



Liver Transplantation Following Hepatocellular Carcinoma Rupture and Long-Term Immunotherapy: A Case Report

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Abstract

Aim To report a case of advanced hepatocellular carcinoma (HCC) complicated by tumor rupture, successfully downstaged with combined oncolytic immunotherapy (Pexa-Vec) and a PD-1 inhibitor (Nivolumab), ultimately enabling liver transplantation (LT). This report highlights the potential role of immune checkpoint inhibitors (ICIs) as bridging therapy in otherwise ineligible patients.

Methods A 54-year-old male with HCV-related cirrhosis presented with multifocal, unresectable HCC (BCLC C) complicated by hemoperitoneum. Surgery was not indicated. He was enrolled in a Phase I/IIa trial of intralesional Pexa-Vec and intravenous Nivolumab (240 mg every 14 days). Percutaneous biopsies confirmed Edmondson–Steiner grade 2 HCC. Clinical, laboratory, and imaging follow-up were performed throughout therapy. Pre-transplant screening was performed after 4 years of stable disease.

Results The patient received three intralesional Pexa-Vec injections and 93 cycles of Nivolumab over four years, with only mild, transient adverse events. Imaging showed stable disease without extrahepatic spread. Pre-LT evaluation confirmed preserved liver function (Child-Pugh A5, ECOG 0). Immunotherapy was suspended 12 weeks before LT, and LT was performed successfully in September 2023. Post-transplant follow-up (24 months) revealed no recurrence of HCC or graft rejection. HCV was eradicated with direct-acting antivirals. Explant pathology showed complete necrosis in injected nodules and regressive changes in other lesions.

Conclusions ICIs alone or in combination with oncolytic immunotherapy may serve as novel downstaging strategies in advanced, ruptured HCC. Successful LT with long-term disease-free survival challenges traditional concerns about peritoneal seeding. Larger studies are required to define optimal patient selection, timing, and safety of pre-transplant ICIs.

Lay summary A 54-year-old man with advanced, ruptured liver cancer had an unexpectedly stable course over four years while receiving immunotherapy and an oncolytic virus. He later underwent a liver transplant and remains cancer-free two years later, illustrating the unpredictable nature of some severe liver cancer cases.

Clinical trial registration Not applicable.

Keywords Hepatocellular Carcinoma · Liver Transplantation · Immune Checkpoint Inhibitors · Hemoperitoneum · Pexa-Vec

Abbreviations

HCC Hepatocellular Carcinoma
AFP Alpha-fetoprotein
CT Computed Tomography
DAAs Direct-Acting Antivirals

ECOG-PS Eastern Cooperative Oncology Group
ICIs Immune Checkpoint Inhibitors
LT Liver Transplantation
PCR C-Reactive Protein
PD-1 Programmed Cell Death Protein

Extended author information available on the last page of the article

PD-L1	Programmed Death-Ligand 1
Pexa-Vec	Pexastimogene Devacirepvec
TKI	Tyrosine Kinase Inhibitor

Introduction

Liver transplantation (LT) provides the highest chance of long-term survival in patients with hepatocellular carcinoma (HCC) and cirrhosis, treating both the tumor and underlying liver disease [1]. Access is restricted by strict selection criteria to minimize post-transplant recurrence, excluding many patients with intermediate- or advanced-stage HCC.

Downstaging strategies aim to expand eligibility, integrating tumor burden, biology, and treatment response into decision-making [2, 3]. Systemic therapy for advanced HCC has evolved: after the era of multikinase inhibitors, immune checkpoint inhibitors (ICIs) have reshaped treatment paradigms, demonstrating survival benefits with favorable safety [4, 5].

Combination approaches are emerging. Oncolytic virotherapy, such as Pexa-Vec (JX-594), selectively infects tumor cells, induces oncolysis, activates the immune system, and exerts antiangiogenic effects [6–8]. Viral-mediated immune priming may enhance PD-1 inhibitor efficacy, providing theoretical synergy [6].

Spontaneous HCC rupture carries a poor prognosis due to a high risk of peritoneal dissemination, often precluding LT [9, 10]. The role of immunotherapy-based bridging strategies in this context is largely unexplored. We report a case of ruptured, multifocal advanced HCC successfully managed with prolonged combined immunotherapy, enabling LT without recurrence.

Case Report

In June 2019, a 54-year-old Italian male presented to a Spanish hospital with acute abdominal pain, nausea, vomiting, diaphoresis, and hypotension. History included controlled hypertension and active smoking. CT revealed a large hemoperitoneum and multifocal liver lesions (most significant: 8 cm in segment VIII, 4 cm in segment III), consistent with advanced HCC without biliary invasion or portal vein thrombosis. Alpha-fetoprotein (AFP) was 219.8 ng/mL. Tumor rupture was presumed to be the source of bleeding.

Transferred to our tertiary center, ultrasound-guided biopsy confirmed grade 2 HCC (Edmondson–Steiner) and HCV-related cirrhosis. Given multifocal BCLC C disease, surgical or locoregional therapy was not indicated. Preserved performance status (ECOG 0) and liver function (Child-Pugh A5) allowed enrollment in a Phase I/IIa trial evaluating intralesional Pexa-Vec plus Nivolumab (240 mg IV every 14 days) as first-line therapy.

Three intralesional Pexa-Vec injections (on days 1, 15, and 29) were administered into a segment V lesion. Nivolumab started concurrently. Mild adverse events included transient right bundle branch block and minor laboratory inflammatory changes. After the start of systemic therapy, there was a drop-out of AFP, which remained constantly at values lower than 3 ng/mL. Therapy continued post-trial closure until March 2024 (93 infusions).

Serial imaging demonstrated stable disease without extrahepatic spread. In 2023, after nearly 4 years of disease control, a multidisciplinary evaluation found LT feasible. Immunotherapy was discontinued in May 2023, and LT was performed in September 2023, 12 weeks later (Fig. 1).

Explant Pathology

Histology confirmed cirrhosis and chronic HCV infection. The Pexa-Vec-injected lesion showed complete necrosis and fibrosis, with no viable tumor. Other nodules showed regressive changes; microvascular invasion was absent. No peritoneal seeding or extrahepatic disease was observed.

At 24 months post-LT, the patient remains well, without HCC recurrence or graft rejection. HCV was eradicated with sofosbuvir/velpatasvir. The most recent CT (May 2026) confirmed the absence of recurrent disease (Figs. 2 and 3).

Discussion

This case illustrates exceptional long-term disease control in advanced, ruptured, multifocal HCC, which has historically been considered ineligible for LT [1, 9]. Systemic therapy in this setting was traditionally palliative. ICIs now enable durable responses in selected patients [4, 5].

The prolonged stability of Nivolumab over 4 years demonstrates that extended exposure is feasible with careful monitoring. Durable responses may enable systemic therapy to serve as a biologic selection tool for LT, aligning with multiparametric treatment strategies [2, 3].

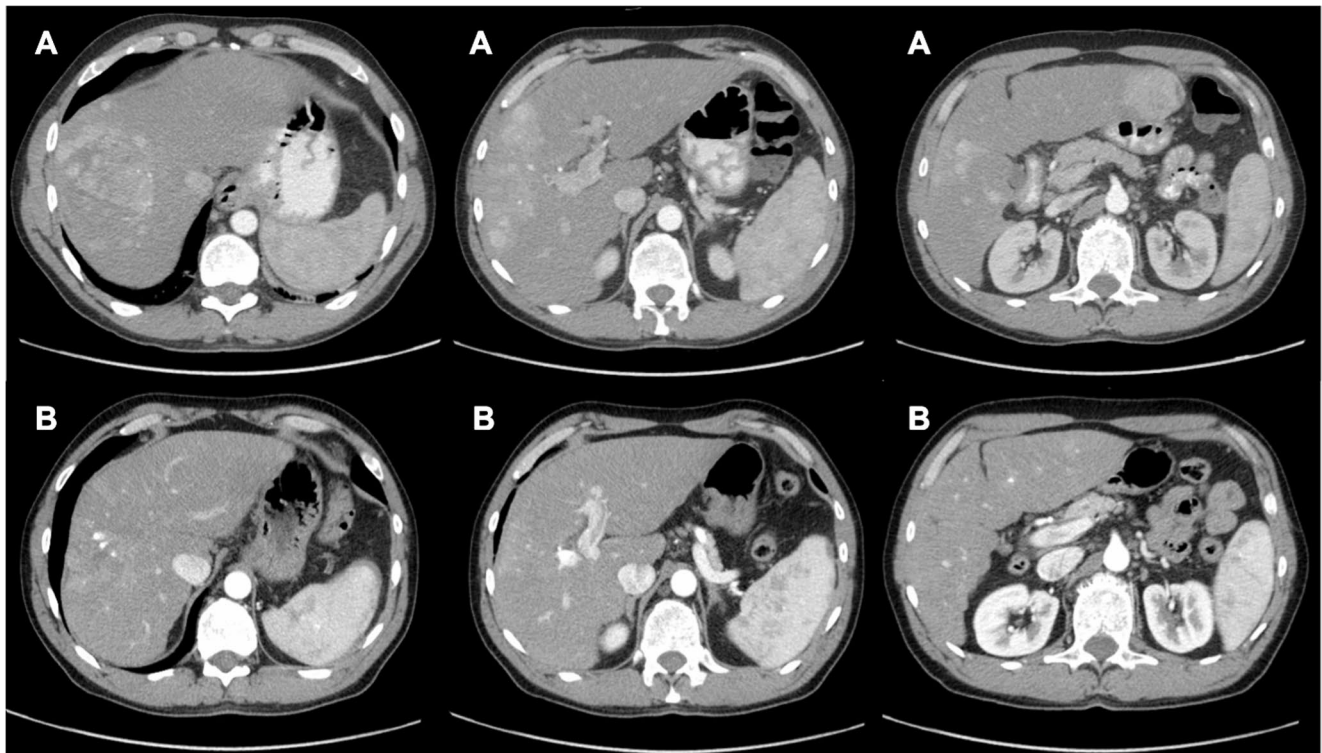


Fig. 1 A: CT scan at baseline. B: CT scan after 93^h of Nivolumab infusion



Fig. 2 Last follow-up abdominal CTscan after Liver Transplant (May 2026)

While the contribution of Pexa-Vec is uncertain, explant pathology supports a local effect. Pexa-Vec induces tumor lysis, immune activation, and antiangiogenic activity, potentially synergizing with PD-1 blockade [6–8].

Ruptured HCC usually precludes LT because of the risk of peritoneal seeding [9, 10]. The absence of peritoneal disease in this case suggests that systemic immune control may mitigate spread, warranting further investigation.

Pre-LT ICIs raise concerns about allograft rejection. Recent systematic reviews and meta-analyses suggest that, with appropriate washout, pre-LT ICIs may be feasible [11–13].

Ethical considerations were addressed through trial approval, institutional oversight, and evaluation by a multidisciplinary transplant committee. LT was performed only after prolonged disease stability and ICI discontinuation to minimize the risk of rejection.

Conclusion

We report a patient with ruptured, multifocal, advanced HCC who achieved prolonged disease control with combined immunotherapy and underwent LT without recurrence. Although generalization is limited, this case supports further study of ICIs, alone or with oncolytic virotherapy, as downstaging strategies for highly selected patients.

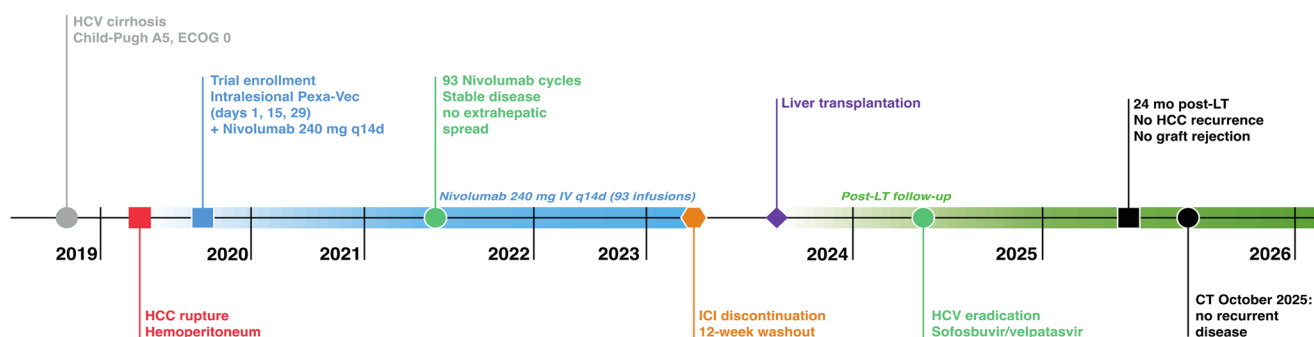


Fig. 3 Timeline of clinical history

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Author Contributions All authors had full access to the data in the study and take responsibility for its integrity and the accuracy of the data analysis. Conceptualization LDM, MS, NDM, FDB; writing original draft LDM, MS; writing review and editing LDM, AP, NDM, AC, VB, SDS, FDB, MS, SDS, BC, MD, FC, CC, AP, and AS; Supervision FDB, SDS, MD, AC. All authors read and agreed to the published version of the manuscript.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval, consent to participate, and permission for publication have been obtained We confirmed that all methods followed the relevant guidelines and the Declaration of Helsinki.

Consent for Publication We have obtained the patient's consent for publication, which is stored and available in the patient's documentation at our facility.

Competing interests The authors declare no competing interests.

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References

- Bhoori S, Sposito C, Germini A, Coppa J, Mazzaferro V. The challenges of liver transplantation for hepatocellular carcinoma on cirrhosis. *Transpl Int*. 2010;23(7):712–22. <https://doi.org/10.1111/j.1432-2277.2010.01111.x>. Epub 2010 May 14. PMID: 20492616.
- Vitale A, Cabibbo G, Iavarone M, Viganò L, Pinato DJ, Ponziani FR, HCC Special Interest Group of the Italian Association for the Study of the Liver. Personalised management of patients with hepatocellular carcinoma: a multiparametric therapeutic hierarchy concept. *Lancet Oncol*. 2023;24(7):e312–e322. [https://doi.org/10.1016/S1470-2045\(23\)00186-9](https://doi.org/10.1016/S1470-2045(23)00186-9). PMID: 37414020.
- Mazzaferro V, Citterio D, Bhoori S, Bongini M, Miceli R, De Carlis L et al. Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial. *Lancet Oncol*. 2020;21(7):947–56. doi: 10.1016/S1470-2045(20)30224-2. Erratum in: *Lancet Oncol*. 2020;21(8):e373. [https://doi.org/10.1016/S1470-2045\(20\)30387-9](https://doi.org/10.1016/S1470-2045(20)30387-9). PMID: 32615109.
- Llovet JM, Castet F, Heikenwalder M, Maini MK, Mazzaferro V, Pinato DJ, et al. Immunotherapies for hepatocellular carcinoma. *Nat Rev Clin Oncol*. 2022;19(3):151–72. <https://doi.org/10.1038/s41571-021-00573-2>. Epub 2021 Nov 11. PMID: 34764464.
- Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY et al. IMbrave150 Investigators. Atezolizumab plus Bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894–905. <https://doi.org/10.1056/NEJMoa1915745>. PMID: 32402160.
- Raja J, Ludwig JM, Gettinger SN, Schalper KA, Kim HS. Oncolytic virus immunotherapy: prospects for oncology. *J Immunother Cancer*. 2018;6(1):140. <https://doi.org/10.1186/s40425-018-0457-3>. PMID: 30455826; PMCID: PMC6230443.
- Heo J, Reid T, Ruo L, Breitbach CJ, Rose S, Bloomston M, et al. Randomized dose-finding clinical trial of oncolytic immunotherapeutic vaccinia JX-594 in liver cancer. *Nat Med*. 2013;19(3):329–36. <https://doi.org/10.1038/nm.3089>. Epub 2013 Feb 10. PMID: 23396206; PMCID: PMC4268543.
- Breitbach CJ, Burke J, Jonker D, Stephenson J, Haas AR, Chow LQ et al. Intravenous delivery of a multi-mechanistic cancer-targeted oncolytic poxvirus in humans. *Nature*. 2011;477(7362):99–102. <https://doi.org/10.1038/nature10358>. PMID: 21886163.

9. Xu L, Zhou J. Interpretation of NCCN guidelines for hepatobiliary tumors V3 update in 2021. *Hepatobiliary Surg Nutr.* 2021;10(5):682–5. <https://doi.org/10.21037/hbsn-21-355>. PMID: 34760973; PMCID: PMC8527422.
10. Wang W, Meng T, Chen Y, Xu YC, Zhao YJ, Zhang Y, et al. Propensity score matching study of 325 patients with spontaneous rupture of hepatocellular carcinoma. *Hepatobiliary Surg Nutr.* 2022;11(6):808–21. <https://doi.org/10.21037/hbsn-21-45>. PMID: 36523928; PMCID: PMC9745608.
11. DeLeon TT, Salomao MA, Aqel BA, Sonbol MB, Yokoda RT, Ali AH, et al. Pilot evaluation of PD-1 inhibition in metastatic cancer patients with a history of liver transplantation: the Mayo Clinic experience. *J Gastrointest Oncol.* 2018;9(6):1054–62. PMID: 30603124; PMCID: PMC6286929.
12. Tabrizian P, Abdelrahim M, Schwartz M. Immunotherapy and transplantation for hepatocellular carcinoma. *J Hepatol.* 2024;80(5):822–5. <https://doi.org/10.1016/j.jhep.2024.01.011>. Epub 2024 Jan 20. PMID: 38253289.
13. Rezaee-Zavareh MS, Yeo YH, Wang T, Guo Z, Tabrizian P, Ward SC, et al. Impact of pre-transplant immune checkpoint inhibitor use on post-transplant outcomes in HCC: a systematic review and individual patient data meta-analysis. *J Hepatol.* 2025;82(1):107–19. Epub 2024 Jul 10. PMID: 38996924; PMCID: PMC11655254.

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