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Letter to the Editor

Clinical Insights Derived from Sequential Transarterial Chemoembolization after Stereotactic Body Radiation Therapy for Recurrent Hepatocellular Carcinoma

Wen-Wen Luo[1#], Da-Long Yang[1#], Jian-Hong Zhong[1,2,3], Yi-Li Ma[4] and Zhen-Zhen Li[4*]

[1] *Department of Hepatobiliary Surgery, Guangxi Medical University Cancer Hospital, Nanning, Guangxi Zhuang Autonomous Region, China;* [2] *Key Laboratory of Early Prevention and Treatment for Regional High Frequency Tumors (Guangxi Medical University), Ministry of Education, Nanning, Guangxi Zhuang Autonomous Region, China;* [3] *Guangxi Key Laboratory of Early Prevention and Treatment for Regional High Frequency Tumors, Nanning, Guangxi Zhuang Autonomous Region, China;* [4] *Department of Pathology, Guangxi Medical University Cancer Hospital, Nanning, Guangxi Zhuang Autonomous Region, China*

[#] *Contributed equally to this work.*

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Dear Editors,

We read with great interest the study by Wu *et al.*, which reported that sequential stereotactic body radiation therapy (SBRT) followed by transarterial chemoembolization (TACE) was associated with a 5-year overall survival approaching 70% in patients with recurrent hepatocellular carcinoma (HCC), a finding that is higher than the approximately 55% 5-year overall survival observed in our multicenter cohort of patients with recurrent HCC meeting the Milan criteria treated with curative resection or ablation.[2] Given this finding, we wish to raise several methodological considerations that may help readers better interpret the validity and generalizability of the results.

First, this retrospective single-center study enrolled 152 patients over a 9-year period (2011–2020), so conclusions should be interpreted with caution given the relatively modest sample size and selected patient population. Given the long enrollment window, improvements in physician experience and treatment techniques across calendar years may introduce temporal heterogeneity in clinical outcomes. For studies with prolonged enrollment periods, sensitivity analyses of temporal trends may be useful. Notably, approximately 70% of included patients had extrahepatic metastases. Subgroup analyses focusing on this subset may help clarify associations with outcomes after subsequent TACE. Furthermore, it was not reported whether patients receiving concurrent systemic therapies were excluded. If such patients were included, subgroup analyses stratified by systemic treatment status would be warranted to address potential confounding.

Second, the manuscript lacks information regarding tumor response assessment based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and modified RECIST (mRECIST) after SBRT. The prognostic implications of treatment response are well established, as patients with a favorable tumor response have been shown to experience significantly better survival outcomes than those with stable or progressive disease.[4,5] Furthermore, the reasons for treatment discontinuation in the SBRT alone arm were not clearly specified, nor were the criteria for stopping therapy defined. In our own experience, patients who achieved radiological or clinical complete response according to mRECIST following antitumor therapy experienced favorable long-term outcomes, with a substantial proportion successfully discontinuing interventional procedures.[6,7] By extension, we hypothesize that patients who achieve both a radiological complete response according to mRECIST and normalization of tumor markers after SBRT, potentially reflecting treatment response, might be spared from subsequent TACE, offering a more conservative and potentially less morbid management approach for selected responders. However, although mRECIST has advantages, SBRT-related changes in tumor morphology may complicate treatment response assessment.

Third, the authors suggest in their discussion that sequential TACE after SBRT could eliminate residual tumor tissue. This is a plausible hypothesis. However, it remains to be determined whether imaging assessment combined with normalization of tumor markers (such as α-fetoprotein and PIVKA-II) can reliably identify residual disease after SBRT. Moreover, longitudinal monitoring of circulating tumor DNA methylation patterns may help clinicians distinguish true tumor clearance from radiological pseudoprogression, potentially sparing a subset of patients from the financial burden and procedural morbidity associated with TACE. Recent studies have found that circulating tumor DNA

***Correspondence to:** Zhen-Zhen Li, Department of Pathology, Guangxi Medical University Cancer Hospital, Nanning, Guangxi Zhuang Autonomous Region 530021, China. ORCID: https://orcid.org/0009-0006-3591-4787. Tel: +86-15296561499, E-mail: lizhenzhen202310@163.com.
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detection has been significantly associated with poorer prognosis in patients with HCC.

Notwithstanding these limitations, we acknowledge the authors' valuable efforts in generating real world evidence for recurrent HCC. We anticipate subsequent investigations to address these issues, which may further clarify the clinical utility of sequential SBRT and TACE for this patient population. More importantly, the safety profile of SBRT alone and SBRT plus TACE could be compared, particularly regarding potential additive or synergistic toxicities in this population.

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Conflict of interest

JHZ has been an Editorial Board Member of Journal of Clinical and Translational Hepatology since 2020. The other authors have no conflict of interests related to this publication.

Author contributions

Drafting of the manuscript (WWL, DLY, JHZ, YLM, ZZL); critical revision and approval of the final manuscript (WWL, DLY, JHZ, YLM, ZZL). All authors have approved the final version and publication of the manuscript.

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