The Convergence of Viral Precision and Locoregional Therapy in HCC

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Purpose

- Hepatocellular Carcinoma (HCC) is the third leading cause of death globally and is the most prevalent type of liver cancer.
- Locoregional therapies are the standard of care for nonresectable HCC.
- Traditional Locoregional therapies, including Transarterial Chemoembolization (TACE), Transarterial Embolization (TAE), and radiotherapy, have modest survival metrics in advanced HCC cases[1].
- The success and efficacy of TACE decrease with repeat procedures, and further treatment worsens liver function[2].
- Oncolytic Viruses can operate through an array of mechanisms to kill tumor cells, including direct oncolysis, induction of tumor immune response, disruption of tumor angiogenesis, alteration of the tumor microenvironment (TME), or induction of apoptosis[1,3].
- Combining Oncolytic Virotherapy (OV) with other locoregional therapies could provide an alternative solution for advanced and TACE-refractory HCC.

Methods

A review of the published literature covering the use of oncolytic virotherapy in HCC is conducted to identify the latest advances in treatment. Data is collected from the latest clinical and preclinical trials, meta-analyses, and systematic reviews. Findings are presented in text and figure format, comparing the efficacy of different therapies, limitations, and future directions of the field.

Results

- The combination of degradable starch microspheres (DSM) with vesicular stomatitis virus into the hepatic artery led to significantly decreased CD31+ endothelial staining compared to DSM alone, indicating the effectiveness of this combination therapy in reducing tumor angiogenesis[4].
- Recombinant human type 5 adenovirus with TACE increased the overall survival time (p=0.046) and progression-free survival time (p=0.044) when compared to TACE alone[5].
- Immunohistochemical staining of oncolytic herpes simplex virus type 2 showed that the virus was able to replicate and infect neighboring cancer cells after transarterial viroembolization (TAVI) under hypoxic environments[6], leading to increased killing of oncogenic cells.
- TAVI was found to have a more expansive distribution of the oncolytic virus across the tumor compared to tumor injection and IV administration[6].
- A hypoxia-replicative oncolytic adenovirus (HYAD) combined with polyvinyl alcohol (PVA) embolization outperformed HYAD alone, wild type (WT) adenovirus, and WT with PVA in terms of repression of tumor proliferation and intrahepatic metastasis[7].
- Radiofrequency Ablation promotes the entry and replication of oncolytic viruses into tumor cells- there is a consequent increase of tumor-associated antigens and a greater infiltration of CD8 T lymphocytes[8].

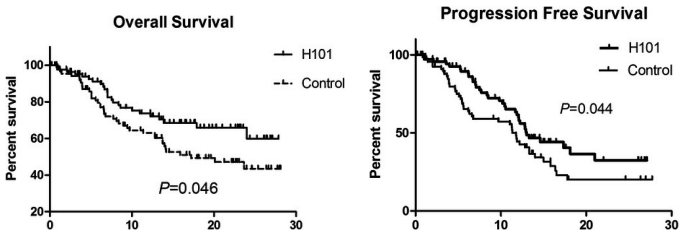

Fig. 1[5]. Kaplan-Meier analysis comparing Overall Survival and Progression Free Survival for H101 adenovirus and TACE combination to TACE alone (control).

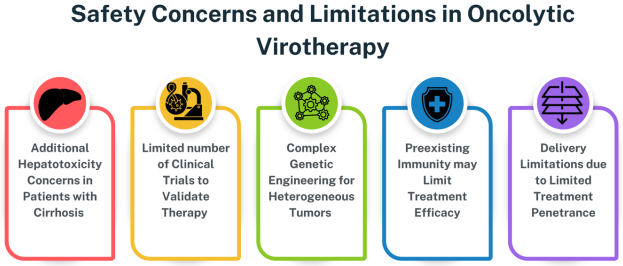

Fig. 2. Visual representation of the discussed Safety Concerns and Limitations of Oncolytic Virotherapy.

Safety Concerns and Limitations

- Additional hepatotoxicity associated with OV which are compounded by the fact that many HCC patients have underlying cirrhosis[9].
- Limited number of clinical trials investigating OV and locoregional therapy in HCC.
- OV genetic engineering poses significant complexities, particularly when reengineering viruses to target the heterogeneous tumor environment of HCC[8].
- Preexisting immunity to the viruses has been shown to reduce treatment efficacy; studies utilizing multiple OV doses show limited induction of tumor-specific immune responses with subsequent doses[10].
- Concerns with the rapid clearance of viruses limit the therapeutic window duration in which OV is effective[9].
- Delivery limitations due to the need to penetrate dense extracellular matrices and heightened pressures in the interstitial space[11].

Future Directions

- Precision engineering will allow for improved tumor selectivity through the targeting of tumor genotypes as well as inserting genes coding for immunoregulatory molecules[11].
- Reconfiguration of vaccines as immuno-virotherapy for TME modulation[12].
- Investigation of delivery systems through the use of stem cells and nanoparticles to increase OV payload[12].
- Further combinations of OV with other immunotherapies, such as immune checkpoint inhibitors and CAR-T cell therapies, to further enhance anti-tumor immune response[11].

Discussion

Locoregional therapies remain the mainstay and established treatment for unresectable HCC; however, their effectiveness is limited in TACE-refractory cases of HCC. OV poses as a promising solution and additional modality, expanding treatment possibilities for advanced and refractory HCC. Different virus strains have been tested and engineered to work through an array of mechanisms, including the disruption of angiogenesis, rupture of cells via constant replication, and activation under hypoxic conditions after embolization. Clinical trials with animal models have shown promising results, synergistically improving multiple outcomes compared to OV and locoregional therapy alone.

While locoregional therapy has been found to improve the distribution of viruses across the tumor environment, several obstacles have hindered the expansion of this treatment modality into clinical practice; there are concerns regarding the safety of OV in HCC patients, who may have limited hepatic reserves. Additionally, the efficacy of OV avoiding systemic clearance or operating when hosts have preexisting immunity is questionable. To see this therapy's wider adoption in clinical practice, randomized controlled trials are required to validate OV and address its unanswered questions.

References

[1] Zhu L, Lei Y, Huang J, et al. Recent advances in oncolytic virus therapy for hepatocellular carcinoma. Front Oncol 2023;13. https://doi.org/10.3389/fonc.2023.1172292.

[2] Choi J, Lee D, Shim JH, et al. Evaluation of transarterial chemoembolization refractoriness in patients with hepatocellular carcinoma. PLOS ONE 2020;15:e0229696. https://doi.org/10.1371/journal.pone.0229696.

[3] Du W, Na J, Zhong L, et al. Advances in preclinical and clinical studies of oncolytic virus combination therapy. Front Oncol 2025;15. https://doi.org/10.3389/fonc.2025.1545542.

[4] Altomonte J, Braren R, Schulz S, et al. Synergistic antitumor effects of transarterial viroembolization for multifocal hepatocellular carcinoma in rats. Hepatology 2008;48:1864–73. https://doi.org/10.1002/hep.22546.

[5] Lin X, Li Q, Lao X, et al. Transarterial injection of recombinant human type-5 adenovirus H101 in combination with transarterial chemoembolization (TACE) improves overall and progressive-free survival in unresectable hepatocellular carcinoma (HCC). BMC Cancer 2015;15:707. https://doi.org/10.1186/s12885-015-1715-x.

[6] Cao Y, Xiong F, Kan X, et al. Transarterial viroembolization improves the therapeutic efficacy of immune-excluded liver cancer: Three birds with one stone. Pharmacological Research 2023;187:106581. https://doi.org/10.1016/j.phrs.2022.106581.

[7] Zhang H, Xiong F, Qian K, et al. Transcatheter arterial embolization combined with hypoxia-replicative oncolytic adenovirus perfusion enhances the therapeutic effect of hepatic carcinoma. Cancer Management and Research 2019;11:981–96. https://doi.org/10.2147/CMAR.S189208.

[8] Abd MA, Asiri M, Farhan SR, et al. Update on Application of Oncolytic Virus-Based Combination Therapy in the Treatment of Hepatocellular Carcinoma. Journal of Biochemical and Molecular Toxicology 2025;39:e70327. https://doi.org/10.1002/jbt.70327.

[9] Altomonte J, Ebert O. Sorting Out Pandora's Box: Discerning the Dynamic Roles of Liver Microenvironment in Oncolytic Virus Therapy for Hepatocellular Carcinoma. Front Oncol 2014;4. https://doi.org/10.3389/fonc.2014.00085.

[10] Groeneveldt C, van den Ende J, van Montfoort N. Preexisting immunity: Barrier or bridge to effective oncolytic virus therapy? Cytokine & Growth Factor Reviews 2023;70:1–12. https://doi.org/10.1016/j.cytogfr.2023.01.002.

[11] Alwithenani A, Hengswat P, Chiocca EA. Oncolytic viruses as cancer therapeutics: From mechanistic insights to clinical translation. Molecular Therapy 2025;33:2217–28. https://doi.org/10.1016/j.ymthe.2025.03.035.

[12] Omolekan TO, Folahan JT, Tesfay MZ, et al. Viral warfare: unleashing engineered oncolytic viruses to outsmart cancer's defenses. Front Immunol 2025;16. https://doi.org/10.3389/fimmu.2025.1618751