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CORRESPONDENCE

Can Stereotactic Body Radiotherapy Really Be Considered the Preferred Treatment in Large Hepatocellular Carcinoma?

TO THE EDITOR: The recent retrospective series by Wahl et al[1] reported the results of 224 patients with inoperable nonmetastatic hepatocellular carcinoma (HCC) treated with radiofrequency ablation (RFA) or stereotactic body radiotherapy (SBRT). The authors acknowledged the unbalanced populations and used an inverse probability of treatment weighting in the Kaplan-Meier method and Cox models to account for the treatment-related bias.

The article by Wahl et al[1] has the merit of addressing the following two important aspects: the need for randomized studies including SBRT in the treatment of HCC and, more generally, the role of SBRT in this clinical context. Indeed, despite the growing evidence of a potential curative role of SBRT in the multidisciplinary approach of HCC,[2] radiotherapy often remains a palliative option in the international guidelines.[3,4] Moreover, this study confirms that SBRT can be safe and efficient in the management of HCC, despite a relatively short follow-up.

At our institution, we strongly support the introduction of SBRT in the treatment of HCC; however, in our opinion, the data presented in this study could not support the use of SBRT "as preferred treatment for larger HCC,"[1] as stated by the authors at the end of the Discussion. Indeed, some methodologic aspects of this study could have affected the results and the final statement.

RFA has been described as a potential treatment for large single tumors, but this indication has never been endorsed by international societies. Thus, worse results in the RFA group with larger lesions could be expected, simply because RFA is not indicated for larger lesions.[3-5] Target size is not a limit for SBRT; the major variables to be taken into account to avoid radiation-induced toxicities are the dosimetric constraints and the proximity of some organs at risk (ie, bowel, duodenum, stomach).[6] Theoretically, when the target is well located and the treatment plan respects the dose and volume constraints, there are no limits in the dose that can be delivered. Moreover, at the dose levels usually delivered with SBRT, HCC seems to be a radiotherapy-sensitive tumor.[7]

The criteria of efficacy are also quite critical. Wahl et al[1] used Response Evaluation Criteria in Solid Tumors (RECIST) to define the freedom from local progression rate in the SBRT arm. By definition, to define a relapse with the RECIST criteria, it is necessary to have a lesion that is larger than before the treatment. Moreover, a recent study showed that the RECIST and modified RECIST criteria are probably not the best tools for evaluating the response of HCC to SBRT.[8] Last but not least, the evaluation of HCC response and/or recurrence after SBRT remains challenging, even with magnetic resonance imaging using advanced diffusion imaging modalities, because of the absence of large studies showing a correlation between imaging and pathologic specimen after SBRT for HCC. In the RFA group, all the relapses inside or at the border of the RFA area were considered recurrences. All of these issues negatively influence the analysis of the efficacy results, disfavoring RFA.

Looking at the treatments groups, the SBRT group had lower pretreatment Child-Pugh scores ($P = .003$) but higher pretreatment α-fetoprotein levels ($P = .04$) and a greater number of prior liver-directed treatments ($P = .001$). However, in the RFA group, the population was larger and follow-up was longer (20 *v* 13 months in the RFA and SBRT groups, respectively). The shorter follow-up in the SBRT group should be taken into account in the evaluation of the results, both in terms of efficacy (because late relapses and/or late complete responses could still happen) and late toxicity.

The observed low toxicity rate in the SBRT arm confirms the data of other available prospective trials. However, the toxicity rate in the RFA arm seems relatively high, compared with the rate of 2.2% reported in large multicentric studies.[9,10] A possible explanation is that this toxicity occurred in patients presenting with larger lesions. Unfortunately, the authors did not detail the diameter of the lesions of patients presenting with severe toxicity in the RFA arm.

In conclusion, SBRT has already proven its efficacy and safety in the treatment of HCC in several prospective trials and could be considered one of the potential therapeutic options in the clinical context of large single tumors. The heterogeneity of these patients makes any retrospective comparison with available therapeutic options complex. We believe that well-designed randomized trials comparing SBRT with radioembolization or transarterial chemoembolization in homogeneous groups of patients could be of significant interest for our patients.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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