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Scientific Article

Intensity Modulated Proton Therapy for Hepatocellular Carcinoma: Initial Clinical Experience

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Abstract

Purpose: Our purpose was to assess the safety and efficacy of intensity modulated proton therapy (IMPT) for the treatment of hepatocellular carcinoma (HCC).

Methods and Materials: A retrospective review was conducted on all patients who were treated with IMPT for HCC with curative intent from June 2015 to December 2018. All patients had fiducials placed before treatment. Inverse treatment planning used robust optimization with 2 to 3 beams. The majority of patients were treated in 15 fractions (n = 30, 81%, 52.5-67.5 Gy, relative biological effectiveness), whereas the remainder were treated in 5 fractions (n = 7, 19%, 37.5-50 Gy, relative biological effectiveness). Daily image guidance consisted of orthogonal kilovoltage x-rays and use of a 6° of freedom robotic couch. Outcomes (local control, progression free survival, and overall survival) were determined using Kaplan-Meier methods.

Results: Thirty-seven patients were included. The median follow-up for living patients was 21 months (Q1-Q3, 17-30 months). Pretreatment Child-Pugh score was A5-6 in 70% of patients and B7-9 in 30% of patients. Nineteen patients had prior liver directed therapy for HCC before IMPT. Eight patients (22%) required a replan during treatment, most commonly due to inadequate clinical target volume coverage. One patient (3%) experienced a grade 3 acute toxicity (pain) with no recorded grade 4 or 5 toxicities. An increase in Child-Pugh score by ≥ 2 within 3 months of treatment was observed in 6 patients (16%). At 1 year, local control was 94%, intrahepatic control was 54%, progression free survival was 35%, and overall survival was 78%.

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All data generated and analyzed during this study are included in this published article. Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Conclusions: IMPT is safe and feasible for treatment of HCC.

Introduction

In the United States, the incidence of hepatocellular carcinoma (HCC) and HCC-related annual deaths have approximately doubled over the past 2 decades.[1] Worldwide, HCC remains a leading cause of cancer-related mortality. Aside from liver transplantation, surgical resection and local ablation are considered curative treatments for patients with adequate liver function and limited tumor burden.[2] Yet, many patients are not candidates for surgical therapies and require alternative treatment strategies. For these patients, transarterial therapies (chemo-embolization, radio-embolization) and external beam radiation therapy (EBRT) have shown efficacy.[3]

Historically, the utility of EBRT for treating HCC was constrained by technical limitations in controlling dose to the uninvolved liver. With recent advances in radiation therapy techniques, EBRT is now considered a reasonable treatment option for patients with localized HCC, alongside transarterial therapies. One of those advances that has helped improve EBRT treatment of HCC is proton beam therapy. Compared with photon radiation therapy, proton therapy has markedly less exit dose because the dose deposited by the protons is at a maximum near the end of their range. Thus, proton therapy may improve the therapeutic ratio by decreasing dose to the liver uninvolved by tumor.

Prior studies examining proton therapy for HCC used passive-scatter proton therapy technology. Compared with passive-scatter proton therapy, spot-scanning proton therapy allows for intensity modulation of the proton beam (IMPT), providing a more conformal dose distribution and sparing more uninvolved liver and adjacent organs. However, IMPT may be more vulnerable to uncertainties in dose delivery due primarily to target motion and the interplay effect.[4]

We report our initial clinical experience of IMPT for the treatment of HCC with the hypothesis that IMPT can be delivered safely for this aggressive malignancy. Better treatment strategies are needed to decrease the risk of liver injury while maintaining disease control in these patients who are at risk for liver decompensation.

Methods and Materials

Patient selection

After institutional review board approval, we retrospectively reviewed electronic medical records of consecutive patients with HCC who were treated with IMPT from June 2015 through December 2018. These patients were treated at 2 tertiary sites within the same institution. Inclusion criteria were age $\geq$18 years, clinical or pathologic diagnosis of HCC without metastatic disease, and IMPT treatment with curative intent. Prior HCC-directed therapy was allowed.

Radiation planning and treatment

The decision to treat with IMPT (vs photon stereotactic body radiation therapy [SBRT]) was at the discretion of the treating physician (subject to insurance approval), although IMPT was generally used for patients with tumors $\geq$4 cm, multifocal disease, or portal vein thrombosis. The majority of patients were treated with 67.5 or 58.5 Gy (relative biological effectiveness [RBE]) in 15 fractions or 50 Gy (RBE) in 5 fractions (stereotactic body proton therapy [SBPT]).

All patients had fiducials placed in the liver adjacent to the tumor before simulation. Two patients had a surgical spacer placed between the liver and nearby bowel before simulation. Patients were simulated and treated with a full body vacuum cushion (BlueBag, Elekta Instrument AB) or a vacuum cushion under the arms and a knee cushion. A less common treatment position used an Orfit set-up (Orfit Industries NV) with a thorax thermoplastic mask and leg vacuum cushion (n = 4). A free-breathing 4 dimensional computed tomography was performed and the motion of the fiducials was assessed. The median fiducial motion was 10 mm (first through third quartile [Q1-Q3], 8-15 mm). For fiducial motion $<$10 mm and no overlap of the internal target volume (ITV) with a critical organ at risk (OAR), patients were primarily treated free breathing with isolayer repainting (n = 6, 16%) with only 1 (3%) patient who was treated with free breathing alone as fiducial motion was only 6 mm. For fiducial motion $\geq$10 mm and/or overlap of the ITV with a critical OAR, patients were treated with inspiratory breath hold (n = 15, 41%), phase-based respiratory gating (n = 8, 22%), or free breathing with isolayer repainting (n = 7, 19%). Both noncontrast and intravenous contrast scans were performed at simulation, but treatment planning was performed using noncontrast images. All patients had pretreatment magnetic resonance imaging used for planning purposes with the majority (n = 31, 84%) being in treatment position.

The gross target volume included the parenchymal disease and associated vascular involvement. An ITV was determined based on an appropriate margin to account for

tumor motion. A clinical target volume was generally equal to the ITV but a 5 to 10 mm margin could be added to the ITV based on physician preference. The majority of patients (n = 24, 65%) were treated with 3 fields, with the remaining patients (n = 13, 35%) treated with 2 fields. Twenty patients (54%) were planned using single-field optimization and 17 patients (46%) were planned with multifield optimization. Robust treatment planning was used, with a goal to have 95% of the target covered by 95% of the dose with translational shifts of ±5 mm in x, y, and z directions and range uncertainty of ±5%. An RBE of 1.1 was assumed.

Dose constraints for OARs were followed according to institution guidelines. Relevant dose constraints for the 15 fraction regimen were the following: cord volume receiving 37.5 Gy (RBE) (V37.5) $\leq$ 0.50 cc, small bowel V45 $\leq$ 0.5 cc, large bowel V48 $\leq$ 0.5 cc, liver minus target mean dose $\leq$ 27 Gy (RBE). For the 5 fraction regimen, constraints included: cord D0.03 cc $<$ 30 Gy (RBE), small bowel D0.03 cc $<$ 32 Gy (RBE), large bowel D0.03 $<$ 38 Gy (RBE), liver minus target mean $<$ 17 Gy (RBE).

All patients were treated with daily image guidance using orthogonal kilovoltage x-rays and a 6° of freedom robotic couch. An initial alignment was performed to the spine to adjust for variation in general patient positioning, and then the final alignment was performed to the fiducials. Imaging was generally performed before each treatment field with a tolerance of 5 mm to the fiducials. Verification computed tomography scans were obtained once per week for patients receiving 15 fractions and once during the initial 3 days of treatment for patients receiving 5 fractions.

Follow-up and disease outcomes

Follow-up data were collected through April 2020. Patients underwent standard clinical and imaging evaluations, generally every 3 months after treatment. Outcomes (local control [LC], intrahepatic control, progression free survival [PFS], and overall survival [OS]) were determined using Kaplan-Meier methods. LC was defined as no evidence of growth on follow-up imaging of the treated tumor. Intrahepatic failure was defined as appearance of new liver tumors or growth of liver tumors outside the treated volume on follow-up imaging. PFS was defined as no evidence of local or intrahepatic failure or appearance of metastatic disease outside the liver.

Liver disease indices

Child-Pugh (CP), albumin-bilirubin (ALBI), and model for end-stage liver disease were used to estimate the severity of end-stage liver disease and survival prediction. CP was calculated using an assigned point system for the following patient variables: total bilirubin, albumin, international normalized ratio, presence of ascites, and presence of encephalopathy.[5] ALBI was calculated with a weighted equation that takes into account the patient's bilirubin and albumin levels.[6] Finally, the model for end-stage liver disease score was calculated using an assigned point system for the following laboratory values: creatinine, total bilirubin, international normalized ratio, and sodium.[7]

Results

Patient and tumor characteristics

Thirty-seven patients met inclusion criteria for this study. Patients were followed until death or with a median follow-up of 21 months in survivors (Q1-Q3 17-30 months). Patient and treatment characteristics are detailed in Tables 1 and 2, respectively.

Table 1 Patient characteristics

	Number (%) or median (Q1-Q3)
Age, years	69 (64-76)
Sex	
Male	25 (68%)
Female	12 (32%)
Race	
White	32 (87%)
Non-white	5 (13%)
ECOG	
0	14 (38%)
1	17 (46%)
2	4 (11%)
3	2 (5%)
Cirrhosis	
Present	27 (73%)
Absent	10 (27%)
Etiology of cirrhosis	
Alcoholic	6 (22%)
HCA	1 (4%)
HBV	1 (4%)
HCV	8 (30%)
NAFLD	8 (30%)
Other	3 (11%)
Child-Pugh	
A (5-6)	26 (70%)
B (7-9)	11 (30%)
ALBI score	-2.42 (-2.76 to -2.08)
MELD score	9 (7-11)
Alpha-fetoprotein (ng/mL)	20 (5-516)
Disease status	
Newly diagnosed	18 (49%)
Locally recurrent	19 (51%)

Abbreviations: ALBI = albumin bilirubin; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; HCA = hemochromatosis; HCV = hepatitis C virus; MELD = model for end-stage liver disease; NAFLD = nonalcoholic fatty liver disease.

Table 2 Tumor and radiation therapy characteristics

	Number (%) or median (Q1-Q3)
Median tumor size, cm	5 (3-8)
<5 cm	19 (51%)
5-10 cm	14 (38%)
>10 cm	4 (11%)
Vascular thrombosis	
Present	14 (38%)
Absent	23 (62%)
Previous therapy to target	
Yes	18 (49%)
No	19 (51%)
Most recent previous target therapy (n = 18)	
Ablation	3 (17%)
External beam (photon) radiation therapy	1 (6%)
TACE	6 (33%)
TAE bland	3 (17%)
TARE	1 (6%)
Surgery	1 (6%)
Systemic therapy	3 (17%)
Any prior therapy	
Yes	24 (65%)
No	13 (35%)
Dose fractionation	
67.5 Gy (RBE) in 15 fx	15 (41%)
58.5 Gy (RBE) in 15 fx	13 (35%)
52.5 Gy (RBE) in 15 fx	2 (5%)
50 Gy (RBE) in 5 fx	6 (16%)
37.5 Gy (RBE) in 5 fx	1 (3%)

Abbreviations: RBE = relative biological effectiveness; TACE = transarterial chemoembolization; TAE = transarterial embolization; TARE = transarterial radioembolization.

Recorded dose volume histogram indices are presented in Table 3. The median of the uninvolved liver mean dose was 12 Gy (RBE) (Q1-Q3 8-16 Gy). During the IMPT course, 8 patients (22%) required replans, with 1 patient requiring 3 replans. Reasons to replan included the following: 6 replans to improve clinical target volume coverage (2 for ascites and 4 for changes in respiratory motion), 3 to decrease the dose to the duodenum, and 1 because the patient did not tolerate the initial treatment position.

Table 3 Dose-volume histogram indices

	Median (Q1-Q3)
GTV (cc)	158 (70-434)
GTV V100% (%)	100 (99-100)
GTV V95% (%)	100 (100-100)
CTV volume (cc)	170 (77-533)
CTV V100% (%)	99 (98-100)
CTV V95% (%)	100 (99-100)
Liver volume (cc)	1799 (1300-2316)
Liver - CTV mean (Gy [RBE])	12.3 (7.6-15.8)

Abbreviations: CTV = clinical target volume; GTV = gross tumor volume; RBE = relative biological effectiveness.

Outcomes

Three patients (8%) experienced a local failure of the target lesion for a 1-year LC of 94% (Fig 1A). Nineteen patients (51%) experienced a nontarget intrahepatic failure, and 7 patients (19%) developed distant metastases. Median PFS was 10 months (95% confidence interval, 4-13 months). At 1 year, intrahepatic control was 54% and PFS was 35%. Nineteen patients (51%) died during the study period for a median and 1-year OS of 19 months (95% confidence interval, 13-24 months) and 78%, respectively (Fig 1B). One patient underwent liver transplant 9 months after completion of IMPT treatment.

Toxicities

Four patients (8%) experienced a Common Terminology Criteria for Adverse Events version 5.0 grade 2 toxicity (anorexia, fatigue, nausea, pain), which was not

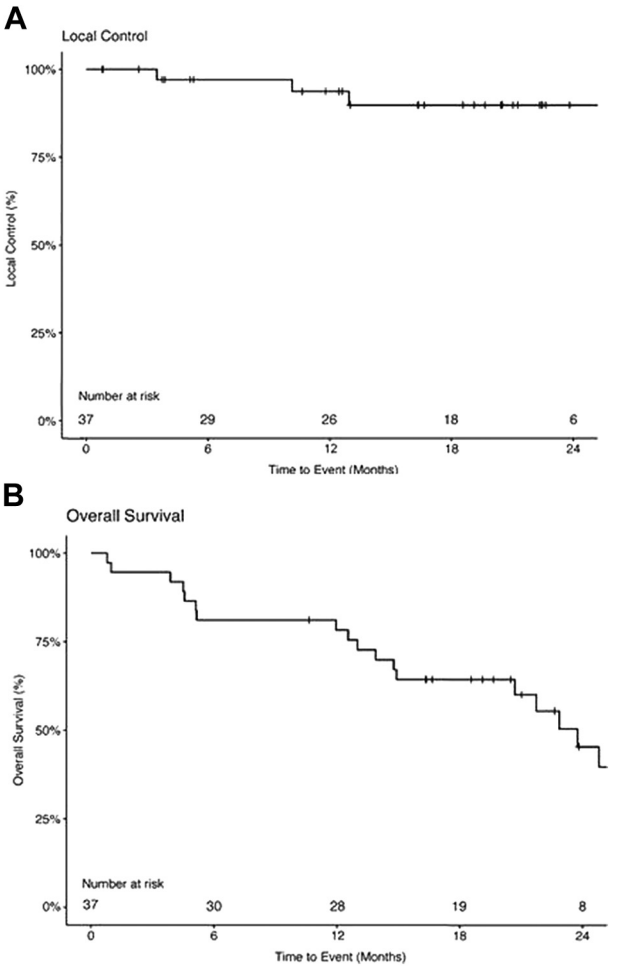

Figure 1 (A) Local control; (B) Overall survival.

present at baseline. One patient (3%) experienced grade 3 toxicity (pain) at the end of treatment. No grade 4 or 5 toxicities were recorded.

With regard to delayed effects on liver function, 13 patients (35%) experienced an increase in CP score within the first 3 months, but only 6 patients (16%) experienced an increase in CP score by 2 points (Table 4). An increase in ALBI grade was observed in 10 patients (27%); 9 of those were an increase in only 1 grade (from ALBI grade 1-2 to 2-3).

Discussion

HCC is an aggressive malignancy with local therapy playing a central role in its treatment, particularly in patients who are not transplant candidates. IMPT is both feasible and well-tolerated in the treatment of localized HCC.

In the current series, 1-year LC was 94%, PFS was 35%, and OS was 78%. These results are similar to what has been published in the literature, both for photon SBRT and hypofractionated proton radiation therapy (Table 5).[8-13] MD Anderson Cancer Center (MDACC) published their hypofractionated proton therapy for HCC series (46 patients) with a 2-year LC of 81% and OS of 62%.[11] More recently, a South Korean phase II study of hypofractionated passive scatter proton beam therapy for HCC in 45 patients demonstrated a 3-year LC of 95%, although the median tumor size treated was small (1.6 cm compared with 5 cm in our study).[14] In the United States, the Proton Collaborative Group published their experience treating unresectable liver tumors in 63 patients, reporting a 1-year LC of 91% for patients with HCC.[15] However, 25 of these patients had intrahepatic cholangiocarcinoma, and they did not differentiate between those patients who received passive scatter proton therapy versus IMPT. Given the excellent LC in the current report, the uncertainties associated with IMPT can be mitigated with appropriate motion management and treatment techniques outlined earlier.

Table 4 Pre- and posttreatment liver indices

	Pre	Post
Child-Pugh		
A (5-6)	26 (70%)	19 (54%)
B (7-9)	11 (30%)	14 (40%)
C (10-15)	0 (0%)	2 (6%)
Child-Pugh increase (any)		
Present		13 (35%)
Absent		24 (65%)
Child-Pugh increase by 2 with 3 months		
Present		6 (16%)
Absent		31 (84%)
ALBI score		
Median (Q1-Q3)	-2.42 (-2.76 to -2.08)	-2.02 (-2.59 to -1.72)
ALBI grade		
1	14 (38%)	9 (26%)
2	23 (62%)	22 (63%)
3	0 (0%)	4 (11%)
Not reported	0 (0%)	2 (NA)
MELD score		
Median (Q1-Q3)	9 (7-11)	10 (8-15)
MELD		
<10	22 (60%)	19 (51%)
10-20	14 (38%)	13 (35%)
>20	1 (3%)	5 (14%)

Abbreviations: ALBI = albumin bilirubin; MELD = model for end-stage liver disease.

IMPT was well-tolerated in the current series, with only 1 patient (3%) experiencing a grade 3 toxicity. In terms of liver prognostic indices, an increase in CP score by 2 points was found in 6 patients (16%), which is similar to the 10% to 15% range reported in recent studies using proton therapy.[9,11] An increase in CP score by 2 points has been used as a measure of radiation-induced hepatic toxicity and was found to be associated with OS of patients treated with radiotherapy.[16] Compared with baseline CP score, baseline ALBI score has been suggested to be a more important prognostic factor for radiation-induced hepatic toxicity and OS in patients with a CP score of 5 to 6.[17] The current series found 4 patients (11%) were ALBI grade 3 within 3 months of treatment completion, whereas no patients were grade 3 before treatment.

Hepatic toxicity has been associated with increased liver dose and level of underlying cirrhosis.[17,18] In our study, the median value for mean liver-target dose was 12.3 Gy (RBE) —well below our institutional constraint of 27 Gy (RBE) for the 15 fraction regimen. Dosimetric factors predicting radiation-induced hepatic toxicity have included increased mean liver dose and increased dose to 800 cc of the liver.[19] In a dosimetric comparison study for liver tumors, proton therapy resulted in a significantly decreased mean liver dose as well as liver volume receiving at least 30 Gy (RBE).[20] More recently, a multi-institutional dosimetric analysis of patients undergoing proton therapy identified unirradiated liver volume (liver receiving <1Gy [RBE]) as an independent predictor of CP increase by 2 points.[21]

The importance of minimizing radiation-related liver injury is supported by 2 separate clinical comparisons of proton and photon therapy for HCC. In a multicenter study, patients who received proton therapy had significantly improved OS compared with those who received photon therapy and also had a significantly decreased risk of developing a CP increase by 2 points.[22] However, when stratified by those patients who developed a CP increase by 2 points, the survival benefit for proton therapy only remained significant when comparing the 2

Table 5 Selected proton studies for hepatocellular carcinoma

Author year	Institution(s)	Study type	Number of patients	Proton technique	Most common dose/ fractionation	Median follow-up (months)	Local control	PFS	OS	Grade ≥ 3 CTCAE (acute or late)	Patients with CP increase by 2
Bush 2011[10]	Loma Linda University Medical Center	Prospective	76	Passive scatter	63 GyE / 15 fx	NR	NR	2 year: 30%*	2 year: 25%*	0%	NR
Komatsu 2011[12]	Hyogo ion beam medical Center	Prospective	242	Passive scatter	53-84 GyE / 4-38 fx	31	5 year: 90.2%	NR	5 year: 38%	3%	NR
Mizumoto 2011[13]	University of Tsukuba	Prospective	266	Passive scatter	66 GyE / 10 fx	NR	1 year: 98% 3 year: 87%	1 year: 56% 3 year: 21%	1 year: 87% 3 year: 61%	3%	NR
Hong 2016[8]	MGH, MDACC, Upenn	Prospective	44‡	Passive scatter	67.5 GyE / 15 fx	20†	2 year: 94.8%‡	1 year: 56.1%‡ 2 year: 39.9%‡	1 year: 76.5%‡ 2 year: 63.2%‡	2%‡	4%†
Chadha 2019[11]	MDACC	Retrospective	46	Passive scatter	67.5 GyE / 15 fx	15	1 year: 95% 2 year: 81%	1 year: 74% 2 year: 57%	1 year: 73% 2 year: 62%	13%	9%
Kim 2020[14]	National Cancer Center (South Korea)	Prospective	45	Passive scatter	70 GyE / 10 fx	35	1 year: 98% 2 year: 95%	1 year: 78% 2 year: 48%	1 year: 98% 2 year: 92%	0%	0%
Parzen 2020[15]	Proton Collaborative Group (United States)	Retrospective	30‡	NR	58.05 GyE / 15fx	8‡	1 year: 91%‡	1 year: 60%‡	1 year: 72%‡	3%‡	NR
Current Series	Mayo Clinic	Retrospective	37	IMPT	67.5 GyE / 15 fx	19	1 year: 94%	1 year: 35%	1 year: 78%	3%	16%

Abbreviations: CP = Child-Pugh; CTCAE = Common Terminology Criteria for Adverse Events; HCC = hepatocellular carcinoma; IMPT = intensity modulated proton therapy; OS = overall survival; PFS = progression free survival; NR = not reported.

* Estimated from provided survival curves (Milan criteria patients for PFS, nontransplant patients for OS)

† Includes both patients with HCC and intrahepatic cholangiocarcinoma.

‡ Includes only patients with HCC reported in the manuscript.

modalities in patients who experienced this radiation-related liver toxicity. A propensity-matched analysis from Taiwan also found a significantly improved median survival for patients who received proton therapy compared with those who received photon therapy (not reached vs 17.4 months, $P < .01$).[23] Similarly, they reported a significantly decreased risk of radiation-related liver injury in the proton group compared with the photon group (12 vs 36%, $P < .01$). The current report includes 11 patients (30%) with CP 7 to 9 disease, and notably, 3 of these patients (8%) had CP 9 disease (the latter were not included in the previously mentioned MDACC retrospective series).[11] Thus, the ability to minimize dose to uninvolved liver with IMPT may be a considerable advantage over the use of photon SBRT. A more challenging question to answer is whether IMPT would provide significant benefit in treating HCC over passive scatter proton therapy. Given the importance of minimizing hepatic toxicity in these patients, IMPT may demonstrate benefit over passive scatter technology by providing a dosimetric advantage with regard to decreasing dose to the uninvolved liver, particularly for larger tumors. A recent propensity-matched analysis from South Korea, however, did not find any significant difference in disease outcomes or toxicity when comparing patients treated with passive scatter proton therapy to those treated with IMPT.[24]

Our series includes 7 patients (19%) treated with an SBRT regimen (5 fractions or fewer) using protons (SBPT). Published proton series have primarily studied hypofractionated regimens (typically 15 fractions) as noted previously, and the fewest number of fractions included in the MDACC series was 6. To date, SBPT has primarily been studied in the setting of hepatic metastases and seems to be a safe treatment technique.[25,26] The use of SBPT for HCC is intriguing, as proton therapy was an independent predictor of better OS in an National Cancer Database (NCDB) analysis comparing proton therapy to photon SBRT.[27]

The current study is limited by its retrospective nature. Patient selection, both in terms of tumor burden and liver function, is particularly important when reporting toxicity and outcomes of HCC treatment. Although the majority of patients were CP A5-6 (70%), this cohort may have represented patients with more aggressive disease, as approximately half had experienced a local recurrence before IMPT treatment. The small size of this series and limited follow-up may also be considered limitations. However, given that selection of HCC treatment is related to technique availability and institutional preference, the number of patients included in the current study is reasonable. Additionally, patients in our series were treated over a smaller time period (3 years) compared with other larger proton series.[10,11]

We demonstrate that IMPT is a clinically feasible and well-tolerated treatment for HCC. Further studies with prospective and preferably randomized evidence for IMPT are warranted to demonstrate effectiveness in comparison to other treatment modalities. NRG Oncology is currently conducting a phase III randomized trial comparing photon to proton therapy for unresectable or locally recurrent HCC (NRG-GI003, NCT03186898), and we look forward to the publication of their results.

References

1. Kim HS, El-Serag HB. The epidemiology of hepatocellular carcinoma in the USA. *Curr Gastroenterol Rep*. 2019;21:17.
2. Raza A, Sood GK. Hepatocellular carcinoma review: Current treatment, and evidence-based medicine. *World J Gastroenterol*. 2014;20:4115-4127.
3. Dimitroulis D, Damaskos C, Valsami S, et al. From diagnosis to treatment of hepatocellular carcinoma: An epidemic problem for both developed and developing world. *World J Gastroenterol*. 2017; 23:5282-5294.
4. Bert C, Grözinger SO, Rietzel E. Quantification of interplay effects of scanned particle beams and moving targets. *Phys Med Biol*. 2008; 53:2253-2265.
5. Child CG, Turcotte JG. Surgery and portal hypertension. *Major Probl Clin Surg*. 1964;1:1-85.
6. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: A new evidence-based approach-the ALBI grade. *J Clin Oncol*. 2015;33:550-558.
7. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001; 33:464-470.
8. Hong TS, Wo JY, Yeap BY, et al. Multi-institutional phase ii study of high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol*. 2016;34:460-468.
9. Durand-Labrunie J, Baumann AS, Ayav A, et al. Curative irradiation treatment of hepatocellular carcinoma: A multicenter phase 2 trial. *Int J Radiat Oncol Biol Phys*. 2020;107:116-125.
10. Bush DA, Kayali Z, Grove R, Slater JD. The safety and efficacy of high-dose proton beam radiotherapy for hepatocellular carcinoma: A phase 2 prospective trial. *Cancer*. 2011;117:3053-3059.
11. Chadha AS, Gunther JR, Hsieh CE, et al. Proton beam therapy outcomes for localized unresectable hepatocellular carcinoma. *Radiother Oncol*. 2019;133:54-61.
12. Komatsu S, Fukumoto T, Demizu Y, et al. Clinical results and risk factors of proton and carbon ion therapy for hepatocellular carcinoma. *Cancer*. 2011;117:4890-4904.
13. Mizumoto M, Okumura T, Hashimoto T, et al. Proton beam therapy for hepatocellular carcinoma: A comparison of three treatment protocols. *Int J Radiat Oncol Biol Phys*. 2011;81:1039-1045.
14. Kim TH, Park JW, Kim BH, et al. Phase II study of hypofractionated proton beam therapy for hepatocellular carcinoma. *Front Oncol*. 2020;10:542.
15. Parzen JS, Hartsell W, Chang J, et al. Hypofractionated proton beam radiotherapy in patients with unresectable liver tumors: Multi-institutional prospective results from the Proton Collaborative Group. *Radiat Oncol*. 2020;15:255.
16. Son SH, Jang HS, Jo IY, et al. Significance of an increase in the Child-Pugh score after radiotherapy in patients with unresectable hepatocellular carcinoma. *Radiat Oncol*. 2014;9:101.
17. Murray LJ, Sykes J, Brierley J, et al. Baseline albumin-bilirubin (ALBI) score in western patients with hepatocellular carcinoma treated with stereotactic body radiation therapy (SBRT). *Int J Radiat Oncol Biol Phys*. 2018;101:900-909.

18. Lasley FD, Mannina EM, Johnson CS, et al. Treatment variables related to liver toxicity in patients with hepatocellular carcinoma, Child-Pugh class A and B enrolled in a phase 1-2 trial of stereotactic body radiation therapy. *Pract Radiat Oncol*. 2015;5:e443-e449.
19. Velec M, Haddad CR, Craig T, et al. Predictors of liver toxicity following stereotactic body radiation therapy for hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2017;97:939-946.
20. Wang X, Krishnan S, Zhang X, et al. Proton radiotherapy for liver tumors: Dosimetric advantages over photon plans. *Med Dosim*. 2008;33:259-267.
21. Hsieh CE, Venkatesulu BP, Lee CH, et al. Predictors of radiation-induced liver disease in eastern and western patients with hepatocellular carcinoma undergoing proton beam therapy. *Int J Radiat Oncol Biol Phys*. 2019;105:73-86.
22. Sanford NN, Pursley J, Noe B, et al. Protons versus photons for unresectable hepatocellular carcinoma: Liver decompensation and overall survival. *Int J Radiat Oncol Biol Phys*. 2019;105:64-72.
23. Cheng JY, Liu CM, Wang YM, et al. Proton versus photon radiotherapy for primary hepatocellular carcinoma: A propensity-matched analysis. *Radiat Oncol*. 2020;15:159.
24. Yoo GS, Yu JI, Cho S, et al. Comparison of clinical outcomes between passive scattering versus pencil-beam scanning proton beam therapy for hepatocellular carcinoma. *Radiother Oncol*. 2020;146:187-193.
25. Kang JI, Sufficool DC, Hsueh CT, et al. A phase I trial of proton stereotactic body radiation therapy for liver metastases. *J Gastrointest Oncol*. 2019;10:112-117.
26. Hong TS, Wo JY, Borger DR, et al. Phase II study of proton-based stereotactic body radiation therapy for liver metastases: Importance of tumor genotype. *J Natl Cancer Inst*. 2017;109. https://doi.org/10.1093/jnci/djx031.
27. Hasan S, Abel S, Verma V, et al. Proton beam therapy versus stereotactic body radiotherapy for hepatocellular carcinoma: Practice patterns, outcomes, and the effect of biologically effective dose escalation. *J Gastrointest Oncol*. 2019;10:999-1009.