Review Article

Proton therapy for hepatocellular carcinoma

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Abstract: Proton radiotherapy has seen an increasing role in the treatment of hepatocellular carcinoma (HCC). Historically, external beam radiotherapy has played a very limited role in HCC due to a high incidence of toxicity to surrounding normal structures. The ability to deliver a high dose of radiation to the tumor is a key factor in improving outcomes in HCC. Advances in photon radiotherapy have improved dose conformity and allowed dose escalation to the tumor. However, despite these advances there is still a large volume of normal liver that receives a considerable radiation dose during treatment. Proton beams do not have an exit dose along the beam path once they enter the body. The inherent physical attributes of proton radiotherapy offer a way to maximize tumor control via dose escalation while avoiding excessive radiation to the remaining liver, thus increasing biological effectiveness. In this review we discuss the physical attributes and rationale for proton radiotherapy in HCC. We also review recent literature regarding clinical outcomes of using proton radiotherapy for the treatment of HCC.

Key Words: Proton radiotherapy; hepatocellular carcinoma (HCC)

Submitted Sep 19, 2012. Accepted for publication Oct 24, 2012.
DOI: 10.3978/j.issn.1000-9604.2012.10.09
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Introduction

Hepatocellular carcinoma (HCC) is one of the most significant causes of cancer mortality worldwide (1,2). It generally has a poor prognosis as it is an aggressive tumor often found concomitantly in the setting of cirrhosis. The presence of cirrhosis, hepatitis B, and hepatitis C are key risk factors (3), but HCC is a complex disease involving many patient factors. There are several risk stratification systems which aim to address the challenge of determining prognosis and outcomes of HCC (4). Ultimately, HCC is a rapidly infiltrating malignancy with patients presenting with large, multifocal tumors with vessel invasion. Thus, there is a strong impetus to develop better methods of local treatment for HCC.

Treatment of HCC is most effective in the early stages of disease, but diagnosing early-stage HCC is often difficult since symptoms are vague. Surveillance programs are recommended for individuals with any of the aforementioned key risk factors (5-7) and diagnosis may be established with biopsy or radiographic studies alone. Once the diagnosis of HCC has been established, surgical resection should be the first consideration as it has shown to provide the best long-term survival (8). Unfortunately, most HCC patients do not qualify for surgery due to a number of medical comorbidities. Nor do they meet the strict eligibility for liver transplantation. There is high morbidity and many HCC patients are too ill to tolerate these surgeries (9-11). Several other local treatments are available for unresectable HCC or for tumor down-staging while awaiting liver transplantation. Other ablative therapies include transarterial chemoembolization (TACE), alcohol injection, cryotherapy, radiofrequency ablation, and focused ultrasound therapy. Nonetheless, the patient suitability of each of these local therapy remains rather limited (12).

It is apparent that an effective local-regional therapy is needed which can be applied to a broad range of patients. The 5-year survival rate for patients diagnosed with HCC remains poor at approximately 3-5% (13). The role of

external beam radiotherapy has historically been considered ineffective for treating HCC because the doses of radiation necessary to cure HCC far exceeded liver tissue tolerance to radiation. There is accumulating evidence that dose escalation can improve both tumor response and survival in HCC patients (14,15). One particularly challenging aspect of HCC is the fact that radiotherapy is guided not only by the characteristics of the tumor but also by the function of the cirrhotic liver. Modern three-dimensional radiotherapy techniques have allowed clinicians to increase dose conformity while escalating dose to the tumor while sparing more normal liver, thus, largely avoiding radiation-induced liver disease (RILD). Several reports have shown that high-dose irradiation to a portion of the liver could be delivered safely with reasonable treatment efficacy (16,17). Charged particle therapy, in particular proton therapy, shows great promise in treating HCC since it allows for tumor dose escalation while sparing critical normal structures.

Characteristics of proton therapy

Proton therapy, among other charged-particle therapies, offers distinct dosimetric advantages in comparison to photon radiotherapy. The depth dose characteristics of these two beams are qualitatively different. Due to physical laws, photons are absorbed exponentially in a specific tissue whereas protons exhibit a finite range depending on the initial proton energy.

A proton beam loses its energy via coulombic interactions with electrons as it traverses tissue. The energy loss of a proton beam per unit path length is small until the end of the beam range. Near the end of the proton range the residual energy over the beam is lost over a very short distance and the beam itself comes to rest. This results in a distinctive sharp rise in the dose absorbed by the tissue, known as the "Bragg peak". The low-dose region located between the Bragg peak and the beam entrance is called the "plateau", with its dose being approximately 30% to 40% of the maximum dose.

The Bragg peak is narrow in nature. This poses a problem when it comes to irradiating larger targets. To overcome this, clinical proton beams are modulated to extend the length of the Bragg peak. Several beams of similar energy are closely spaced and superimposed to create a region of uniform dose over length of the target. These extended regions are called "spread-out Bragg peaks" (18).

The rationale for proton therapy in HCC

The above mentioned physical characteristics of proton beams confer significant dosimetric advantages as compared to photon radiotherapy. The extent of scatter which accounts for lateral penumbra of the beam is less in proton beams when compared with photon beams. The dose delivered to tissues by a proton beam rises to a maximum value at a particular depth and then falls off exponentially to lower doses once the Bragg peak depth has been reached. This dosimetric advantage can be seen for each individual beam in a proton radiotherapy treatment plan. This allows for improvements in dose conformity and sparing of normal organs around the liver including the remaining uninvolved liver, heart, spinal cord, kidneys, bowel, and stomach. Proton radiotherapy is also able to completely spare one kidney more often than photon radiotherapy. More modern treatment techniques such as intensity-modulated proton therapy (IMPT) allow for more conformal high dose delivery while sparing nearby tissues at risk. Dose comparison studies have shown significantly reduced dose toxicity to regular tissues when compared to photon plans equivalent target coverage (19). IMPT has also demonstrated considerable sparing of normal liver tissue in comparison to photon-based intensity-modulated radiation therapy (IMRT) (20)

Dose conformity aside, proton radiotherapy delivers lower integral dose to tissue when compared to photon radiotherapy. Many HCC patients have severe liver disease with low functional reserve. Therefore, it is critical to limit the integral dose to the liver as much as possible. Modern photon therapy techniques such as intensity-modulated radiation therapy (IMRT) may achieve prescription conformity similar to that of a proton treatment plan, but the amount of dose scattered to the remainder of the liver is still higher owing to the physical nature of photon beams. There is evidence that normal liver function is significantly positively correlated to the percentage of normal that is not irradiated (21). Reduction of integral dose to remaining liver may help preserve liver function, decrease the risk of secondary malignancies, and also allow for future retreatment of the liver.

HCC radiation treatment planning with proton therapy

The unique physical properties of proton beams pose challenges not encountered in photon radiotherapy. Unlike photon beams, a distal beam edge must be defined for a proton beam. Since the majority of a proton beam's dose is delivered at the end of its range at the Bragg peak it is

