Proton Therapy in Hepatocellular Carcinoma

Subjects: Oncology

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Proton radiation therapy plays a central role in the treatment of hepatocellular carcinoma (HCC). Because of the near-zero exit dose and improved sparing of normal liver parenchyma, protons are being used even in challenging scenarios, including larger or multifocal liver tumors, and those associated with vascular tumor thrombus.

Keywords: hepatocellular carcinoma ; stereotactic body proton therapy ; intensity-modulated proton therapy

1. Introduction

Liver cancer is the sixth most common cancer worldwide, making up around 5% of all new cancer cases in 2020 [1]. It is particularly common in East Asia and Africa [1], but its incidence has been increasing in other parts of the world as well. This includes the United States [2], where it now makes up around 2.2% of all new cases, with an estimated 5-year relative survival rate of only 20.3% [1].

Since the majority of cases develop in patients with underlying cirrhosis, the overall performance status is an important factor to consider in addition to the underlying liver function and cancer stage when deciding on management [3]. Early-stage disease can be managed with local curative options, including ablation, resection, or even liver transplantation. Multifocal disease can be treated with chemoembolization or systemic therapy. In advanced stages, systemic therapy is the mainstay of treatment, with palliative care preserved for terminal cases [3]. Radiation falls under the locoregional therapies available for inoperable or unresectable tumors. The NCCN guidelines allow for the use of proton therapy in the management of primary liver tumors [4].

The application of proton therapy in the management of hepatocellular carcinoma (HCC) has been proposed to decrease toxicity, since protons deposit a dose at a specific depth with no exit dose and a minimal scatter to nearby organs [5][6]. With more centers adopting proton therapy, this advanced modality has been the subject of active research, especially over the past few years [7].

2. Dosimetric Data

Proton beam therapy (PBT) has been shown to be dosimetrically superior to other photon radiation therapy modalities (XRT) in the management of HCC. Li et al. noted reductions in the mean liver dose (Dmean) and V10–V30 Gy when proton plans were compared to 3D conformal radiation therapy (3D-CRT) for stage I disease (V30: 10.66% [PBT] vs. 21.24% [3D-CRT], $p < 0.002$), and to 3D-CRT and intensity-modulated radiation therapy (IMRT) for stage IIa disease (V30: 22.78% [PBT] vs. 44.01% [3D-CRT] and 37.75% [IMRT], $p < 0.002$) [8]. The proton plans were also superior in sparing other organs at risk (OARs), namely the stomach and the right kidney. Another group of researchers compared PBT to helical (H-)IMRT or volumetric-modulated arc therapy (VMAT) [9]. While all three plans were similar in target coverage, PBT significantly lowered the mean liver dose relative to either photon technique ($p < 0.05$), as well as the V5–V45 and V5–V35 when compared to H-IMRT and VMAT, respectively ($p < 0.05$). In yet another comparison, particle therapy decreased the mean dose received by the normal liver ($p < 0.05$), which translated into a dramatically lower estimated risk of classic radiation-induced liver disease (RILD): 22.3% and 2.3% for IMRT and PBT, respectively ($p < 0.05$) [10].

With an improved sparing of both normal liver and other OARs, protons may allow higher doses to be prescribed to the target volume. This was shown in a planning study that included 30 patients with tumors at risk of requiring radiation dose de-escalation [11]. Intensity-modulated proton therapy (IMPT) and VMAT-rapid arc (VMAT-RA) plans were compared, and a maximum dose of 75 Gy was prescribed in three fractions. Two thirds (20/30) of the VMAT-RA plans violated at least one dose constraint compared to just two plans of IMPT. Thus, the proton radiation plans allowed the maintenance of the prescribed 25 Gy per fraction in most patients.

The dosimetric advantage of protons was also evaluated as a function of tumor size. Toramatsu et al. generated both spot scanning proton (SSPT) and IMRT plans for 10 patients with HCC tumors, ranging in size from 3.4 cm to 16.1 cm [12]. Using the Lyman normal tissue complication probability model, the risk of RILD was estimated to increase dramatically for IMRT plans for tumor diameters beyond 6.3 cm, at which point the risk was 94.5% and 6.2% in the IMRT and SSPT plans, respectively. The researchers concluded that protons are especially useful for larger tumors 6.3 cm and above in diameter.

Other researchers further expanded on the interplay between tumor size, tumor location, and liver sparing. They generated different proton- and photon-based SBRT plans with six ”mock” tumors, ranging in size from 1 to 6 cm, in four different locations of the liver: left medial, caudal, dome, and central [13]. The proton plans spared the normal liver to a greater degree and decreased the mean liver dose compared to photons plans (8.4 vs. 12.2 Gy, $p = 0.01$) only for tumors located at the dome or in central locations with diameters of 3 cm and above. In a later study, the researchers included even larger tumors (up to 10 cm) and were able to show that stereotactic body proton therapy (SBPT) plans maintained an adequate target coverage and OAR sparing up to a tumor diameter of 9 cm (vs. 7 cm for photon stereotactic body radiation therapy (SBRT)) [14]. This translates into a lower liver normal tissue complication probability for SBPT plans in cases of larger lesions, particularly if they are located centrally or in the dome of the liver.

3. Evolving Systemic Therapy Options for HCC

While sorafenib monotherapy was the mainstay systemic treatment for patients with advanced unresectable HCC for more than a decade, novel agents have recently been reported to produce a paradigm shift in management [15]. Immune-based combinations have reported superior results in advanced HCC, as witnessed by the IMbrave150 trial that showed improved survival with the use of atezolizumab combined with bevacizumab as compared to sorafenib [16]. The landscape of new immune-based combinations for advanced HCC continues to expand. Abou-Alfa et al., in a large, randomized phase III HIMALAYA trial, reported that durvalumab was non-inferior to sorafenib with a favorable safety profile. The combination of durvalumab plus tremelimumab showed a superior efficacy and favorable benefit-risk profile compared to sorafenib as a first-line treatment for unresectable HCC [17]. Based on the promising results of early-phase clinical trials, pembrolizumab plus lenvatinib also has potential as a novel treatment option in this setting [18]. As suggested by Rizzo et al., investigating the predictors of response to immune checkpoint inhibitors, such as programmed death ligand 1 (PD-L1), gut microbiome, microsatellite instability (MSI), and tumor mutational burden (TMB) is important to allow the proper selection of HCC patients that could derive the most benefit from immunotherapy [15].

For patients with advanced HCC in the setting of Child–Pugh B, De Lorenzo et al. retrospectively analyzed data in a multicenter study that showed that treatment with metronomic capecitabine is a safe option for patients with Child–Pugh B-HCC. Its potential antitumor activity warrants prospective evaluations [19].

There are currently several ongoing trials (e.g., NCT03482102 and NCT03203304) on the combination of immunotherapy with radiation therapy for HCC, mainly using photon-based RT. In the setting of the changing treatment paradigm for unresectable HCC, future studies on proton radiation therapy should take into consideration the evolving systemic therapy options and their impact on outcomes.

4. Discussion

Radiation therapy is an important locoregional treatment modality used in patients with unresectable HCC. Local control of HCC in the liver is crucial to slow or prevent disease progression, and subsequent progression to liver failure. Although modern series of photon stereotactic ablative RT have shown excellent local control outcomes in the treatment of HCC [20], protons have dosimetric advantages, especially in certain clinical scenarios. There is a growing body of evidence supporting the use of proton therapy for HCC [21][22][23][24][25][26][27]. Multiple dosimetric studies have shown its advantage in sparing the nearby organs at risk, namely the normal liver parenchyma, and subsequently decreasing the risk of radiation-induced liver disease [10]. This is particularly important in the setting of treating large tumors (more than 6–7 cm in size) and especially for tumors located centrally or in the dome of the liver. Proton therapy can also be advantageous over photon-based therapy in patients with relatively poor liver function (Child–Pugh B) or a small normal liver reserve, such as patients heavily pretreated by other local modalities. Another scenario where proton therapy could offer an advantage over photon-based therapy is in the sequential or synchronous treatment of multifocal HCC where researchers are usually limited by the dose received by the remaining normal liver volume.

At the institution in New York, researchers have been treating patients with HCC with either intensity-modulated radiation therapy (IMRT) or proton radiation therapy. Patients are allocated to either modality on a case-by-case basis. Protons are

strongly considered for patients with large HCC tumors, multifocal disease, or a Child–Pugh score of ≥B7. Re-irradiation and high tumor/liver volume ratio, where meeting volumetric and mean liver dose constraints cannot be achieved with IMRT, are also indications for proton RT. The patients are treated with ablative doses of radiation therapy (BED > 100 Gy) using either 5, 10, 15, or 25 fractions. Eligible patients for ablative radiation therapy are those with tumors >1 cm from stomach/small bowel who meet the liver constraints. Lower doses may be considered for HCC to meet liver constraints.

Although limited by the heterogeneity of patient characteristics in nonrandomized trials, proton therapy has been associated with a lower toxicity and improved survival compared to photon-based modalities during retrospective analyses. Further studies are currently underway, including a randomized trial of protons versus photons for HCC, to better evaluate outcomes and inform clinical decisions.

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