumab (D) vs sorafenib (S)	STRIDE Grade 3 or 4: 25.8% Grade 5: 2.3% D group Grade 3 or 4: 12.9% Grade 5: 0 S group Grade 3 or 4: 36.9% Grade 5: 0.8%
UMIM000013011[44] (The STRSPH study)	SBRT	Grade 3 or higher: 11.4% Grade 5: 0

Abbreviations: ICI, immune checkpoint inhibitor; RT, radiation therapy; SBRT, stereotactic body radiation therapy; EBRT, electron-beam radiation therapy.

anti-PD-L1 concurrently with RT led to better long-term tumor control compared with delayed administration.[35-37] This combination has shown potential in HCC, suggesting that it could offer better outcomes for this cancer.[21,38,39] Multiple studies are exploring the synergistic effects of combined immunotherapy and RT in HCC. One retrospective case series of 5 patients with unresectable HCC evaluated clinical response when treated with SBRT and checkpoint inhibitors. Out of the 5 patients, 3/5 had hepatitis B infection and 4/5 had BCLC stage C. All patients responded to this combination therapy, with 2 complete and 3 partial responses. The 1-year LC and OS were 100%.[28] Similarly, a phase 2 study evaluated the efficacy and safety of combining SBRT with sintilimab (a PD-1 antibody) in patients with recurrent or oligometastatic HCC. The study involved 25 patients, and the combination treatment resulted in a confirmed overall response rate (ORR) of 96%, with 17 complete responses and 7 partial responses. The 12-month and 24-month PFS rates were 68% and 45.3%, respectively.[40] The adverse effects with a combination of ICI and RT, ICI alone and RT alone as seen in some studies are summarized in **Table 1**.

HBV and HCV drive HCC by promoting genetic mutations, altering the immune response, and creating a tumor-friendly microenvironment. Immunotherapy, particularly PD-1/PD-L1 and CTLA-4 inhibitors, can help counteract immune evasion mechanisms exploited by these viral infections.[17,18] When combined with RT, which enhances antigen release and alters the tumor microenvironment, there is potential to overcome the immunosuppressive effects caused by viral hepatitis.[32] By boosting the immune system's ability to recognize and attack cancer cells, this combination strategy may offer a more effective approach for treating HCC driven by chronic hepatitis infection.

There is no consensus regarding the timing of ICIs and radiation. Concurrent administration of anti-PD-L1 with RT appears to yield better long-term tumor control compared with delayed ICI initiation, while preclinical models also indicate that anti-CTLA-4 is

Table 2. Ongoing Trials on Radiation and Immunotherapy for Patient Outcomes

STUDY NAME	TREATMENT ARMS	DOSE	ENDPOINTS
NCT06313190[45]	SBRT alone vs SBRT + sintilimab.	SBRT: 30-54 Gy in 3 fractions over 1 week Sintilimab: 200 mg every 3 weeks for up to 6 cycles, with the first dose within 1 week after the completion of SBRT.	Primary: PFS; secondary: OS, LC, AEs
NCT06261125[46]	SBRT followed by adebrelimab + lenvatinib in 2 cohorts. Arm A includes patients without prior PD-1/PD-L1 therapy. Arm B includes those with progression after prior PD-1/PD-L1 therapy.	SBRT using VMAT: 33-48 Gy in 6 fractions over 2 weeks. Adebrelimab: 1200 mg every 3 weeks for up to 35 cycles after the completion of SBRT. Lenvatinib: 12 mg/day for bodyweight ≥ 60 kg or 8 mg/day for bodyweight < 60 kg, orally once daily after the completion of SBRT.	Primary: PFS; secondary: OS, ORR, DCR, DOR, AEs
NCT05917431[47]	SBRT + tislelizumab + regorafenib.	SBRT: 8 Gy × 3-5 fractions. Tislelizumab: dose of 200 mg every 21 days. Regorafenib: dose of 120 mg for the first 21 days of a 28-day cycle. Systemic therapy will start concurrently and last 2 years, or until disease progression, intolerable side effects or death.	Primary: PFS; secondary: OS, recurrence pattern

Abbreviations: SBRT, stereotactic body radiation therapy; PFS, progression-free survival; OS, overall survival; LC, local control; AEs, adverse events; VMAT, volumetric arc therapy; DCR, disease control rate; DOR, duration of response.

most effective when administered a few days before RT, likely due to its role in depleting regulatory T cells.[24,43] Further studies on this can help guide upcoming treatment paradigms. There are ongoing clinical trials testing outcomes in patients treated with radiation and immunotherapy (**Table 2**). The addition of local therapy to immunotherapy and its impact on national practice guidelines remain to be determined by ongoing trials as well as the implication and synergism with specific subset of HCC such as viral-mediated disease.[24] Follow-up surveillance should be as per NCCN Guidelines with serial AFP evaluation and imaging response.

Conclusion

HCC remains a critical health concern with an intricate web of etiological factors such as HBV and HCC, and lifestyle choices contributing to its pathogenesis. Emerging treatments, particularly SBRT and ICIs, offer significant potential. Notably, research has shown that HCV-related HCC responds more favorably to SBRT compared with non-HCV etiologies, highlighting the potential for etiology-specific treatment customization. As research progresses, the integration of novel systemic therapies, advancements in radiation technology, and the development of predictive biomarkers will be pivotal in enhancing the management of HCC.

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