Commentary

Stereotactic body radiation therapy and radiofrequency ablation in patients with hepatocellular carcinoma: not a rival but a partner for the cure

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Among various liver-directed local treatments for hepatocellular carcinoma (HCC), stereotactic body radiation therapy (SBRT), which delivers a highly ablative dose to the tumor, has increasingly been adopted in clinical practice and demonstrates favorable outcomes. Given the low priority of SBRT in the current treatment guidelines (1,2), there have been several series comparing SBRT and other local treatments, such as radiofrequency ablation (RFA), transarterial chemoembolization.

A recent meta-analysis by Hong *et al.* included these previous studies and provided overall treatment outcomes of SBRT compared with RFA (3). After analyzing five retrospective studies (1 registry-based and 4 single-institution), the authors concluded that SBRT yielded superior local control but inferior overall survival (OS) outcome compared with RFA. Specifically, 2-year rates of freedom from local progression (FFLP) were 75.7% and 70.6% (P=0.03) and OS were 49.6% and 56.7% (P=0.0001) after SBRT and RFA, respectively.

Failure to translate into improved OS outcomes from improved FFLP outcomes might stem from different baseline characteristics. As the authors mentioned in their forest plot for meta-analysis, four out of five studies performed propensity score-based analysis to minimize the differences between two treatment groups (4-7). Reflecting the current status of SBRT in actual practice, the SBRT group usually had poorer baseline factors than the RFA group resulting in a substantial imbalance between the two groups. Although authors pointed out the potential biases embedded in their analysis, detailed general information on baseline characteristics of each report could clarify this issue. For example, although authors found no differences in tumor size, most series reported larger tumor size in the SBRT group than in the RFA group (4-7). In addition, recurrent tumor status, which is frequently observed in patients who received SBRT, might be associated with inferior OS outcomes regardless of improved FFLP. A recent phase III non-inferiority trial with 144 patients comparing SBRT using proton (66 Gy in 10 fractions) and RFA answered this issue of selection bias (8). Recurrent/residual HCC with small size (<3 cm) and limited numbers (≤2 lesions) were included. In the per-protocol population, the 2-year local progression-free survival rate with SBRT and RFA was 94.8% and 83.9%, meeting the criteria for non-inferiority. Furthermore, they showed comparable 2-year OS outcomes of 88.8% and 92.9% after SBRT and RFA, respectively. There were no grade 4 adverse events or mortality after treatment. Therefore, SBRT and RFA could provide comparable FFLP and OS outcomes in selective patients with HCC.

The tumor location is also an essential factor when selecting liver-directed local treatments. Tumors attached to vascular structures and located in subphrenic area jeopardized local control after RFA (4,5). However, the image-guidance procedure during SBRT liberates performing SBRT regardless of tumor location. A recent

multi-national retrospective study with 2064 patients also showed that SBRT was associated with better local control than RFA for tumors in a subphrenic area (9). Based on these studies, we could assume several clinical scenarios: (I) tumors far from a vessel or located in a non-subphrenic region could be treated either with SBRT or RFA; (II) tumors attached to a vessel or located in a subphrenic region could be treated SBRT. We suggest that SBRT is an effective alternative to RFA for selective tumors.

Another point touched by the authors includes the lack of consensus guidelines for SBRT. The disparity in treatment outcomes in the current analysis could be related to various SBRT dosage, as the authors pointed out. Despite widespread adoption of SBRT in clinical practice, indications, SBRT dose prescription, techniques, and SBRT planning varies among institutions. In this regard, the dose-response relationship in SBRT for HCC could refine the suitable dose prescription for minimizing liver toxicities without compromising FFLP (10). Further investigation and consensus guidelines should be warranted to improve the quality and treatment outcomes of SBRT for HCC.

Hong *et al.*'s comprehensive analysis helped physicians depict overall treatment outcomes after SBRT and RFA reported in multiple retrospective series. Given the strengths and weaknesses of each modality, however, we should acknowledge that SBRT and RFA are not competitive but cooperative/alternative treatment options for HCC.

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