

Is stereotactic body radiotherapy comparable with radiofrequency ablation for the treatment of hepatocellular carcinoma?

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Abstract

For small hepatocellular carcinoma, radiofrequency ablation (RFA) is the standard treatment worldwide. Growing evidence supports that stereotactic body radiotherapy (SBRT) is comparable efficacy and safety with RFA. The editorial outlines the remarkable clinical studies on SBRT as local modality for the treatment of HCC.

Keywords: External beam radiotherapy; Hepatocellular carcinoma; Radiofrequency ablation; Stereotactic body radiotherapy

Editorial

Hepatocellular carcinoma (HCC) is one of the most common cancer and the major cause of cancer-related death worldwide. Liver transplantation and surgical resection remain the standard curative therapies for HCC but only 30–40% of patients are eligible. For inoperable HCC, patients receive various local treatments including radiofrequency ablation (RFA) and external-beam radiotherapy (EBRT) [1]. Historically, the role of EBRT for HCC has been limited for palliation due to low tolerance of the whole liver to RT and the technical uncertainties in RT delivery. The advance of RT techniques including three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, stereotactic body radiotherapy (SBRT), charged-particle therapy (proton beam therapy [PBT] and carbon-ion radiotherapy), however, has expanded the indication from palliation to a cure.

Among these, SBRT delivers a high dose of radiation to the tumor using a small number of fractions with a high degree of precision, and improves the efficacy for HCC than EBRT using conventional fractionation. Recent systematic review and meta-analysis on SBRT for liver-confined HCC showed that 3- and 5-year local control rates were 84% (95% confidence interval [CI], 77%–90%) and 82% (95% CI, 74%–88%), and the 3- and 5-year overall survival (OS) rates were 57% (95% CI, 47%–66%) and 40% (95% CI, 29%–51%), respectively [2]. Although a lot of studies on SBRT for HCC has been published, long-term outcomes are accumulated, and comparable results with RFA are reported, there was no phase 3 study comparing SBRT with RFA, which is the standard local modality for HCC. Therefore, the level of evidence on SBRT as a local modality for the treatment of HCC is still insufficient.

Under this circumstance, one phase 3 study comparing SBRT with RFA for HCC was finally published this year. Xi et al. [3] randomly assigned 166 patients with single recurrence HCC ≤ 5 cm to receive either SBRT ($n = 83$) or RFA ($n = 83$) in China. Primary endpoint was the 2-year local progression-free survival (LPFS) with a superiority design. After the median follow-up time of 43 months, the 2-year LPFS rates were 93% in the SBRT group and 76% in the RFA group (hazard ratio [HR], 0.45 [95% CI, 0.24–0.87]; $P = 0.014$), respectively. The 2-year OS rates were 98% in the SBRT group and 94% in the RFA group (HR, 0.91 [95% CI, 0.37–2.22]; $P = 0.830$), respectively. Acute and late toxicity occurred in 58% and 37% in the SBRT group, and

68% and 31% in the RFA group without statistical significance. In conclusion, SBRT achieved significantly superior LPFS than that of RFA, whereas OS and safety were comparable between the two local modalities. This result is similar with another phase 3 study comparing PBT with RFA. In 2021, one phase 3 study randomly assigned 144 patients with recurrent HCC (size < 3 cm, number ≤ 2) to receive either PBT ($n = 72$) or RFA ($n = 72$) in Korea [4]. The primary endpoint was 2-year LPFS with a non-inferiority design in the per-protocol (PP) population, considering that crossover was allowed. In the PP population, the 2-year LPFS rates were 95% in the PBT group and 84% in the RFA group (HR, 0.51 [95% CI, 0.26–1.03]; $P = 0.114$), meeting the criteria for non-inferiority. The 2-year OS rates were 89% in the PBT group and 93% in the RFA group (HR, 1.19 [95% CI, 0.62–2.27]; $P = 0.600$), respectively. Authors documented that PBT is not inferior to those of RFA.

In addition, two retrospective studies using propensity score matching (PSM) analysis were published. A multicenter study reviewed 174 patients with recurrent HCC ≤ 5 cm, and selected 84 patients after PSM (ratio 1:1) [5]. After PSM, the 1-, 3-, and 5-year OS rates were 98%, 86%, and 79% in the SBRT group, and 98%, 64%, and 41% in RFA group ($P = 0.012$), respectively. On subgroup analysis, SBRT achieved significant OS benefits than those with RFA if the tumor located in the subphrenic or subcapsular segments ($P = 0.032$), and tumor size > 2.5 cm ($P = 0.039$). Ueno et al. [6] reviewed 140 patients with single HCC ≤ 3 cm, and selected 93 patients after PSM (ratio 1:2). After PSM, perivascular and subphrenic tumors were significantly common in SBRT group. There was no local recurrence in the SBRT group, whereas, 6 cases were identified in the RFA group ($P = 0.024$). OS was not significantly different (HR, 1.32 [95% CI, 0.60–2.89]; $P = 0.401$). RFA has the possible risk of suboptimal ablation to avoid toxicities according to tumor location or larger tumor size. One hybrid meta-analysis suggested that RT can be more effective than RFA for tumors > 2 –3 cm or for specific locations in the liver (subphrenic or perivascular sites), with moderate quality of evidence [7]. Recent meta-analysis including these studies and other retrospective studies stated that SBRT and RFA exhibit comparable efficacy and safety, regardless of tumor size, initial/recurrence, and study design [8].

Growing evidence supports that SBRT is comparable with RFA for the treatment of HCC. The Barcelona Clinic Liver Cancer 2025 up-

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date guideline cited RT as a local treatment for the first time [1]. To strength evidence of SBRT, however, there are several considerations. First, there is only one phase 3 study. Further prospective studies should be needed to confirm the efficacy of SBRT. Second, we need more evidence on SBRT for treatment-naïve HCC. Patients with HCC initially try to receive the standard treatment if possible, and is consulted for SBRT in case of insufficient response or recurrence. Therefore, most patients in published studies had history of previous treatment with various course. The outcomes of treatment-naïve HCC are essential to establishing SBRT as the first-line therapy for a cure. Lastly, current evidence shows favorable LPFS of SBRT than that of RFA, but an improvement in LPFS dose not translate into an improve-

ment in overall survival. The ongoing phase 3 studies (NCT05433701 and ACTRN1262100144875) will give us some answers.

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Conflict of Interest Statement

There are no conflicts of interest to declare.

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