

# Charged particle therapy for hepatocellular carcinoma: a commentary on a recently published meta-analysis

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Submitted Dec 11, 2015. Accepted for publication Dec 14, 2015.

doi: 10.3978/j.issn.2305-5839.2015.12.36

View this article at: <http://dx.doi.org/10.3978/j.issn.2305-5839.2015.12.36>

The incidence of hepatocellular carcinoma (HCC) continues to increase worldwide. HCC represents the second-leading cause of cancer-related deaths worldwide, accounting for 745,000 deaths per year (1). While there are effective curative treatments for HCC, including orthotopic liver transplantation, resection, or radiofrequency ablation for small tumors, the majority of patients are not candidates for these therapies due to tumor size, multifocality, vascular invasion, or poor baseline hepatobiliary function.

Prior to the development of modern imaging and radiotherapy techniques, liver-directed radiotherapy was limited to the palliative setting. Liver-directed radiotherapy often consisted of whole-liver irradiation, which in turn required the use of low doses of radiotherapy due to the potential risk of radiation-induced liver disease (RILD) (2,3). However, modern radiotherapy treatment planning and delivery techniques have enabled the safe and effective delivery of ablative radiotherapy doses to tumors while sparing normal hepatic parenchyma. Numerous prospective single-arm studies and retrospective series have reported low toxicity rates and impressive local control and survival rates with modern liver-directed radiotherapy (4-6), including for patients with advanced disease and tumor vascular invasion (4,7,8).

There has been particular interest in the use of charged particle-based therapy, including proton and carbon ion therapy, in the treatment of HCC. Unlike photon radiotherapy, charged particle therapy (CPT) is characterized by steep dose fall-off which can theoretically be exploited to maximize dose to the tumor while sparing uninvolved tissue. Single institution series have demonstrated lower mean hepatic doses and improved

normal tissue sparing with CPT as compared to photon radiotherapy (9,10). A phase II multi-institutional trial of proton therapy for unresectable HCC or intrahepatic cholangiocarcinoma (IHC) demonstrated that proton therapy was well-tolerated and effective, with 2-year local control rates of 94.8% for patients with HCC (11). However, there are no randomized data comparing the efficacy and toxicity of CPT with photon radiotherapy.

To help answer this question, Qi *et al.* (12) conducted a systematic review and meta-analysis of the literature to compare outcomes associated with the treatment of HCC with CPT *vs.* photon radiotherapy. Employing methodology adherent to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statements (13), they identified 73 cohorts from 70 non-randomized studies published after 1990 which included a total of 5,204 patients with HCC. They divided patients into three cohorts based on treatment modality: CPT (n=1,627), photon SBRT (n=1,423), and conventional photon radiotherapy (CRT) (n=2,104). Median follow-up was longer in the CPT cohort (23 months) compared with the SBRT cohort (18 months) and the CRT cohort (18.4 months) (P=0.064). Median tumor size was larger in the CRT cohort (9.0 cm) compared to the CPT cohort (4.5 cm) and the SBRT cohort (4.4 cm) (P=0.064). There was also a higher percentage of patients in the CRT cohort with tumor vascular thrombosis (33%) as compared to the SBRT cohort (4.5%) or the CPT cohort (19%). While this difference was not statistically significant (P=0.064), it may have had a significant clinical impact as the presence of vascular invasion can alter radiotherapy treatment fields. For example, in some cohorts of patients with vascular invasion, only the area of thrombosis, not the entire primary lesion,

was included in the treatment volume. This could certainly impact both local control and survival (14).

To assess overall survival (OS), progression-free survival (PFS) and locoregional control (LRC), the authors calculated the event rates of outcomes associated with CPT, CRT, and SBRT. Compared with conventional radiotherapy, CPT was associated with an improvement in OS at 1, 3, and 5 years. There was also an improvement in PFS and LRC for patients receiving CPT as compared to CRT. By contrast, when compared with the CPT cohort, the patients in the SBRT cohort had similar rates of OS and LRC. There was a possible trend towards an improvement in PFS in the CPT cohort compared with the SBRT cohort, but this was not statistically significant.

Toxicity, particularly hepatotoxicity, is a significant concern in the treatment of HCC given the often compromised hepatobiliary function of these patients. Of note, the vast majority of patients in the studies in this meta-analysis had Child-Pugh Class A cirrhosis. Toxicity rates were low overall, but there was an increase in grade  $\geq 3$  overall toxicity and hepatotoxicity in the CRT cohort when compared with the CPT cohort. Specifically, the rate of acute hepatotoxicity was 3.1% (95% CI, 1.3–7.6%) in the CPT cohort, and 9.9% (95% CI, 6.0–16%) in the CRT cohort. There was also a significant increase in the rate of late toxicity in the CRT cohort (6.9%; 95% CI, 3.9–12%) compared with the CPT cohort (2.5%; 95% CI, 1.3–4.9%). When the CPT cohort was compared with the SBRT cohort, there was a slight increase in late toxicity in the SBRT cohort (6.4%; 95% CI, 4.0–10.1%) compared with the CPT cohort (2.5%; 95% CI, 1.3–4.9%) ( $P=0.011$ ). There was no significant difference in the rates of acute grade  $\geq 3$  toxicities between the CPT and SBRT cohorts.

While the results presented are intriguing, there are several limitations. First, although 1990 was chosen as the entry cutpoint to exclude patients treated prior to the development of modern radiotherapy techniques, the review does include patients treated with whole-liver irradiation (15), which is not a current accepted curative treatment modality. Second, there was no assessment of outcomes based on the intent of treatment—there were several studies within the CRT cohort which included patients treated with palliative intent. Inclusion of these patients in the CRT cohort would have certainly biased the results in favor of CPT. Third, the toxicity criteria were not clearly delineated and may have varied between studies. Fourth, the authors correctly acknowledge the high likelihood of both selection bias and publication bias within the analysis cohorts, and noted that

they were unable to account for publication bias due to significant heterogeneity between studies.

In summary, while the authors show an improvement in outcomes with CPT as compared to conventional radiotherapy, this advantage did not persist when CPT was compared with SBRT. Liver-directed radiotherapy is a safe and effective treatment for both early-stage and advanced HCC, but further study is needed to determine which patients would most benefit from CPT as opposed to photon radiotherapy. Prospective trials including both CPT and photon radiotherapy are ongoing and will provide valuable data to guide treatment recommendations.

### Acknowledgements

None.

### Footnote

*Provenance:* This is a Guest Commentary commissioned by Section Editor Wenjie Cai (Department of Radiotherapy Oncology, First Hospital of Quan-Zhou, Affiliated to Fujian Medical University, Fujian, China).

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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**Cite this article as:** Keane FK, Hong TS. Charged particle therapy for hepatocellular carcinoma: a commentary on a recently published meta-analysis. *Ann Transl Med* 2015;3(22):365. doi: 10.3978/j.issn.2305-5839.2015.12.36