



Editorial

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The position of loco-regional therapy in the management of hepatocellular carcinoma with extrahepatic metastases

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Systemic therapy is currently the standard of care for individuals with hepatocellular carcinoma (HCC) who have experienced extrahepatic metastases (EHM).¹ Transarterial chemoembolization (TACE), as an alternative to sorafenib, has been regarded as an effective modality despite the introduction of sorafenib, which was the first approved systemic therapy with proven survival benefit.² This was primarily because sorafenib has limited efficacy in reducing tumor burden with only marginal survival benefit, especially in cases of macrovascular invasion and/or EHM. Recently, the treatment paradigm for advanced HCC has changed substantially due to the advent of novel regimens that go beyond sorafenib, such as a new tyrosine kinase inhibitor like lenvatinib, or immunotherapy (IO)-based doublet regimens like atezolizumab plus bevacizumab, nivolumab plus ipilimumab, and tremelimumab plus durvalumab, as first-line regimens with promising outcomes. Furthermore, the survival outcome may be prolonged with repeated systemic treatment due to the availability of numerous types of second-line regimens, such as regorafenib, cabozantinib, or ramucirumab.³ Therefore, no one can deny the importance of systemic therapy to manage advanced HCC.

On the other hand, based on the finding that in patients with advanced HCC, mortality is usually attributed to the progression of intrahepatic disease rather than the EHM itself,⁴ and many studies have demonstrated that if liver function is preserved, repeated TACE with or without systemic therapy can significantly improve survival, even in patients with EHM.⁵ Therefore, it is necessary to reevaluate function of TACE in

managing HCC patients with EHM in light of current therapeutic options.

In this edition of the *Journal of Liver Cancer*, Song et al.⁶ compared the prognostic effects of systemic therapy with those of TACE as the initial treatment for patients with HCC who had EHM at the time of diagnosis. They demonstrated that TACE was linked to a longer median overall survival (OS) than sorafenib: 15.1 (95% confidence interval [CI], 11.1-22.2) vs. 4.7 (95% CI, 3.7-7.3) months, respectively, with a hazard ratio (HR) of 1.97 ($P < 0.001$). After adjusting for potential confounders, TACE was also linked to statistically comparable median OS as compared to those of lenvatinib (8.0 [95% CI, 6.5-11.0] months; HR, 1.21; $P = 0.411$) and IOs (14.3 [95% CI, 9.5-27.0] months; HR, 1.01; $P = 0.973$). It is not surprising that TACE was linked to greater survival advantages compared to more recent systemic therapies for intrahepatic tumors less than 5 cm in size, again demonstrating the efficacy of TACE for intrahepatic tumor suppression. However, a few important factors must be considered when interpreting these findings.

First, compared with patients who underwent TACE, those who received systemic therapy had higher albumin–bilirubin grades, greater tumor markers, more intrahepatic tumors, larger tumors, and more frequent portal vein invasion. This indicates that physicians should be more inclined to recommend systemic therapy over TACE when patients present with a large tumor burden in the liver, although the authors demonstrated that the OS rates of the two modalities were comparable after controlling for important variables. This is mainly due to concerns re-

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garding the possibility of liver function deterioration following TACE. Therefore, further carefully planned prospective studies are necessary to determine the generalizability of the conclusions of this study. Second, the true tumor burden of EHM among the enrolled patients is another problem. Quantitative estimation of the gross tumor burden of EHM is not simple. The concept of EHM encompasses metastases other than those to the liver, ranging from single and oligo-, to many metastases. External beam radiation therapy (EBRT) may be able to effectively manage tumors in cases with single or oligometastases, especially when the primary liver lesion has been well-controlled.^{7,8} Further research should evaluate the effects of combining EBRT with other therapeutic methods, such as TACE, systemic therapy, or both, as both the eligibility of EBRT itself and the use of EBRT can impact the course of the disease. Lastly, the use of TACE for intrahepatic tumor management in patients with HCC and EHM should be viewed positively, as innovative systemic regimens with encouraging outcomes in HCC therapy have been progressively used to treat intermediate-stage HCC. Nevertheless, as there are presently at least three workable IO-based regimens, the study direction should more closely align with systemic therapy with/without loco-regional therapy (e.g., TACE and/or EBRT), rather than loco-regional therapy with/without systemic therapy. Therefore, research into the best ways to combine systemic and loco-regional therapies to improve therapeutic efficacy and patient tolerance should be conducted as soon as possible.^{9,10}

In summary, primarily because TACE offered an OS equivalent to that of the more recent systemic therapies in the present study, its use in controlling intrahepatic tumors in patients with HCC and EHM continues in this era of novel systemic medicines. Nevertheless, more careful prospective studies are required to properly determine the efficacy and application of TACE. Furthermore, it is important to emphasize the use of a multimodal approach to provide optimal therapy at the individual level.

Conflicts of Interest

Beom Kyung Kim is an editorial board member of *Journal of Liver Cancer*, and was not involved in the review process of this article. Otherwise, the author has no conflicts of interest to disclose.

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