

86183\_Auto\_Edited.docx

**Unresectable Hepatocellular carcinoma with portal vein tumor thrombus achieved long-term survival after radiotherapy-antiangiogenesis-immune checkpoint blockade combination therapy: A case report**

Ying Zhao, Guo sheng He, Gong Li

**Abstract**

**BACKGROUND**

Portal vein tumor thrombus (PVTT) is a common complication, accounting for 44%-62.2% of Hepatocellular carcinoma (HCC), and often indicates the poor prognosis. There is no global consensus for the treatment of unresectable HCC with PVTT. In the present case, we reported a novel strategy of radiotherapy-antiangiogenesis-immune checkpoint blockade combination, which showed better response and prolonged survival.

**CASE SUMMARY**

A 51-year-old male diagnosed with HCC (Child-Pugh class A), chronic hepatitis B virus infection and Cheng's type III PVTT, was given radiotherapy to part of the lesion plus targeted therapy as the first-line therapy, and achieved partial remission (PR). After radiotherapy, lenvatinib plus pembrolizumab was used as maintenance therapy, and complete remission (CR) was achieved. The patient remains alive 46 months after the diagnosis of the HCC with PVTT.

**CONCLUSION**

This case of unresectable HCC patient with PVTT treated by radiation-lenvatinib-pembrolizumab combination therapy shows apparent clinical efficacy, which demonstrates that local radiotherapy plus antiangiogenesis and immune checkpoint blockade (RACIB) could also benefit patients with advanced HCC.

## INTRODUCTION

<sup>15</sup> The incidence of hepatocellular carcinoma (HCC) among patients with portal vein tumor thrombus (PVTT) has been reported to be 44-62.2% <sup>19</sup> [1]. The incidence of portal vein tumor thrombus (PVTT) among patients with hepatocellular carcinoma (HCC) has been reported to be 44-62.2% <sup>19</sup> [1], which is well-known poor prognostic factor for HCC [2-6]. For patients with tumor thrombus involving only the segmental branches of portal vein, or left/right portal vein (Cheng's type I/II), surgical resection provides the only chance for radical treatment if the primary tumor can be resected. However, for patients whose tumor thrombus has invaded the main portal vein trunk and above (Cheng's type III/IV), surgery is not possible and the median overall survival(OS) is usually only 6-8 mo [7].

<sup>17</sup> There is no global consensus or guideline for the treatment of HCC patients with PVTT. European and American guidelines followed the Barcelona Clinic Liver Cancer Staging (BCLC), regarded HCC with macroscopic vascular invasion at BCLC Stage C, and recommended systemic therapy as the therapeutic strategy, including atezolizumab plus bevacizumab, sorafenib or lenvatinib [6-10]. <sup>2</sup> On the contrary, experts from Asian countries (e.g., China) recommended multidisciplinary therapies, including surgery, transcatheter arterial chemoembolization (TACE), radiotherapy (RT), and molecular targeted therapy, which may achieve satisfactory outcomes [11-14].

However, the best comprehensive treatment is still inconclusive and the clinical needs of such patients need to be met urgently. In the present case report, we found that radiotherapy-antiangiogenesis-immune checkpoint blockade combination therapy

showed a marked response and prolonged survival, contributing to promising outcomes.

7

## **CASE PRESENTATION**

### ***Chief complaints***

A 51-year-old male was admitted to our hospital with chief complaints of anorexia and fatigue of 2 mo duration.

### ***History of present illness***

In February 2018, the patient felt anorexia and fatigue without any apparent inducements, accompanied by a weight loss of 5 kg during 2 mo. Routine blood tests showed no abnormalities, while biochemical tests showed albumin (ALB) level of 32 g/L, total bilirubin (TBIL) level of 23.3  $\mu\text{mol/L}$ , and prothrombin time (PT) of 13.9 s, which were all abnormal. Besides, alpha-fetoprotein (AFP) level was significantly higher than the expected value (8,875 ng/mL). Ultrasonography showed multiple lesions in the liver, of which the largest one was about 10 cm in the left lobe of the liver, and tumor thrombus was expanded into the portal vein. The dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI) revealed a 10.6×8.3-cm nodule a 10.6×8.3 cm mass in the left lobe of the liver (Figure 1A, ellipse), and multiple metastases were found in the right lobe of the liver. Tumor thrombus was detected in the inferior vena cava and major portal vein (Figures 1B and 1C).

### ***History of past illness***

11

The patient had a history of chronic hepatitis B virus (HBV) infection for 20 years, and underwent regular antiviral therapy with Entecavir that reduced HBV-DNA level to the normal range.

### ***Personal and family history***

none

### *Physical examination*

The abdominal examination revealed epigastric tenderness. The patient's body temperature was 38.3 °C, with blood pressure of 130/85 mmHg, heart rate of 93 beats per min, respiratory rate of 18 breaths per min, and oxygen saturation on room air was 99%.

### *Laboratory examinations*

Routine blood tests showed no noticeable abnormalities, and biochemical tests showed ALB of 32 g/L, TBIL of 23.3 μmol/L, and PT of 13.9 s, which were all abnormal.

### *Imaging examinations*

---

**Figure 1. The dynamic contrast-enhanced MRI showed hepatocellular carcinoma, IVCTT and MPVTT before and after therapy.** A-C: Images before treatment (March 2018), the liver tumor (A, ellipse): IVCTT (B, arrow), the MPVTT (C, arrow). D-F: Images of 2 mo after radiotherapy (June 2018), partial remission of the tumor (D, ellipse), partial remission of the IVCTT (E, arrow), and partial remission of the MPVTT (F, arrow). G-I: Images of 36 mo after radiotherapy (May 2021), complete remission of tumor (G), complete remission of IVCTT (H), and complete remission of MPVTT (I).

## FINAL DIAGNOSIS

The final diagnosis of the present case was hepatocellular carcinoma (Child-Pugh class A), chronic hepatitis B virus infection and Cheng's type III PVTT.

## TREATMENT

The patient underwent four-dimensional computed tomography (4DCT) simulations. The respiratory cycle was divided into 0%-90% respiratory phase images based on the respiratory signal, which were reconstructed by the system (Elekta, Sweden) for treatment planning. Thermoplastic shell was used as custom immobilization device in the simulation. RT was delivered to lesion using the volumetric modulated arc therapy (VMAT) technique. Cone-beam CT images matching the target volume were used for daily imaging guidance.

The gross tumor volume (GTV) of liver lesion was defined as a visible tumor on fusion images of CT with MRI. The internal target volume (ITV) was the envelope of all GTVs from the ten respiratory phases. The clinical tumour volume (CTV) of the primary tumour was generated by adding 5 mm to the ITV in all directions. The PTV of the primary tumour was expanded to include a 5mm margin from the CTV. At least 95% of the PTV was covered by the prescribed dose, which was prescribed to the periphery of the PTV.

As PVTT can cause HCC cells to be disseminated, and considering the dose constraints of normal liver and neighboring organs at risk, meanwhile reducing disease burden to the greatest possible extent for helping to optimize responses to ICI, we had partial irradiation. RT, which irradiated only on the whole PVTT and left part of the tumor (Figure 2), was started on March 15, 2018, with a prescription dose of 300 cGY×12F and oral administration of lenvatinib (12 mg, QD). Lenvatinib was used not only during radiotherapy, but also continuously for 2 mo after radiotherapy. In June 2018, 2 mo after RT, the DCE-MRI scan showed that the size of lesions in the left lobe of the liver was significantly reduced (Figure 1D, ellipse), a part of the primary tumor had become cystic lesions and necrotic, the metastatic lesions were decreased and narrowed,

and the tumor thrombus was shrunk (Figures 1E and F, arrow). No side effect of grade III or above was observed during treatment. The patient achieved partial remission (PR) according to the Response Evaluation Criteria in Solid Tumors (RECIST, Ver. 1.1). From June 2018, maintenance therapy with pembrolizumab (200 mg IV, 1/3W) and lenvatinib (12 mg, QD) was performed for 41 months, and no severe side effect was recorded in this period.

### **OUTCOME AND FOLLOW-UP**

Two months after RT, the size of the liver tumor was significantly reduced, and the tumor thrombus was shrunk. All symptoms were relieved after radiotherapy. During the follow-up (until December 2021), the tumor was well controlled (complete remission (CR)) without recurrence (Figures 1, G-I), and the AFP level was reduced to 1.92 ng/mL. The patient has been survived for 46 months since the diagnosis of advanced HCC with PVTT.

### **DISCUSSION**

Surgical resection is the radical treatment method for initially resectable HCC and good survival can be achieved in R0 patients. However, unresectable advanced stage HCC accounts for more than two-thirds of newly diagnosed HCC. In this case, the patient was unsuitable for radical resection because of the tumor thrombus in the main vessels. European and American guidelines followed the Barcelona Clinic Liver Cancer Staging (BCLC), regarded HCC with PVTT at BCLC Stage C, and recommended systemic treatments based on the positive outcomes of phase III randomized trials [15].

However, radiotherapy is an effective treatment for HCC with PVTT. Patients with type III/IV PVTT receiving radiotherapy alone could achieve an ORR of 40-57.7% and a median survival of 9.2-9.6 mo, which is the best level achievable with all single treatments [16]. The partial or complete disappearance of tumor thrombus after radiotherapy can effectively improve intrahepatic blood supply and facilitate the efficacy of drug therapy. A randomized controlled study conducted at the Shanghai

Oriental Hepatobiliary Hospital compared the efficacy of neoadjuvant radiotherapy followed by surgery with direct surgery in patients with hepatocellular carcinoma combined with PVTT. Of the 164 patients enrolled, half were randomized to receive neoadjuvant radiotherapy. The results showed that the neoadjuvant radiotherapy group had significantly lower liver cancer-related mortality (HR 0.35, 95% CI 0.23-0.54) and recurrence rates (HR 0.45, 95% CI 0.31-0.64) than the surgical group [17].

Kamiyama T *et al* compared preoperative RT to PVTT in the main trunk or first branch in patients who underwent hepatectomy with those without preoperative RT, the total dose was 30–36 Gy in 10–12 fractions, and found that preoperative RT improved the prognosis of patients, and complete necrosis of PVTT was 53.3%, which showed that radiation is sensitive to PVTT [18].

In basic research, anti-VEGF therapy improves local intra-tumor oxygenation by improving vascular endothelial status, which can have a synergistic effect with radiation therapy. A phase II study enrolled 40 patients with unresectable locally advanced hepatocellular carcinoma who were not suitable for TACE treatment and were given conventional radiotherapy to the liver lesion in combination with sorafenib in parallel and sequential administration of sorafenib until disease progression. The 1 mo ORR after radiotherapy for the entire group was 55%, and the 2-year OS and PFS in the irradiated field were 32% and 39%, respectively [19]. Considering that complete resection was extremely difficult in this patient, to further reduce tumor loading, we combined RT with lenvatinib. Unexpectedly, the therapeutic response was significantly improved, and the majority of lesions achieved remission. The existing evidence suggested a positive correlation between total radiation dose and tumor response [20]. The effects of RT on the survival of cancer patients are generally interpreted as the consequence of improving local control of the tumor, directly attenuating systemic spread. Experimental data from multiple cancer models have provided sufficient evidence to propose a paradigm shift, whereby some of the effects of radiation contribute to systemic antitumor immunity [21,22]. We used fractionated RT, because it has been reported that fractionated RT could more noticeably enhance

immunomodulation [23]. Meanwhile, considering the radiation sensitivity of PVTT, the dose constraints of normal liver and neighboring organs at risk, and radiation immunogenicity, we have chosen a total radiation dose of 36 Gy delivered in 12 fractions.

Multiple studies have confirmed that RT has a modulatory effect on the immune system. First, RT mediates immunogenic cell death, which releases tumor-specific antigens in the form of apoptotic vesicles, along with damage-associated molecular patterns [24,25]. It promotes tumor recruitment of dendritic cells (DCs) and the capture of tumor cell antigens by DCs, activating tumor-specific T cells [26]. Second, DNA damage caused by RT activates the cytoplasmic DNA-sensing cyclic GMP-AMP synthase-stimulator of interferon genes (STING) pathway [27], which induces the production of type I interferons (IFN- $\alpha$  and IFN- $\beta$ ). In addition, RT can reprogram the immune microenvironment, which ultimately makes tumor-infiltrating lymphocytes (TILs) to increase and activate cytotoxic T lymphocytes (CTLs) [28,29].

Mounting evidence suggests that radiation stimulates the immune system and this contributes to the abscopal effect, which is defined as “response at a distance from the irradiated volume.” Although this phenomenon was first described by Mole in 1953, it only gained widespread clinical attention recently [30]. Preclinical trials support the phenomenon of the abscopal effect, but there are few clinical reports, which suggesting that the immune system activated to translate into clinically visible therapeutic responses that still need to be further explored. Nergiz Dagoglu et. al reported 94 cases in 52 articles between 1960 and November 2018 and found a total of 24 cases in 15 reports that demonstrated an abscopal effect finally [31]. In our case, the therapeutic strategy of radiation-immunotherapy combination showed remarkable response-complete remission, including the disappeared right part of the lesion which was not in the irradiation area.

However, the optimal combinations to generate an abscopal effect are unclear. Fortunately, many clinical trials are reported as ongoing or planned investigating the use of RT with immunotherapy. The PACIFIC study concentrated on patients with

stage III unresectable non-small cell lung cancer, in which maintenance therapy combined with durvalumab after chemoradiotherapy (CRT) was associated with a significantly improved survival compared with placebo as the maintenance therapy (4-year survival rates of 49.6% and 38.3%, respectively) [32]. To date, few studies have concentrated on maintenance treatment for HCC, as RT could induce upregulation of immune checkpoint gene expression, elevate mutational load and neoantigen load, and increase the number of CD8+ TILs in the microenvironment. Pembrolizumab was used as maintenance treatment in our case report. In addition, lenvatinib was continued during maintenance therapy, which referred to another combination therapy for advanced HCC with promising early-phase data (KEYNOTE-524) [33], and reported an ORR of 46.0% (95% confidence interval (CI), 36.0% to 56.3%) and a median DOR of 8.6 mo (95%CI, 6.9 mo to not estimable [NE]). The median OS was 22 mo, and this study included portal vein invasion with Vp1-3. To our knowledge, this is the first report on immunotherapy combined with maintenance therapy after RT of HCC patients.

## **CONCLUSION**

Based on the characteristics of this case and other reports in the literature for advanced HCC with PVTT, radiation plus antiangiogenesis and immunotherapy combination can achieve good local control and prolonged survival, which was markedly greater than our expectation. To our knowledge, this is the first patient who was treated by the mentioned therapy, and our findings may provide new insights into the therapy of such patients.

## **ACKNOWLEDGEMENTS**

The authors appreciate Dr. Chen Wenting from MSD China for his significant suggestions and proofreading of the manuscript.

18%

SIMILARITY INDEX

---

PRIMARY SOURCES

---

- |  |  |                |
|--|--|----------------|
| <div style="background-color: red; color: white; width: 40px; height: 40px; display: flex; align-items: center; justify-content: center; margin-bottom: 10px;">1</div>     | <a href="http://www.ncbi.nlm.nih.gov" style="color: red;">www.ncbi.nlm.nih.gov</a><br><small>Internet</small>  | 100 words — 4% |
| <div style="background-color: magenta; color: white; width: 40px; height: 40px; display: flex; align-items: center; justify-content: center; margin-bottom: 10px;">2</div> | <a href="http://www.karger.com" style="color: magenta;">www.karger.com</a><br><small>Internet</small>  | 60 words — 2%  |
| <div style="background-color: purple; color: white; width: 40px; height: 40px; display: flex; align-items: center; justify-content: center; margin-bottom: 10px;">3</div>  | <a href="http://pubmed.ncbi.nlm.nih.gov" style="color: purple;">pubmed.ncbi.nlm.nih.gov</a><br><small>Internet</small>   | 41 words — 2%  |
| <div style="background-color: teal; color: white; width: 40px; height: 40px; display: flex; align-items: center; justify-content: center; margin-bottom: 10px;">4</div>    | <a href="#">Toshiya Kamiyama. "Efficacy of preoperative radiotherapy to portal vein tumor thrombus in the main trunk or first branch in patients with hepatocellular carcinoma", International Journal of Clinical Oncology, 10/22/2007</a><br><small>Crossref</small> | 26 words — 1%  |
| <div style="background-color: green; color: white; width: 40px; height: 40px; display: flex; align-items: center; justify-content: center; margin-bottom: 10px;">5</div>   | <a href="http://pesquisa.bvsalud.org" style="color: green;">pesquisa.bvsalud.org</a><br><small>Internet</small>  | 22 words — 1%  |
| <div style="background-color: brown; color: white; width: 40px; height: 40px; display: flex; align-items: center; justify-content: center; margin-bottom: 10px;">6</div>   | <a href="http://www.targetedonc.com" style="color: brown;">www.targetedonc.com</a><br><small>Internet</small>  | 22 words — 1%  |
| <div style="background-color: darkred; color: white; width: 40px; height: 40px; display: flex; align-items: center; justify-content: center; margin-bottom: 10px;">7</div> | <a href="#">Zhao-Ran Li, Yu-Ling Zhou, Qi Jin, Yin-Yin Xie, Hong-Mei Meng. " mutation in a case of cerebrotendinous xanthomatosis: A case report ", World Journal of Clinical Cases, 2022</a><br><small>Crossref</small>   | 16 words — 1%  |

8	Martina Catalano, Andrea Casadei-Gardini, Gianmarco Vannini, Claudia Campani, Fabio Marra, Enrico Mini, Giandomenico Roviello. "Lenvatinib: established and promising drug for the treatment of advanced hepatocellular carcinoma", Expert Review of Clinical Pharmacology, 2021 <small>Crossref</small>	15 words — 1%
9	<a href="http://www.unboundmedicine.com">www.unboundmedicine.com</a> <small>Internet</small>	15 words — 1%
10	<a href="http://f6publishing.blob.core.windows.net">f6publishing.blob.core.windows.net</a> <small>Internet</small>	14 words — 1%
11	<a href="http://publinestorage.blob.core.windows.net">publinestorage.blob.core.windows.net</a> <small>Internet</small>	14 words — 1%
12	<a href="http://test.dovepress.com">test.dovepress.com</a> <small>Internet</small>	14 words — 1%
13	Jeong Il Yu, Su Jin Lee, Jeeyun Lee, Ho Yeong Lim, Seung Woon Paik, Gyu Sang Yoo, Changhoon Choi, Hee Chul Park. "Clinical significance of radiotherapy before and/or during nivolumab treatment in hepatocellular carcinoma", Cancer Medicine, 2019 <small>Crossref</small>	13 words — 1%
14	<a href="http://spiral.imperial.ac.uk">spiral.imperial.ac.uk</a> <small>Internet</small>	13 words — 1%
15	<a href="http://tailieu.vn">tailieu.vn</a> <small>Internet</small>	13 words — 1%
16	<a href="http://www.science.gov">www.science.gov</a> <small>Internet</small>	13 words — 1%

---

17 Cheng Shuqun, Chen Minshan, Cai Jianqiang. 12 words — < 1%  
"Chinese expert consensus on multidisciplinary  
diagnosis and treatment of hepatocellular carcinoma with  
portal vein tumor thrombus: 2016 edition", Oncotarget, 2016  
Crossref

---

18 ro-journal.biomedcentral.com 12 words — < 1%  
Internet

---

19 schedule.radiology.ucla.edu 12 words — < 1%  
Internet

---

EXCLUDE QUOTES ON  
EXCLUDE BIBLIOGRAPHY ON

EXCLUDE SOURCES OFF  
EXCLUDE MATCHES < 12 WORDS