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)

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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

crucial to define accurately where the beam stops. The use of compensators in the treatment gantry allows the physician to control the location of the beam's distal edge. A "smearing algorithm" is then applied to ensure dose coverage along the entire extent of the target region. However, due to variations in daily patient setup a certain amount of normal tissue beyond the distal extent of the target will receive some dose of radiation. At some institutions, 4-dimensional CT treatment planning is utilized which takes into account the patient's free breathing. One method is a breath-hold technique whereby the patient is asked to inhale deeply and hold his breath until the scan is complete. Other institutions apply a respiratory gating technique which maps a sinusoidal pattern of the patient's respiratory motion. The beam is then synced and turned during the same phase of each breathing cycle. Image acquisition during the portal venous and arterial enhancement phases may show differences in tumor and normal tissue attenuation. Thus, it is essential for each institution to develop a scanning protocol that allows for optimal target delineation (22).

The aforementioned variation in daily patient set-up and target motion is a challenge encountered in photon radiotherapy as well. However, range uncertainty is a unique problem encountered by proton radiotherapy. In the setting of external beam radiotherapy there is variable beam attenuation seen in the beam path. This occurs when the radiation beam traverses tissues of different density along its path. Proton beams deposit nearly all its energy within the tissue with very little exit dose. These range uncertainties stem from artifacts in computed tomography (CT) scans and errors in converting CT Hounsfield units into proton stopping power. These errors occur due to changes in organ motion during normal respiration or variations in daily set-up. For example, a high-density rib adjacent to air-filled lung moving into and out of the beam path during normal respiration creates uncertainty in the beam path. A similar phenomenon may be seen if the beam traverses loops of bowel which shift position each day. Ultimately, this range uncertainty may result in areas of target and normal tissues unexpectedly being overdosed or underdosed.

The relative biological effective (RBE) of proton beams, as compared with photons, is assigned a value of 1.1 by consensus at most institutions. This means that a physical dose of 1 Gy delivered using a proton beam is considered biologically equivalent to 1.1 Gy delivered using a photon beam. The assignment of relative biological effectiveness (RBE) is dependent on a number of biological endpoints which are often unpredictable (23,24). Because of this unpredictability and the aforementioned issue of range uncertainty, beam arrangements are often selected so that they do not stop directly in front of critical organs or structures.

From a dosimetric standpoint, liver tumors have a benefit of being located within a relatively homogenous liver organ. There is less variable density within the liver itself. On that same note, however, dose conformality may be restricted if the beam angle selection to confined to only those that travel entirely through liver tissue. Doing so may also increase the integral dose delivered to the normal liver since the beam is traversing more normal liver tissue and the proximal extent of the beam is often less conformal than the distal extent. However, dose conformality with sparing of adjacent normal liver may lend itself to post treatment dosimetic verification utilizing CT changes in order to assess geometric accuracy of treatment delivery (25).

Dose constraint models for proton-based planning

The liver is a relatively radiosensitive organ which has a limited ability to tolerate the significant dose needed to control HCC. Radiation induced liver disease (RILD) is a clinically defined entity that occurs in the liver after being exposed to high doses of radiotherapy. It is associated with a 2- to 4-fold increase in hepatic enzymes, ascities, fatigue, and anicteric hepatomegaly. The normal tissue complication probability model for RILD developed at the University of Michigan has found widespread application in clinical practice. However, this model is based on RILD that arose in patients treated with hyperfractionated photon radiotherapy (26). Many proton radiotherapy protocols for HCC utilize hypofractionated treatment regimens which are not well-represented by this model.

Another biological model based on the equivalent uniform dose (EUD) was developed by the proton radiotherapy group at Massachusetts General Hospital (27). In this model the 2-dimensional information from the dose-volume histogram (DVH) of inhomogenously irradiated liver is expressed as a single dose value. The EUD expresses mean dose while taking into account volume irradiated. Early application of this model found tumor dose escalation to be limited by adjacent non-liver normal tissues, such as biliary stenosis, rather than liver toxicity.

Aside from reducing the risk of RILD, patients with cirrhosis often undergo advancement of their Child-Pugh score after a course of radiotherapy to the liver. This

portends to worse outcomes and decreased quality of life. The volume of normal liver sparing has been associated with a decreased risk of advancing Child-Pugh class in cirrhotic patients (28). Other structures in the beam path such as ribs post a risk of late post-radiotherapy complication. Rib fracture has been reported as a late complication following external beam radiotherapy. One series looked at 310 ribs which were irradiated during a course of hypofractionated proton radiotherapy (29). Twenty-seven (8.7%) of these irradiated patientsdeveloped rib fracture. The volume of rib receiving at least 60 Gy (V60) was found to be the most statistically significant parameter predicting late rib fractures. Other parameters which were found useful for estimating rib fracture risk were V30, V120, and maximum dose (Dmax) to a point.

There are also reports of a two-step surgical treatment which involves the surgical placement of a spacer into the gastrointestinal tract (30). The intent of the spacer is to create a firm, reproducible separation between the radiation target and adjacent normal tissues. Of course, placement of this spacer as a second surgery will expose the patient to the additional risks also seen in other surgeries. The variety of tissue-sparing precautions selected for any individual patient must take into account medical comorbidities and underlying conditions. Nonetheless, it is evident that great care must be taken while findings ways to assess and limit normal organ toxicity during hypofractionated proton radiotherapy.

Clinical outcomes of HCC treated with proton radiotherapy

Many of the studies looking at the use of proton radiotherapy in liver tumors were performed in Asia (31). One of the first large retrospective series was presented by Chiba *et al*. (32). In this series 162 patients were treated with proton radiotherapy, all treatments delivered with hypofractionated regimens (3.5-5 CGE) with total doses ranging from 50 CGE (10 fractions) to 84 CGE (24 fractions) with a median dose of 72 CGE in 16 fractions over 29 days. Portal vein thrombus was seen in 25 patients (15%). At a median follow-up interval of 31.7 months, the 5-yearlocal control rate was 86.9% and overall survival rate was 23.5%. However, over 50% of deaths were due to complications from cirrhosis rather than tumor progression. The acute side effects in this study were limited primarily to liver enzyme elevation. Only 3% of the patients experienced grade 2 or higher late toxicity. Several recent retrospective studies show similar overall survival and local control rates in a similar population (33,34).

More recently, Komatsu *et al*. reported on the retrospective review of 343 consecutive patients with HCC treated at the Hyogo Ion Beam Medical Center with proton or carbon ion therapies (35). For the 285 patients for which both proton and carbon ion beams were available, treatment planning with both modalities were performed and the better treatment plan was selected based on dosimetric criteria. A total of 242 patients were treated with proton therapy using 8 different dose and fractionation protocols from 2001-2009. Pooled results show for proton therapy show 5 year local control rates of 90.2% with 5 year overall survival of 38%. Results of carbon ion therapy appear non-inferior, but limitations with treatment delivery resulted in the majority of patients (66%) being treated with proton therapy.

Patients with portal venous thrombosis may especially benefit from the dosimetric advantages offered by proton radiotherapy. Larger volumes of liver often need to be irradiated in the setting of portal venous thrombosis. Many of these patients have poor functional reserve remaining in the liver and photon therapy may result in unacceptable toxicity. A series of 35 patients with HCC portal venous thrombosis received treatment of 50 to 72 CGE which resulted in local control rates of over 45% at 2 years. Only 3 of these patients developed severe acute toxicity (36). The excellent conformality of proton beams may open up the possibilities for retreatment in the case of HCC progression or for synchronous tumors arising elsewhere in the liver. The Tsukuba proton radiotherapy group has reported on the efficacy, feasibility, and safety of HCC retreatment in a series of 27 patients with 68 total lesions (37). The median dose delivered was 66 CGE in 16 fractions with a median time interval of 24 months between the first and second course of treatment. They reported a 5-year local control rate of 87.8% and 5-year overall survival rate of 56%.

As mentioned before, cirrhotic patients have very little functional reserve in the liver and are at high risk for hepatic insufficiency. A study examining proton therapy in HCC showed correlation with grade of cirrhosis and toxicity. One third of the patients in this study had Child-Pugh class B cirrhosis with a 40% rate of grade 3 toxicity and 27% of patients eventually developing hepatic insufficiency (38). Damage to the alimentary tract is another cause of great concern as the doses necessary to control HCC are high and often greater than bowel tolerance. One series of 47 patients with HCC located within 2 cm of the alimentary

tract underwent treatment of 72.6 CGE in 22 fractions or 77 CGE in 35 fractions (39). After a median follow-up period of 23 months the overall survival was 50% and progression free survival 88.1%. Grade 2 and 3 alimentary tract hemorrhage was observed in 6.4% and 2.1% of patients, respectively. Beams were edited off of bowel in this study to avoid excess radiation delivered to the alimentary tract.

Prospective data for the use of proton radiotherapy in HCC is rather limited. One randomized study from Japan looking at 30 patients with local HCC reported a 3 year overall survival rate of 62% and local control rate of 95%. All tumors in this study did not invade into the gastrointestinal tract. Well-compensated hepatitis C was present in 90% of the patients with bilirubin <3.0 mg/dL. The dose delivered was 76 CGE in 20 fractions to the tumors which were entirely encompassed within the target volume (38). Another more recent randomized study of 51 patients in Japan reported a 5 year overall survival of 38.7% and local control of 87.8%. A dosing scheme of 66 CGE in 10 fractions was delivered to the tumor. This study included larger tumors as well as patients with symptomatic hepatitis C infections. Approximately two-thirds of the patients in this study had received prior local therapy as well (40).

One of the larger prospective studies was a phase II trial examining outcomes of proton radiotherapy in HCC patients with cirrhosis demonstrated a 66% 2-year overall survival rate after delivering 76 CGE in 3.8 CGE daily fractions (36). Loma Linda University reported results of the largest prospective phase II trial describing the use of proton radiotherapy in patients with HCC. Patients without cirrhosis, with extrahepatic metastases, tense ascites, or greater than 3 liver lesions were excluded. Patients were eligible regardless of tumor size, transplant candidacy, or alpha-fetoprotein (AFP) level. All patients had documented stability of ascites. Fluctuating levels of ascites could impact treatment planning by altering the path of beam attenuation. Shifting fluid content during the course of treatment due procedures such as a paracentesis would affect the targeting of treatment volumes. As such, all patients were required to have documented stability of ascitic fluid levels prior to treatment. Preliminary results were initially reported with 34 cases of unresectable HCC were treated with 63 CGE in 15 fractions (41). The 2-year overall survival rate was 55% and the local control rate was 75%. Mild acute radiation-induced toxicity was noted in 60% of patients but no radiation induced liver disease (RILD) was observed. Patients continued to be enrolled on this trial and updated results were recently reported (42). In this report, 42 additional patients were accrued for a total of 76 evaluable patients. Median progression-free survival for the entire group was 36 months, with a 60% 3-year progression free survival in patients within the Milan criteria. Eighteen patients subsequently underwent liver transplantation, with 6 explants showing complete pathological complete response and 7 explants showing only microscopic residual. The overall survival rate was significantly better in patients receiving liver transplant in comparison to those who did not, 70% *vs*. 10%, respectively.

Post treatment toxicity was minimal with no patients exhibiting RILD or significant changes in MELD scores. Grade 2 GI toxicity was noted in 5 patients with GI bleeding and/or endoscopic evidence of ulceration. All cases were managed medically without surgical intervention. All 5 cases were observed in the first 30 patients as greater care was taken to reduce field margins when tumors occurred adjacent to the bowel after the toxicities were observed. Overall, this is the largest prospective study reported with extensive follow-up that shows that proton therapy is safe and effective for the treatment of HCC. A randomized control trial is underway, comparing proton therapy to transarterial chemoembolization.

Overall, proton radiotherapy has demonstrated some of the most promising outcomes in terms of HCC treatment. The potential for toxicity in treating HCC is highly variable based on the location of the tumor within the liver and baseline liver function. The dosimetric advantages seen with proton radiotherapy appear to allow more feasible tumor dose escalation.

Conclusions

Historically, radiation therapy did not play a prominent role in HCC treatment. Earlier radiation techniques often delivered substantial doses to the liver causing a high incidence of RILD. The liver has a rather limited ability to tolerate substantial doses of radiation. Computerized and three-dimensional treatment planning has allowed better dose conformity thus allowing dose escalation to the tumor. The distinctive physical properties of proton beams confer unique advantages over photon radiotherapy. Many HCC patients have a number of morbidities which make them non-candidates for surgical resection or transplantation. The excellent toxicity profiles and durable in-field local control rates make proton radiotherapy an attractive option for localized HCC.

In principle, it is likely that the greater sparing of uninvolved liver using proton radiotherapy may be safer in patients with cirrhosis or poor liver reserve. The importance of normal liver-sparing is also evident in patients with portal venous thrombosis, since they often require greater volumes of liver to be irradiated. Centrally located lesions or lesions located near critical structures such as vessels may be especially suitable for proton radiotherapy. Proton radiotherapy is becoming increasingly available globally. Nearly 30 clinical proton radiotherapy facilities have been established worldwide. The integration of proton radiotherapy into treatment algorithms requires a great deal of multidisciplinary collaboration and highly individualized optimization for each patient. Nevertheless, there is accumulating evidence demonstrating the safety and efficacy of proton radiotherapy for liver-directed HCC therapy.

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