# The evolving evidence for the efficacy and safety of charged particle therapy for hepatocellular carcinoma—a commentary

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Qi and coauthors (1) present a systematic review and meta-analysis of outcomes and toxicity for hepatocellular carcinoma (HCC) patients treated with charged particle therapy (CPT) or photon-based radiation therapy [conventional radiotherapy (CRT) or stereotactic body radiation therapy (SBRT)]. Due to a lack of randomized data comparing these two modalities, the authors utilize data collected from 70 observational studies to draw the conclusion that CPT offers superior survival outcomes compared to CRT and decreased toxicity compared to both CRT and SBRT. The authors conclude that these data may provide evidence for an advantage of CPT in HCC radiation treatment, although definitive conclusions cannot yet be drawn. They acknowledge the lack of high-quality data and bias inherent in the comparison of observational studies and recommend additional prospective trials comparing these modalities.

Treatment of HCC presents a unique challenge because it typically arises in the setting of established liver dysfunction caused by viral hepatitis, alcohol abuse, non-alcoholic steatohepatitis, or aflatoxin exposure (2). Since this underlying liver dysfunction is a competing cause of death in HCC patients, preserving functioning non-cancerous liver is as much a priority of treatment (3) as eradicating cancer cells within the diseased liver and achieving tumor control. If patient medical comorbidities and tumor characteristics allow for surgery, liver transplantation or surgical resection has traditionally been the preferred treatment for non-metastatic disease confined to the liver, as they provide the best chance of durable local control and long-term survival. However, an overwhelming majority of patients are not candidates, and alternative liver-directed therapies are needed.

Building upon a growing body of evidence that sparing portions of non-cancerous liver allows significant radiation dose escalation to partial liver volumes harboring tumor, there has been an abundance of recent literature demonstrating the benefits of radiation therapy for treating HCC. In parallel with this recognition that liver tumors can be safely treated with radiation therapy as long as the entire liver is not irradiated, advances in technology have allowed for improved delivery of conformal photon radiotherapy. Given the success of SBRT in achieving recurrence rates comparable to surgery in other disease sites (4), it is reasonable to consider this modality in patients with unresectable HCC. The challenge lies in delivering tumoricidal doses of radiation therapy while sparing the remaining, often already impaired, liver. Unfortunately, even with these improvements in treatment planning and delivery, the large volume low dose bath characteristic of photon radiation plans often limits dose escalation (5). Therefore, alternatives to conventional photon-based radiation therapy with this potential are worth considering.

Many investigators have capitalized on alternative radiation therapy techniques with unique and advantageous physical properties for HCC treatment. Charged particles such as protons or carbon ions are characterized by higher relative biological effectiveness and lack of exit dose along the beam path (6). There have been a number of successful studies, detailed in this meta-analysis, which lend credence to the utility of CPT in the treatment of HCC; however, there is currently no randomized data available

to substantiate the outcome and toxicity advantages of this therapy. While the authors have assembled a comprehensive collection of observational studies in an attempt to compare modalities and draw conclusions, there are inherent challenges to achieving this objective.

The biggest challenge that individual HCC studies face is defining a uniform cohort of patients for treatment with any liver-directed therapy. With the studies included here, although tumor size, vascular invasion, ECOG performance status and Child Pugh class seemed comparable across treatment groups, it is not self-evident that the proportion of patients with viral hepatitis (B, C or both), cirrhosis, well-differentiated tumors, unifocal disease, extrahepatic disease, percentage of liver involved and/or gastrointestinal mucosal proximity was comparable. Although the authors report no significant differences amongst the cohorts with respect to tumor size, the CRT group had median tumor size of 9.0 cm compared to 4.5 and 4.4 cm in the CPT and SBRT cohorts, respectively, with a nearly significant P value of 0.06. Tumor size has been reported to predict for vascular invasion and poor outcome in HCC patients (7). Similarly, the median number of patients with vascular thrombus (presumably, per cohort) was higher in the CRT group [33] compared to the CPT [19] and SBRT [4.5] groups, and these patients are known to have few therapeutic options and a very poor prognosis (8).

Another challenge encountered while conducting clinical trials in HCC is that of overcoming institutional treatment biases especially with utilization of liver-directed therapies. Over and above inherent selection bias arising from availability of CPT and SBRT at only specialized centers, institutional expertise with specific liver-directed therapies and in-house algorithms often dictate the sequencing of treatment and when/which patients are referred for radiation therapy as well as determine the intent of radiation therapy. Others have noted a discrepancy in treatment intent between patients in the CPT, CRT and SBRT subgroups of this study (9). For instance, the disproportionate number of patients treated with palliative intent in the CRT cohort (with a corresponding significantly lower median radiation dose than CPT) could certainly contribute to decreased local control and, therefore, overall survival compared to the CPT cohort. In addition to treatment administered before radiation therapy and whether radiation was used palliatively *vs.* definitively or adjuvantly *vs.* as salvage, it is unclear if patients received additional therapy after radiation treatment that could have altered survival outcomes. Also, as these treatments have evolved over decades, the patients in each of the cohorts received quite varied treatment doses and schedules. Although median doses are reported, the effect of fraction size and delivery schedule is not negligible, and this makes comparing across cohorts difficult. It would be helpful to know the median biologically effective dose for all the cohorts, as this gives a much better sense of treatment when SBRT and hypofractionated radiation are included.

The authors acknowledge that toxicity data is scarcely available, and it is not possible to adequately compare acute and late toxicity data. It is also unclear if the toxicity data were translated into a common scale before analysis and, if so, which system was used. They report fewer late toxicities in the CPT group, but the nature of these is unclear. Reliable toxicity comparisons are once again limited by the few number of patients, variation in treatment schedules, and even the limited overall survival of this patient population (which precludes report of many late toxicities).

The studies included are heavily weighted towards patients treated in eastern countries, where HCC incidence is higher and there have historically been more charged particle treatment facilities than in western countries. Therefore, it is unclear whether these results can be translated to a western population of patients with greater proportions of hepatitis C and non-alcoholic steatohepatitis patients than cohorts of patients in eastern countries where hepatitis B and aflatoxin exposure are more prevalent. Lastly, the fair quality and retrospective nature of the studies included limits the ability to draw broad conclusions, even with increasing patient numbers through pooled analyses. Nevertheless, a pooled meta-analysis is a more rigorous methodology to evaluate studies such as those included and the conclusions are, accordingly, more robust than discernable from compilation of a collection of single-institution non-randomized single-arm studies.

At our institution, we appreciate the unique characteristics of proton radiotherapy and employ CPT more commonly in a group of patients with certain clinical features. Typically, we choose this modality for patients with limited functional liver reserve, as we feel that they derive the greatest benefit from omission of low dose radiation to the remaining liver. We also ensure that the tumor location does not abut critical structures, namely bowel, which would be put in jeopardy by a CPT plan with high dose and increased range uncertainty when compared to photons. We also appreciate the greater influence of changes in tissue density with CPT compared to CRT, and take measures to ensure careful dosimetric planning and motion

 

management (6). Others have developed decision tools to determine clinical situations in which protons supersede photons; they conclude that protons should be considered for dome and central tumors >3 cm and any tumors >5 cm that are difficult to treat with photons (10).

In the end, we are encouraged by these results and certainly feel that there is a unique role for CPT, specifically, as well as radiotherapy as a whole, in the treatment of HCC. The authors have succeeded in a thorough assessment of patients treated with CPT and compared them systematically with patients treated with photon therapy, both using conventional radiation techniques as well as SBRT. They report both improved outcomes as well as decreased toxicity. They attribute the increased efficacy of CPT seen in this study (as compared to other reviews) to the addition of carbon ion data and more recent studies, which have reported better results. Unfortunately, inherent bias limits the broad generalizability of these data to effect a change in standard of care. Randomized studies with uniform patient cohorts, treatment intent, radiation doses, and prospectively collected toxicity metrics are needed to further characterize the benefit derived from treatment with CPT compared to photon-based radiation therapy for HCC patients.

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## Footnote

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