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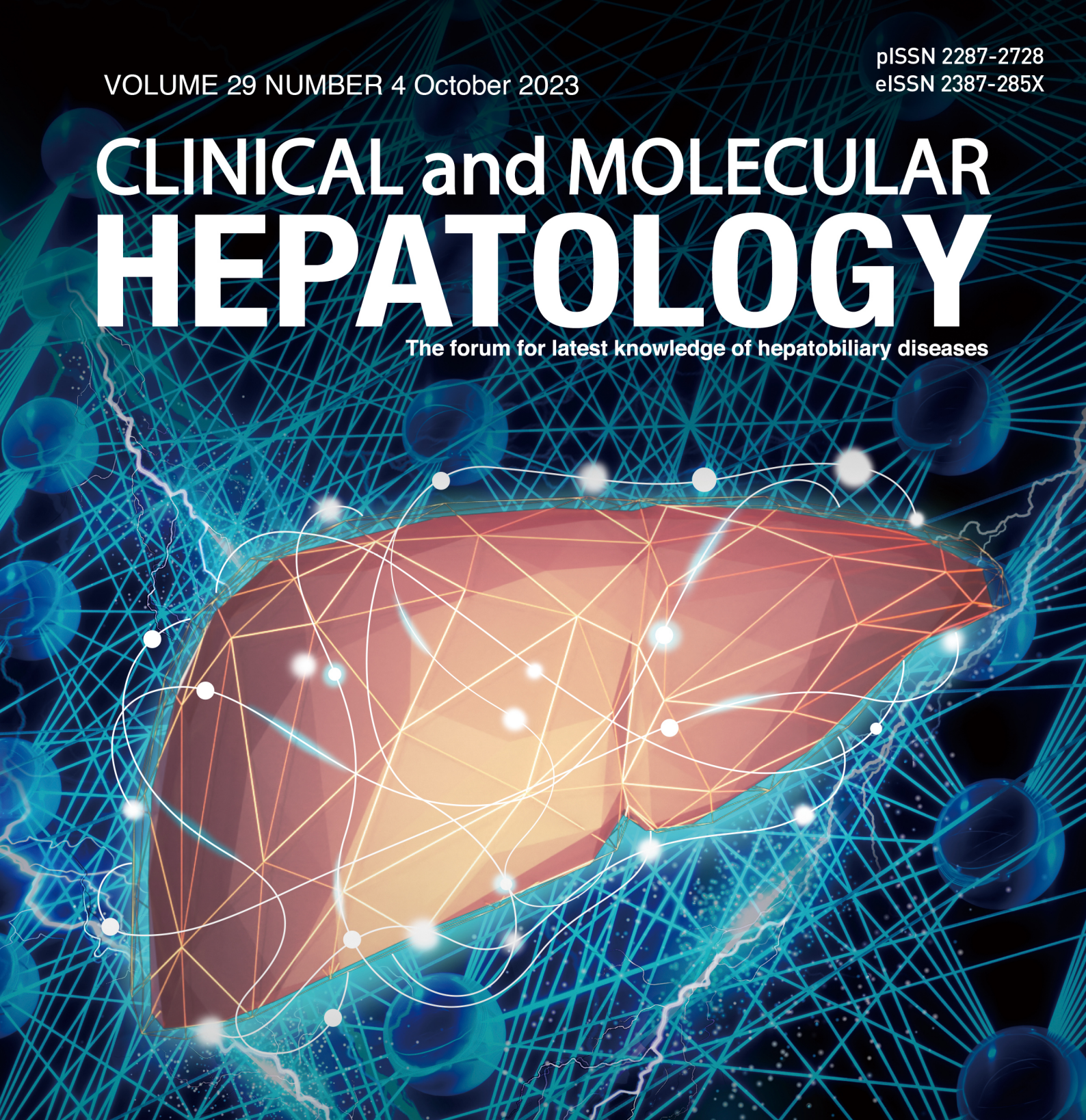

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Editorial

Novel paradigm in the treatment of hepatocellular carcinoma: Anticipating breakthroughs with particle therapy

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Keywords: Hepatocellular carcinoma; Radiotherapy; Proton beam therapy; Carbon ion radiotherapy

See Article on Page 945
See Article on Page 958

Hepatocellular carcinoma (HCC) is usually developed in the background of chronic liver disease, including cirrhosis, the optimal treatment modality should be determined by tumor stage and baseline hepatic function as well. Although most HCC treatment guidelines suggest the recommended treatment for each stage,[1,2] there are many cases in which alternative treatment options have to be selected for above mentioned reason.[3] Moreover, the major failure pattern is intrahepatic recurrences after initial treatment; however, there are no clear recommendations for the management of recurrent HCC.[4] Due to the complexity of treatment decisions and involvement of multiple disciplines in the management of HCC, a multidisciplinary approach should be considered to improve outcomes of HCC patients.[1,5]

Historically, external beam radiotherapy (RT) had a very limited role in the treatment of HCC, due to the uncertain treatment planning, beam delivery, and a consequence of deterioration of hepatic function even after limited doses, RT had been used in some patients with extrahepatic lesions for symptom palliation.[6] However, recent improvement of computer technology into radiotherapy techniques, including three-dimensional conformal RT, intensity-modulated RT, 4-dimensional computed tomography with strategies for respiratory motion management, and image-guided RT has allowed a more precise treatment to enhance the efficacy and minimize treatment-related complications.[4] Therefore, the role of RT as an alternative treatment method in the management of HCC has steadily increased, and its effectiveness has been emphasized more recently.[3] According to the recent publications, stereotactic body RT, which refers to the delivery of high doses of radiation to the tumor in few fractions, offers potentially curative local therapy for patients with small HCC who are not candidates for hepatic resection or thermal ablation.[7,8] In addition, RT, combined with transarterial chemoembolization or other locoregional therapies, can

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be used as a first-line treatment for patients with advanced HCC showing macroscopic vascular invasion for better progression-free and overall survival rates.[9,10]

In addition to the development of RT using X-ray (photon) as mentioned above, the use of particle therapy for treating HCC is also a new technical advance among the RT methods. Particle therapy that can be used in the management of HCC is mainly divided into proton beam therapy (PBT) and carbon ion RT (CIRT).[11,12] The main physical characteristics of particle therapy is the absorbed dose curve shows a slow initial increase with the penetration through matter, than a steep rise to the maximum, known as the Bragg peak, followed by a sharp fall in energy absorption toward the end of the beam range.[13] This unique characteristics can be able to provide a more precise dose delivery to the tumor, while minimizing radiation effect to the surrounding normal tissues effectively. The potential benefits of particle therapy, particularly in HCC, may be grounded in the following rationales: HCC mainly occurs as a consequence of pre-existing liver cirrhosis, which imposes limitations on remnant hepatic volume compared with non-cirrhotic healthy liver. In addition, since intrahepatic recurrence is frequent, it is necessary to preserve the uninvolved liver as much as possible during one treatment session to help determine the following treatment at the time of recurrence. In this issue of *Clinical and Molecular Hepatology*, Lee and Kim[12] demonstrated that PBT was a highly effective local therapeutic option for early-to-advanced stage HCC, with favorable survival outcomes and a low toxicity rate. They also mentioned PBT had been used successfully in challenging clinical conditions, such as major vascular invasion and re-irradiation.[12] Recently, the first phase III randomized controlled trial demonstrated that PBT was associated with local progression-free survival rates that were comparable to those observed for thermal ablation in patients with recurrent small (<3 cm) HCC.[14]

In addition to aforementioned advantage of particle therapy, CIRT possesses further distinctive attributes. The heavy charged ions have less lateral scattering than other particles; therefore, the degree of lateral penumbra for CIRT is smaller than that of PBT.[15] Moreover, CIRT has biological effectiveness which is detailed in another review article in the current issue of *Clinical and Molecular Hepatology*.[11] To summarize briefly, carbon ions are high linear energy transfer (LET) radiations and high-LET radiation tends to have a higher relative biological effectiveness (RBE) than low-LET radiations. The local RBE values for carbon ions can reach as high as 2.0–3.5 depending on their position within the treatment beam (RBE of X-rays: 1, RBE of PBT: 1.1).[11] Through these biological advantages, CIRT can offer clinical benefits in controlling hypoxic or radioresistant tumors.[11,16] As CIRT is a relatively new approach and is installed in a few institutions, there are limited well-controlled clinical trials, including for HCC. Further studies are necessary to provide robust clinical evidence of CIRT in treating HCC in the future.

The development of RT techniques in treating HCC undoubtedly holds the potential to enhance therapeutic efficacy and broaden its applicability. However, several points must be considered for future research. Firstly, there is a need for answers regarding the clinical scenarios in which particle therapy would provide more benefits compared with RT using X-rays. More comprehensive dosimetric studies along with the consensus reports from the expert could contribute to making an informed decision.[17] Secondly, while a higher RBE could enhance treatment outcomes for tumors, it is necessary to investigate whether the uncertain RBE might lead to increased toxicities in surrounding organs, including the uninvolved liver especially for CIRT. Lastly, research pertaining to cost-effectiveness should also be undertaken.

In summary, with the progress of cutting-edge technology, RT has emerged as a safe and more efficacious modality for treating HCC. As more clinical experiences and research on particle therapy unfold in the future, it is anticipated that better outcomes might be achieved for patients with HCC, surpassing the current standards.

Conflicts of Interest

The authors have no conflicts to disclose.

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Abbreviations:

CIRT, carbon ion radiotherapy; HCC, hepatocellular carcinoma; LET, linear energy transfer; PBT, proton beam therapy; RBE, relative biological effectiveness; RT, radiotherapy

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