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Reappraisal of transarterial radioembolization for liver-confined hepatocellular carcinoma with portal vein tumor thrombosis: Editorial on “Transarterial radioembolization versus tyrosine kinase inhibitor in hepatocellular carcinoma with portal vein thrombosis”

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Hepatocellular carcinoma (HCC) is a hypervascular tumor and has a tendency to invade portal vein (PV).¹ HCC with portal vein tumor thrombosis (PVTT) has a very poor prognosis, with a median overall survival (OS) of 2.7 months without treatment and less than 15 months despite appropriate treatment.^{2,3} HCC invasion of PV can result in rapid intrahepatic tumor spread. In addition, PVTT may lead to deterioration of liver function, as well as increased risk of portal hypertensive complications.⁴ Thus, it is graded as Barcelona Clinic Liver Cancer (BCLC) stage C (advanced-stage) HCC, and the standard first-line treatment for HCC with PVTT is systemic therapy.

Prior to the appearance of atezolizumab plus bevacizumab treatment in 2020,⁵ the tyrosine kinase inhibitor (TKI) (sorafenib or lenvatinib) was the recommended first-line

systemic therapy for HCC with PVTT from 2008. However, even with TKI treatment, HCC with PVTT is still prone to rapid tumor spread.⁶ Further, TKI is often related to poor tolerability and discontinuation, and dose reduction due to adverse effects such as hand-foot skin reaction and diarrhea.⁷ Therefore, considerable centers around the world, especially in Eastern countries, perform locoregional therapy such as chemoembolization in HCC patients with PVTT in which the main PV is not invaded.⁸

Transarterial radioembolization (TARE) (Fig. 1), another option of locoregional therapy for HCC, has gained popularity due to similar efficacy with chemoembolization, a lower toxicity profile and less post-embolization syndrome.^{9,10} In previous retrospective studies, TARE showed an excellent safety profile with median OS ranging from 10 to 14.1 months in the treatment of HCC with PVTT.^{9,11-13} On the strength of these encouraging clinical outcomes, two randomized controlled trials (RCTs) (SARAH and SIR-

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veNIB) comparing TARE and sorafenib were conducted in the setting of locally advanced HCC, but failed to confirm a meaningful survival benefit provided by TARE.^{14,15} However, these two studies did not specifically focus on the subset of HCC patients with PVTT, and a large proportion of HCC patients with main PVTT (34%) were enrolled in the TARE group of SARAH trial.¹⁴ Strictly speaking, HCC with main PVTT should be regarded as extrahepatic spread due to its location. Typically, TARE is ineffective for HCC with tumor thrombosis spreading into main PV.¹¹ Furthermore, the radiation dose used in TARE in the SARAH and SIRveNIB trials seemed to be suboptimal in the light of the current time. For instance, a recent DOSISPHERE-01 trial¹⁶ compared the personalized boosted dosimetry (≥ 205 Gy) and the standard dosimetry (120 ± 20 Gy) subgroups of locally advanced HCC patients and showed a better median OS (27 vs. 11 months, $P=0.01$) and a higher objective response rate (71% vs. 36%, $P=0.007$) in the former group than in the latter group. This study may challenge the conclusions of previous two RCTs, in which the standard dosimetry was

used.

Most recently, Hur et al.¹⁷ presented a retrospective multicenter study comparing the outcomes of TARE ($n=124$) and TKI (sorafenib or lenvatinib) ($n=92$) therapy in treatment-naïve patients with liver-confined HCC with segmental or lobar PVTT. This study may have a significant clinical impact because there has never been such a sizable study before. In this multicenter study, the median OS of the TARE group was significantly longer than that of the TKI group in the unmatched cohort (28.2 vs. 7.2 months, $P<0.001$) and in the matched cohort (60 pairs) (24.2 vs. 8.4 months, $P=0.004$). The OS difference was more prominent in the subgroups with Vp1 (segmental) or Vp2 (second-order branch) PVTT than in the subgroup with Vp3 (lobar) PVTT. Regarding the safety issue, the rates of adverse effects (ascites, hepatic encephalopathy, and liver function deterioration) were significantly lower in the TARE group than in the TKI group. According to the results of this study, it was suggested that TARE may provide superior OS and fewer adverse effects compared to sorafenib or lenvatinib

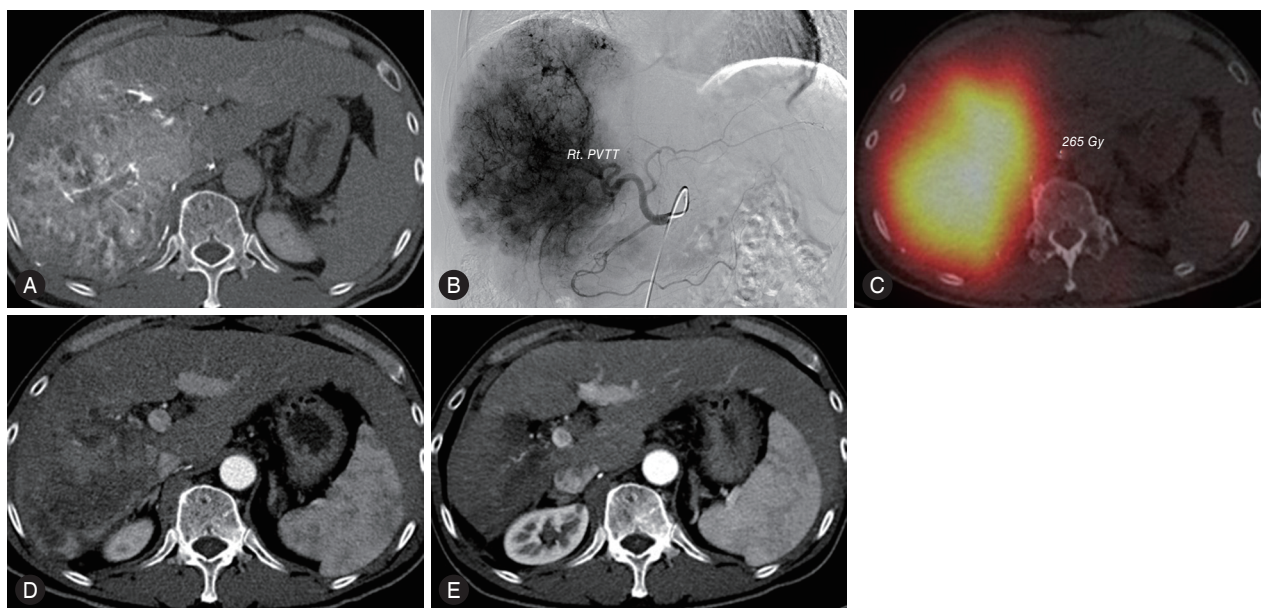


Figure 1. A 56-year-old man with hepatocellular carcinoma (HCC) and right lobar portal vein tumor thrombosis (PVTT). CT arteriography (A) and arteriography via a common hepatic artery (B) showing huge infiltrative HCC with right lobar PVTT. (C) Transarterial radioembolization (TARE) using personalized boosted dosimetry (265 Gy) was carried out. Follow-up CT 3 months after TARE (D) and 8 months after TARE and subsequent atezolizumab plus bevacizumab treatment (E), showing a dramatic decrease in tumor sizes.

Abbreviations:

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; OS, overall survival; PV, portal vein; PVTT, portal vein tumor thrombosis; RCTs, randomized controlled trials; TARE, transarterial radioembolization; TKI, tyrosine kinase inhibitor

in the setting of liver-confined HCC with Vp1-Vp3 PVTT.¹⁷ Unlike the results of the SARAH and SIRveNIB trials,^{14,15} two important factors may have contributed to the superior outcomes of TARE in the study by Hur et al.¹⁷: appropriate patient selection (exclusion of patients with main PVTT) and delivering high-dose radiation (median, 3.6 GBq vs. 1.4 GBq in the SARAH trial or 1.6 GBq in the SIRveNIB trial). Delivering high-dose radiation without increasing major complications may result in favorable outcomes. Nowadays, many centers have moved on from the use of the standard dosimetry to the use of the personalized boosted dosimetry.

Despite the strengths of the study, the retrospective nature of this study¹⁷ introduces potential biases and limitations inherent in an observational study. A well-designed RCT would be required to prove efficacy of TARE in HCC patients with PVTT in the future. A better systemic treatment option (atezolizumab plus bevacizumab) has emerged,⁵ but long-term follow-up data of atezolizumab plus bevacizumab treatment focusing on HCC with PVTT in a large sample population is still lacking.¹⁸ Thus, RCT comparing TARE and atezolizumab plus bevacizumab would attract a great deal of interest. In addition, TARE is not possible in all patients with liver-confined HCC and segmental or lobar PVTT. For instance, typically TARE is not indicated for HCC with extensive, bilobar liver involvement due to the concern of serious radiation hepatitis. Surely, systemic therapy may play an important role for this specific indication.

HCC with PVTT is a complicated event; prognosis differs significantly according to the tumor burden and extent of PVTT.¹ A personalized approach should be adopted for HCC patients with PVTT, instead of one-size-fits-all systemic therapy. As Hur et al.¹⁷ suggested, locoregional therapy such as TARE can be a better treatment option than systemic therapy if the extension of PVTT and tumor burden is limited. However, best treatment option for this specific group should be further searched in future well-designed comparative studies.

Authors' contribution

Conceptualization: Jin Hyoung Kim. Writing original draft: Jin Hyoung Kim. Review & editing: Gun Ha Kim, Dong Il Gwon.

Conflicts of Interest

The authors have no conflicts of interest to declare.

REFERENCES

1. Hwang H, Shim JH, Kim JH. Hepatocellular carcinoma with macrovascular invasion: need a personalized medicine for this complicated event. *Hepatobiliary Surg Nutr* 2024;13:188-190.
2. Llovet JM, Bustamante J, Castells A, Vilana R, Ayuso Mdel C, Sala M, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology* 1999;29:62-67.
3. Khan AR, Wei X, Xu X. Portal vein tumor thrombosis and hepatocellular carcinoma - The changing tides. *J Hepatocell Carcinoma* 2021;8:1089-1115.
4. Yoon SM, Lim YS, Won HJ, Kim JH, Kim KM, Lee HC, et al. Radiotherapy plus transarterial chemoembolization for hepatocellular carcinoma invading the portal vein: long-term patient outcomes. *Int J Radiat Oncol Biol Phys* 2012;82:2004-2011.
5. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med* 2020;382:1894-1905.
6. Bruix J, Cheng AL, Meinhardt G, Nakajima K, De Sanctis Y, Llovet J. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: Analysis of two phase III studies. *J Hepatol* 2017;67:999-1008.
7. Song DS, Song MJ, Bae SH, Chung WJ, Jang JY, Kim YS, et al. A comparative study between sorafenib and hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis. *J Gastroenterol* 2015;50:445-454.
8. Cho Y, Kim BH, Park JW. Overview of Asian clinical practice guidelines for the management of hepatocellular carcinoma: An Asian perspective comparison. *Clin Mol Hepatol* 2023;29:252-262.
9. Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology* 2010;138:52-64.
10. Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC) Korea. 2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. *Clin Mol Hepatol* 2022;28:583-705.
11. Kulik LM, Carr BI, Mulcahy MF, Lewandowski RJ, Atassi B,

- Ryu RK, et al. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. *Hepatology* 2008;47:71-81.
12. Hilgard P, Hamami M, Fouly AE, Scherag A, Müller S, Ertle J, et al. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. *Hepatology* 2010;52:1741-1749.
13. Spreafico C, Sposito C, Vaiani M, Cascella T, Bhoori S, Morosi C, et al. Development of a prognostic score to predict response to Yttrium-90 radioembolization for hepatocellular carcinoma with portal vein invasion. *J Hepatol* 2018;68:724-732.
14. Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 2017;18:1624-1636.
15. Chow PKH, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, et al. SIRveNIB: Selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. *J Clin Oncol* 2018;36:1913-1921.
16. Garin E, Tselikas L, Guiu B, Chalaye J, Edeline J, de Baere T, et al. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. *Lancet Gastroenterol Hepatol* 2021;6:17-29.
17. Hur MH, Cho Y, Kim DY, Lee JS, Kim GM, Kim HC, et al. Transarterial radioembolization versus tyrosine kinase inhibitor in hepatocellular carcinoma with portal vein thrombosis. *Clin Mol Hepatol* 2023;29:763-778.
18. Park J, Lee YB, Ko Y, Park Y, Shin H, Hur MH, et al. Comparison of atezolizumab plus bevacizumab and lenvatinib for hepatocellular carcinoma with portal vein tumor thrombosis. *J Liver Cancer* 2024;24:81-91.