Editorial

# What is the role of stereotactic body radiotherapy to treat inoperable hepatocellular carcinoma?

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Wahl *et al*., in a recent retrospective analysis, compared patients with inoperable, non-metastatic hepatocellular carcinoma (HCC) treated with radiofrequency ablation (RFA) or stereotactic body radiotherapy (SBRT) (1). Over an 8-year time period, there were 161 in the RFA group and 63 patients in the SBRT group. Treatment plans were made based on multidisciplinary tumor board review. The two groups were similar in tumor size and number of lesions treated per patient. However, the SBRT group had lower Child-Pugh scores and had more prior liver directed treatments. Overall 1-year survival was 70% in the RFA group and 74% in the SBRT group. There was no statistically significant difference in complication rates between the two groups. For tumors >2 cm, the freedom from local progression (FFLP) was worse in the RFA group than the SBRT group (P=0.025). From this finding, the authors concluded that SBRT should be first line treatment for inoperable, larger HCC. This is an important study that examines the role for SBRT in the treatment of HCC. However, the overall conclusion that SBRT is a reasonable first-line treatment of inoperable, larger HCC is premature and is not justified by the data.

Results for the phase I and II trials to examine the safety and efficacy of SBRT to treat HCC were published in 2013 (2). Since that time, clinicians have been working to determine the best timing and application of this technology in the multimodal treatment of HCC. The National Comprehensive Cancer Network guidelines have added external radiation into the treatment algorithm for HCC. In version 2.2016, the guidelines state that SBRT can be considered as an alternative to the ablation and embolization techniques or when these therapies have failed or are contraindicated. The question for most clinician treating HCC is when to use SBRT and where it should fit in the treatment algorithm.

There are several areas of concern with the study by Wahl *et al*. We echo the point made by Yang *et al*. about the timing and inclusion of patients receiving liver transplant in the two groups (3). Liver transplant is an excellent option for patients with cirrhosis and stage II HCC. Wahl *et al*. reported that 21.1% of the RFA group and 6.3% of the SBRT group received a liver transplant (1). It is unclear how these patients were included in the survival data and may skew the outcomes observed in the paper.

Another major concern is the fact that half of the patients in the SBRT study group had solitary tumors <2 cm, which are ideal tumor features for RFA or microwave ablation (4). It is not clear or stated why these patients were not candidates for laparoscopic or percutaneous RFA as primary treatment modality. Eligibility for a liver tumor ablation is usually made by a liver transplant/hepatobiliary surgeon or surgical oncologist for a laparoscopic approach and by an Interventional Radiologist for percutaneous RFA. There is no mention if an ablation approach was considered in these patients or if the appropriate team was involved in the decision-making.

The Wahl *et al*. study was not a randomized controlled clinical trial, and this result in inherent selection bias for treatment modalities. The authors did attempt to correct for imbalances using inverse probability of treatment weighting (IPTW). The SBRT group had lower Childs-Pugh scores and shorter length of follow up. The FFLD was longer in the SBRT group; however this may be skewed by the statistically different length of follow up between the two groups. There was a median follow up of 20 months in the RFA group versus a 13-month follow up in the SBRT group.

On average, the SBRT group had two previous liver directed therapies and the RFA group had an average of zero.

The location of the liver tumors was not noted and is a weakness of the study by the authors. It is known that RFA is effective for smaller lesion, but because of heat sink is not as effective by portal structures. SBRT does not have the heat sink effect and can be used for tumors located close to vein.

As mentioned in two previous editorials on the Wahl *et al.* study, the method used to assess local recurrence is not considered standard (3,5). The authors used the Response Evaluation Criteria in Solid Tumors criteria (RECIST). We agree that using the EASL guidelines or the modified RECIST criteria are perhaps more accurate for assessing recurrence after RFA (6). This could have had a trend towards detecting less HCC recurrences in the SBRT group.

A final concern is the definition of large, inoperable HCC. In the current study, only three patients (3.7%) had tumors >5 cm in the SBRT group, which is the usual definition of "large" HCC. Hence, the current study simply has too small a number of large HCC tumors to draw any meaningful conclusions. In previous literature, RFA was categorized with liver resection and liver transplant with intent to cure (7,8). SBRT was categorized with TACE and Y-90 for larger tumors to slow disease progression and perhaps bridge to transplant. In summary, we do not find the evidence is sufficient to deem SBRT first line treatment for large unresectable HCC. Further studies are warranted to better define the appropriate subset of patients with cirrhosis and HCC that ideal candidates for SBRT therapy, either as first or second line therapies, or as a bridge to liver transplantation.

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