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# Proton Beam Therapy and Carbon Ion Radiotherapy for Hepatocellular Carcinoma

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**Charged particle therapy with proton beam therapy (PBT) and carbon ion radiotherapy (CIRT) has emerged as a promising radiation modality to minimize radiation hepatotoxicity while maintaining high rates of tumor local control. Both PBT and CIRT deposit the majority of their dose at the Bragg peak with little to no exit dose, resulting in superior sparing of normal liver tissue. CIRT has an additional biological advantage of increased relative biological effectiveness, which may allow for increased hypofractionation regimens. Retrospective and prospective studies have demonstrated encouragingly high rates of local control and overall survival and low rates of hepatotoxicity with PBT and CIRT. Ongoing randomized trials will evaluate the value of PBT over photons and other standard liver-directed therapies and future randomized trials are needed to assess the value of CIRT over PBT.**
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## Introduction and Rationale

As described in the accompanying articles in this issue, technological advances in imaging and delivery of radiation therapy and improved understanding of dose and/or volume relationships in the liver have resulted in encouragingly high rates of local control for hepatocellular carcinoma (HCC) patients treated with stereotactic body radiation therapy (SBRT) or high-dose hypofractionated 3D-conformal radiation therapy. Although "classic" radiation-induced liver disease is now rarely encountered after liver radiation, "non-classic" radiation-induced liver disease (ncRILD) toxicity is still being reported. Depending on the toxicity endpoint (eg, Child-Pugh [CP] class progression, CP score + 2) and the patient cohort (eg, CP-A vs CP-B class) being reported, ncRILD has ranged from 3% to 46%,[1-9] and remains an important and clinically relevant issue to consider when treating HCC patients. Mitigating radiation hepatotoxicity while maintaining high local tumor control rates forms the basis for assessing other radiation modalities to improve the therapeutic index. Charged particle therapy (CPT) represents another step in the evolutionary ladder of technological advancement in the treatment of HCC patients. Both proton beam therapy (PBT) and carbon ion radiotherapy (CIRT) have emerged as promising CPTs for these patients.

## Rationale for Proton Beam Therapy

The impetus to use PBT in HCC patients lies in the physical characteristics of proton particles that impart a dosimetric advantage. Compared to photons that deposit dose along the beam path, resulting in exit dose to adjacent normal tissue distal to the tumor, protons have a finite range in tissue. As they enter tissue, protons lose only small amounts of their energy until they reach the end of the beam range, at which point the remaining energy is deposited over a short distance. This sharp dose accumulation and fall-off is called the "Bragg peak" (Fig. 1).[10] To create clinically useful proton beams, multiple Bragg peaks of different energies are stacked together to form a spread-out Bragg peak. This favorable dosimetric characteristic results in little to no exit dose beyond the tumor target, conferring an advantage over photon-based treatments. In HCC patients, this dosimetric advantage translates to significantly lower doses to the normal (nontumor) liver, primarily at low to moderate dose levels, compared to photon-based treatments (Fig. 2).[11-15] Because recent data have suggested that doses as low as 2.5 to 10 Gy may mediate ncRILD in HCC patients,[4,16] particularly for less compensated liver patients, PBT has the potential to reduce the risk of radiation-induced liver disease

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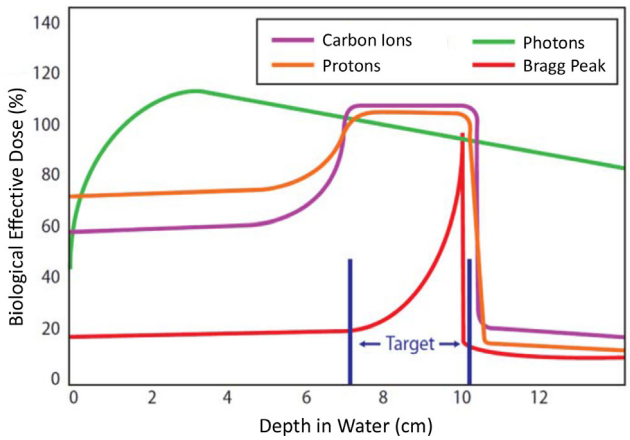


**Figure 1** Depth dose characteristics of photons compared to protons and carbon ions (single beam displayed). Compared to photons, protons and carbon ions deliver less radiation dose proximal and distal to tumors due to the spread-out Bragg peak (SOBP). Compared to protons, carbon ions have a dosimetric advantage of less entrance dose.

(RILD) without compromising the ability to deliver definitive doses of radiation to HCC tumors. Although the relative biological effectiveness (RBE) of protons is thought to be dependent on various factors such as tissue-specific radiosensitivity, biological endpoint, dose level, and oxygen concentration,[17-19] an RBE of approximately 1.1 is routinely used in the clinic for PBT. The benefits of PBT, therefore, lie heavily in the dosimetric and not in the biologic advantages for HCC tumors.

## Rationale for Carbon Ion Radiotherapy

Compared to protons, carbon ions offer comparable physical characteristics with steep dose fall off after the Bragg peak, but with slightly less entrance dose (Fig. 1). However, the biological properties are substantially different. While the RBE for protons is approximately 1.1, the RBE for carbon ions is significantly higher. Depending on the tissue, the endpoint, the depth, and other characteristics, the RBE of carbon ions varies between 2 and 5.[20,21] This higher RBE is due to the high-linear energy transfer radiobiological damage produced by heavier ions: mainly double strand breaks that are difficult to repair by intrinsic cellular repair mechanisms.[22-24] These radiobiological characteristics argue for the use of carbon ions particularly for radiation resistant tumor types, such as chordoma and chondrosarcoma or adenoid cystic carcinoma, but also for HCC.[25] Based on preclinical experiments, RBE values vary between 2 and 4 depending on the HCC subtype and may be potentiated when combined with chemotherapy or targeted agents.[20,26] Although HCC tumors are considered relatively radiosensitive, they often present with a large mass within surrounding normal liver tissue that is also highly sensitive to radiation. For liver tissue, the consideration of delivered tumor dose and irradiated normal liver tissue volume and dose are equally important.[27-29] In this setting, the improved dose distributions of CPT compared to photons, and the slightly superior dose distributions for carbon ions compared to protons may be valuable.[30]

Moreover, the possibility of extremely hypofractionated regimens (less than 5 fractions) may be beneficial in HCC when combined with CIRT. Preclinical experiments have shown that while RBE is decreased with hypofractionation, this decrease is much steeper in normal liver tissue than in

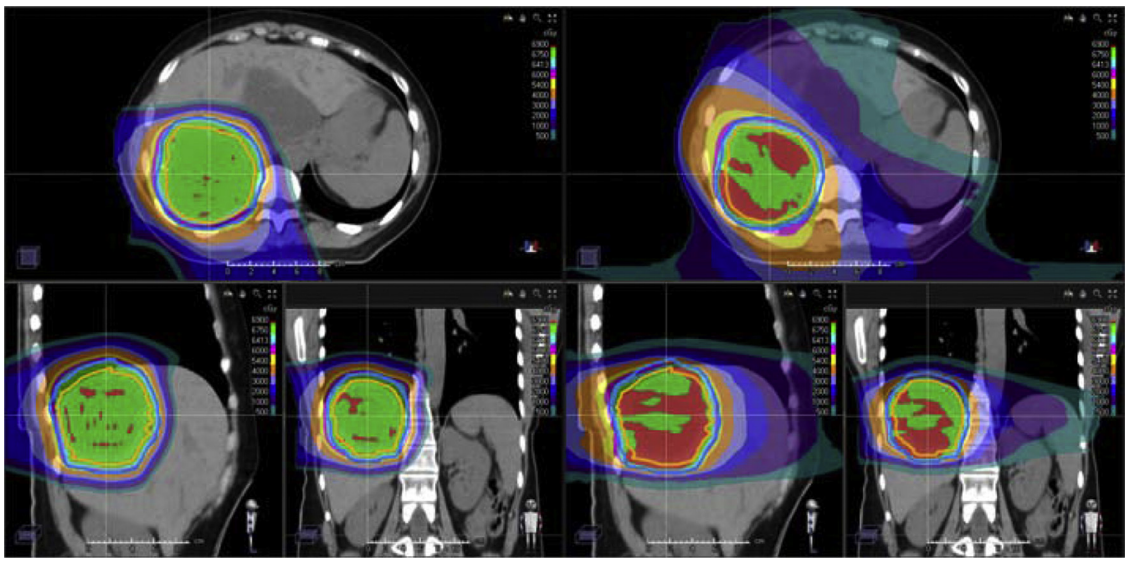

**Figure 2** Proton beam therapy vs intensity modulated radiotherapy (IMRT) plan comparison. Both plans deliver 67.5 Gy over 15 fractions to the tumor. Proton plan (left panel) uses a two-beam approach (right lateral and left posterior oblique) with pencil-beam scanning. IMRT plan (right plan) uses a volumetric modulated arc therapy (VMAT) technique.