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ORIGINAL REPORT

Multi-Institutional Phase II Study of High-Dose Hypofractionated Proton Beam Therapy in Patients With Localized, Unresectable Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma

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ABSTRACT

Purpose
To evaluate the efficacy and safety of high-dose, hypofractionated proton beam therapy for hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC).

Materials and Methods
In this single-arm, phase II, multi-institutional study, 92 patients with biopsy-confirmed HCC or ICC, determined to be unresectable by multidisciplinary review, with a Child-Turcotte-Pugh score (CTP) of A or B, ECOG performance status of 0 to 2, no extrahepatic disease, and no prior radiation received 15 fractions of proton therapy to a maximum total dose of 67.5 Gy equivalent. Sample size was calculated to demonstrate > 80% local control (LC) defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 criteria at 2 years for HCC patients, with the parallel goal of obtaining acceptable precision for estimating outcomes for ICC.

Results
Eighty-three patients were evaluable: 44 with HCC, 37 with ICC, and two with mixed HCC/ICC. The CTP score was A for 79.5% of patients and B for 15.7%; 4.8% of patients had no cirrhosis. Prior treatment had been given to 31.8% of HCC patients and 61.5% of ICC patients. The median maximum dimension was 5.0 cm (range, 1.9 to 12.0 cm) for HCC patients and 6.0 cm (range, 2.2 to 10.9 cm) for ICC patients. Multiple tumors were present in 27.3% of HCC patients and in 12.8% of ICC patients. Tumor vascular thrombosis was present in 29.5% of HCC patients and in 28.2% of ICC patients. The median dose delivered to both HCC and ICC patients was 58.0 Gy. With a median follow-up among survivors of 19.5 months, the LC rate at 2 years was 94.8% for HCC and 94.1% for ICC. The overall survival rate at 2 years was 63.2% for HCC and 46.5% ICC.

Conclusion
High-dose hypofractionated proton therapy demonstrated high LC rates for HCC and ICC safely, supporting ongoing phase III trials of radiation in HCC and ICC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) represent the two most common types of primary liver cancers. Although biologically and clinically distinct entities,[1,2] both share common management issues. Despite surgical options that are potentially curative for both cancers, many patients are not candidates for surgery, either for medical or anatomic reasons.

The role of radiation in the management of liver tumors has been expanding rapidly.[3] Improved technical capabilities have permitted safe delivery of potentially ablative doses of radiation for liver tumors. For HCC, radiation has been shown in single-arm phase II studies to be safe, with high rates of local control (LC),[4] leading to an ongoing phase III evaluation of radiation in unresectable, localized HCC. In contrast, radiation has been studied substantially less for ICC, with the data being primarily retrospective[5] or limited by small numbers.[6,7]

Proton beam therapy is an external beam radiation modality using charged particles. Protons have a distinct physical advantage over standard photon-based radiation. Photons, or high-energy x-rays, deposit energy along the beam path beyond the tumor and through the patient. This exit dose leads to unwanted radiation exposure to normal organs, which is of particular relevance to the liver because the risk of radiation-induced liver disease (RILD) is mediated by the dose delivered and volume of liver radiated.[8] In contrast, protons deposit energy at a prespecified depth without an exit dose, thus providing a theoretical clinical benefit over photon-based radiation by allowing the safe dose escalation, especially in larger tumors.[9] Prior prospective studies of proton therapy for HCC have shown excellent tolerability and LC.[10,11] In this study, we evaluated the safety and efficacy of high-dose, hypofractionated proton beam therapy for HCC and ICC.

MATERIALS AND METHODS

Patients were enrolled in a prospective clinical trial (NCT00976898) approved by the institutional review boards of each of the participating institutions. Adult patients age 18 years or older were required to have biopsy-proven unresectable or locally recurrent HCC or ICC. Single or multinodular tumors (up to three) were permitted. Maximum tumor diameter permitted was 12 cm for solitary tumors, 10 cm if two tumors, and 6 cm if three tumors. Patients were required to have no evidence of extrahepatic tumor by computed tomography (CT) scan and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. In patients with underlying cirrhosis, only a Child-Turcotte-Pugh (CTP) score of A or B was permitted. Adequate organ and marrow function was required and defined as absolute neutrophil count $\geq 750/\mu L$; platelets $\geq 25{,}000/\mu L$; total bilirubin $\leq 4 \times$ institutional upper limit of normal; transaminases $\leq 6 \times$ institutional upper limit of normal; and creatinine ≤ 2 mg/dL. No prior liver radiation, including radioembolization, was permitted. Patients were identified as having unresectable tumors after review with transplant surgery and surgical oncology physicians at the institutional multidisciplinary liver conference. Written informed consent was obtained from all protocol patients before initiation of any study procedures.

Simulation

The patients underwent four-dimensional simulation with intravenous contrast. A clinical target volume expansion of 0 to 1 cm was used at the discretion of the treating physician. The precise clinical target volume varied based on the confidence of the treating physician to identify the borders of the lesion on imaging. The planning target volume (PTV) margin was customized based on the institutional motion management strategy used, but ranged between 0.5 and 1 cm. Respiratory-gating, abdominal compression, or use of an internal target volume were all permitted.

Dose Prescription and Normal Tissue Constraints

The relative biologic effectiveness was set at 1.1 per institutional standard of all three institutions. Thus, the dose unit Gy-equivalent (GyE) was proton dose in Gy $\times$ relative biologic effectiveness of 1.1. The planned dose was 67.5 GyE, delivered in 15 fractions for peripheral tumors (>2 cm from the porta hepatis), and 58.05 GyE, delivered in 15 fractions (3.87 Gy/fraction) for central tumors (within 2 cm of the porta hepatis). Dose de-escalation was permitted to maintain a liver gross tumor volume (GTV) mean dose of ≤ 24 GyE. Nonliver normal tissue constraints were maximum spinal cord dose of 30 GyE, maximum stomach dose of 42 GyE, maximum bowel (including duodenum, small bowel, large bowel) dose of 45 GyE, and kidney volume receiving >14 Gy (V14) $<30\%$. As suggested, the maximum heart dose of 45 GyE, V40 $<10\%$ and chest wall V60 $<$ 2 mL was recommended.

Treatment

All treatments were delivered using three-dimensional passively scattered protons at Massachusetts General Hospital (240 MeV cyclotron), MD Anderson Cancer Center (250 MeV synchrotron), or the University of Pennsylvania (230 MeV cyclotron). Daily imaging for localization was required.

Follow-Up

Patients had follow-up visits every 3 months, with computed tomography scans every 6 months for the first 2 years. For years 3 to 5, patients had follow-up visits every 6 months, with yearly computed tomography scans. Toxicity was scored using the common terminology criteria version 3.0 and was counted only if possibly, probably, or likely related to radiation in attribution. Progression was determined by the interpreting radiologist and confirmed by the treating physician. Central review was not used.

Statistics

The study was designed to demonstrate the LC rate of at least 80% at 2 years for HCC. ICC patients were enrolled in parallel with the goal of obtaining reasonable precision, but no specific hypothesis was proposed because there was no baseline comparative data. LC was defined as the absence of local failure or the absence of tumor growth or regrowth in any direction beyond that present on the pretreatment, baseline studies of the treated lesion(s) by Response Evaluation Criteria in Solid Tumors (RECIST) 1.0. New intrahepatic tumors outside of the radiation field were scored as elsewhere failures. The risk of local recurrence was estimated using the cumulative incidence function, treating death as a competing risk. LC, overall survival (OS), and progression-free survival (PFS) were calculated starting from the first day of radiation. The OS time of a patient still alive at the time of the last follow-up was censored. PFS was measured until a patient had any recurrence documented or died, whichever event was earlier, or otherwise was censored at the date of the last follow-up. OS and PFS rates were estimated by the Kaplan-Meier method, whereas OS comparisons were made using the Cox proportional hazards model when at least four deaths were observed in each subgroup in the analysis of binary covariates. Statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC). All P values were based on a two-sided hypothesis test.

RESULTS

Ninety-two patients signed consent forms from November 2009 to February 2015 (Fig1). Nine patients (five HCC; four ICC) were excluded from the analysis because they never started treatment. The reasons for no treatment were inability to meet dosing constraints[3] (two patients mucosal and cardiac, one mucosal); medically unable to proceed with treatment or did not meet eligibility[3]; patient choice[1]; scheduling issues[1]; and other logistical issues.[1] Of the 83 evaluable patients, 44 had HCC, 37 had ICC, and two had mixed HCC/ICC, which were included with ICC for analysis, yielding 39 patients analyzed with ICC. Patient characteristics are listed in Table 1. For HCC patients, 79.5% had CTP A, and 89.7% of ICC patients had no cirrhosis. For HCC, 32 patients (72.7%) had one lesion, 10 (22.7%) had two lesions, and two (4.5%) had three lesions. For ICC, 34 patients (87.2%) had one lesion, three (7.7%) had two lesions, and two (5.1%) had three lesions.

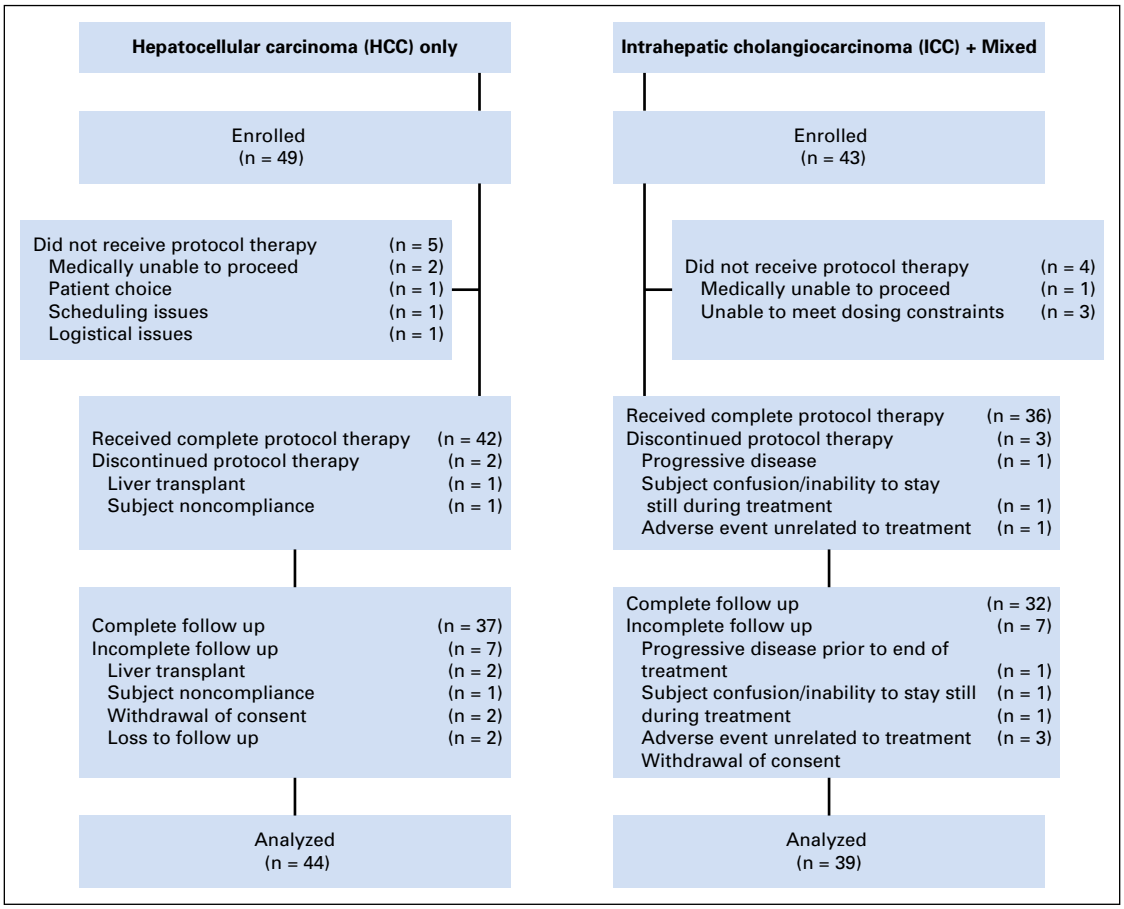

Fig 1. Study CONSORT diagram.

Radiation Dosing

Target volume, liver volume, dose delivered, and the average dose received by the liver that was not involved by the tumor (mean liver-GTV dose [MLD]) parameters are listed in Table 2 for the entire cohort and by diagnosis. The median liver size was 1,600.1 mL (range, 612.9 to 3,369.3). With 42 HCC patients (95.5%) and 36 ICC patients (92.3%) having completed their prescribed dose, the median dose delivered was 58.0 GyE (in 15 fractions; range, 15.1 to 67.5 GyE). The participant who received 15.1 GyE had been taken off study before treatment completion because of confusion and inability to stay still during treatment. The MLD for all patients was 19.2 GyE (range, 3.2 to 29.5 GyE), 18.4 GyE (range, 6.2 to 29.3 GyE) for HCC patients, and 21.4 GyE (range, 3.2 to 29.5 GyE) for ICC patients.

Toxicity

Of the 83 patients, 71 (85.5%) experienced at least one radiation-related toxicity event while in the study, most commonly fatigue (54/83, 65.1%), rash (51/83, 61.4%), nausea (25/83, 30.1%), or anorexia (21/83, 25.3%; Table 3). Four patients (4.8%) experienced at least one grade-3 radiation-related toxicity. One of 44 HCC patients (2.3%) developed grade-3 thrombocytopenia. Three of 39 ICC patients (7.7%) developed grade-3 radiation-related toxicities: liver failure and ascites,[1] stomach ulcer,[1] and elevated bilirubin.[1] Three of 83 patients (3.6%) had worsening CTP score: two patients from CTP A to B at 3 months and one patient from CTP A to B at 6 months. There were no grade-4 or grade-5 radiation-related toxicities.

Disease-Specific Outcomes

Median follow-up among the 50 survivors was 19.5 months (range, 0.6 to 55.9 months). Four participants (two HCC and two ICC) experienced local progression within 2 years of follow-up, making the 2-year LC (LC-2) rate 94.4% (95% CI, 87.2% to 98.2%; Fig 2A). Although the LC-2 rate was similar for HCC and ICC patients (94.8% *v* 94.1%), recurrence beyond 2 years occurred only in the ICC group (Fig 2B) in an additional four patients, for a total of six local recurrences of the 39 patients. All eight participants who progressed locally had received $<$ 60 GyE (Fig 2C).

For patients with HCC, the median PFS was 13.9 months (95% CI, 8.4 to 49.9 months; Fig 3A). The 1-year and 2-year PFS rates were 56.1% and 39.9%, respectively. The median OS (Fig 3B) was 49.9 months (95% CI lower bound, 17.8 months; upper bound not reached), with 1-year and 2-year OS of 76.5% and 63.2%, respectively. Three patients with HCC underwent successful liver transplantation, two of whom remain alive.

For patients with ICC, the median PFS rate was 8.4 months (95% CI, 5.0 to 15.7 months;Fig 3A). The 1-year and 2-year PFS rates were 41.4% and 25.7%, respectively. The median OS (Fig 3B) was 22.5 months (95% CI, 12.4 to 49.7 months), with 1-year and 2-year OS rates of 69.7% and 46.5%, respectively.

Table 1. Patient and Treatment Characteristics

Characteristic	Level	All Patients (N = 83) % (No.) or Median (range)	HCC (n = 44) % (No.) or Median (range)	ICC (N = 39) % (No.) or Median (Range)
Age at radiation start date		67.6 (29.9-89.7)	70.5 (53.6-89.7)	66.9 (29.9-87.0)
Sex	Male	61.4% (51)	84.1% (37)	35.9% (12)
	Female	38.6% (32)	15.9% (7)	64.1% (25)
Race/ethnicity	White	91.6% (76)	90.9% (40)	92.3% (36)
	Black	4.8% (4)	4.5% (2)	5.1% (2)
	Asian	1.2% (1)	0.0% (0)	2.6% (1)
	Hispanic (white or black)	1.2% (1)	2.3% (1)	0.0% (0)
	Unknown	1.2% (1)	2.3% (1)	0.0% (0)
Underlying liver disease	HCV (± others)	33.7% (28)	52.3% (13)	12.8% (5)
	No HCV but HBV (± others)	7.2% (6)	9.1% (4)	5.1% (2)
	No HCV or HBV but EtOH (± others)	9.6% (8)	13.6% (6)	5.1% (2)
	No HCV, HBV, or EtOH but NASH (± others)	3.6% (3)	4.5% (2)	2.6% (1)
	Other	2.4% (2)	2.3% (1)	2.6% (1)
	None	43.4% (36)	18.2% (8)	71.8% (28)
ECOG performance status	0	33.7% (28)	34.1% (14)	33.3% (15)
	1	62.7% (52)	59.1% (26)	66.7% (26)
	2	3.6% (3)	6.8% (3)	0.0% (0)
CTP	A	79.5% (66)	72.7% (32)	87.2% (34)
	B	15.7% (15)	20.5% (9)	10.3% (4)
	No cirrhosis	4.8% (4)	6.8% (3)	2.6% (1)
BCLC stage	A/B		50.0% (16)	
	C		47.7% (17)	
	—		2.3% (1)	
CLIP score	0-1		68.2% (30)	
	≥ 2		31.8% (12)	
	—		0.0% (0)	
Tumor vascular thrombosis	Yes	28.9% (24)	29.5% (15)	28.2% (11)
Disease status	Locally recurrent	6.0% (5)	9.1% (4)	2.6% (1)
	Newly diagnosed	94.0% (78)	90.9% (40)	97.4% (38)
No. of nodular tumors	1	79.5% (66)	72.7% (32)	87.2% (34)
	2	15.7% (15)	22.7% (10)	7.7% (3)
	3	4.8% (4)	4.5% (2)	5.1% (2)
Longest tumor dimension, cm		5.7 (1.9-12.0)	5.0 (1.9-12.0)	6.0 (2.2-10.9)
Sum of longest tumor diameters, cm		5.8 (1.9-12.0)	5.7 (1.9-12.0)	6.0 (2.4-10.9)
Biochemical analysis				
Total bilirubin, mg/dL		0.7 (0.2-3.2)	0.8 (0.2-3.2)	0.6 (0.2-3.2)
Platelets, k/UL		151.0 (55.0-463.0)	132.5 (55.0-336.0)	183.0 (59.0-463.0)
AFP, ng/mL*		7.0 (1.3-66,081)	18.6 (1.3-66,081)	4.6 (1.3-461.9)
CA-19.9 (u/mL)†		38.1 (0.0-10549)	31.0 (0.0-398.0)	72.0 (0.0-10549)
Previous therapy				
Any surgical resection	Yes	4.8% (4)	6.8% (3)	2.6% (1)
Any transarterial chemoembolization	Yes	6.0% (5)	11.4% (5)	0.0% (0)
Any radiofrequency ablation	Yes	2.4% (2)	2.3% (1)	2.6% (1)
Any chemotherapy	Yes	32.5% (27)	6.8% (3)	61.5% (24)
Any other	Yes	15.7% (15)	9.1% (4)	23.1% (9)
None	Yes	54.2% (45)	68.2% (30)	38.5% (14)

Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CA-19.9, cancer antigen 19.9; CLIP, Cancer of the Liver Italian Program; CTP, Child-Turcotte-Pugh; ECOG, Eastern Cooperative Oncology Group; EtOH, ethyl hepatocellularalcohol; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis.
*n = 82.
†n = 76.

Table 2. Treatment Characteristics Overall and by Disease Type

Characteristic	All Patients (N = 83) % (No.) or Median (range)	HCC (n = 44) % (No.) or Median (range)	ICC (n = 39) % (No.) or Median (range)
Gross tumor volume, mL*	127.2 (3.7-2,045.0)	106.4 (4.4-2,045.0)	133.7 (3.7-599.7)
Whole liver volume, mL	1,600.1 (612.9-3,369.3)	1,744.0 (895.0-3,369.3)	1,487.0 (612.9-2,522.4)
Mean liver dose, GyRBE	19.2 (3.2-29.5)	18.4 (6.2-29.3)	21.4 (3.2-29.5)
Dose delivered, GyRBE	58.0 (15.1-67.5)	58.0 (40.5-67.5)	58.0 (15.1-67.5)
Dose completed	94.0% (78)	95.5% (42)	92.3% (36)

Abbreviations: GyRBE, Gy × relative biologic effectiveness.
*n = 82.

The patterns of failure and death for HCC and ICC patients are shown in Table 4. For HCC patients, 56.8% either remained alive with no progression or died before experiencing progression; for ICC patients, the rate was 30.8%. Among HCC patients, 16 (36.4%) experienced hematogeneous progression, two (4.5%) experienced local failure with other progression, and one (2.3%) experienced nodal progression. For ICC patients, 21 (53.9%) experienced hematogeneous progression, one (2.6%) experienced local failure with other progression, and five (12.8%) experienced isolated local failure.

Univariate associations with OS were explored in the HCC and ICC study populations separately (Appendix Table A1, online only). Among HCC patients, the risk of death was not associated with Cancer of the Liver Italian Program (CLIP) score (2+ *v* 0 to 1), ECOG performance status (1 to 2 *v* 0), prior treatment (no *v* yes), dose delivered (< 60 *v* ≥ 60 Gy × relative biologic effectiveness), GTV (continuous), sum of longest tumor diameters (continuous), or tumor vascular thrombosis (presence *v* absence). Among ICC patients, OS did not differ by ECOG performance status, prior treatment, GTV, or sum of longest tumor diameters; but ICC patients with tumor vascular thrombosis had 3.6 times the risk of death compared with other ICC patients ($P = .014$; Appendix Table A1). OS was not compared by CLIP score or dose delivered among the ICC participants because too few deaths were observed in some strata.

DISCUSSION

High doses of radiation reliably ablate small tumors. Stereotactic body radiation therapy (SBRT) has been safe and effective, with 1-year LC rates above 90% for both HCC[4] and hepatic metastases.[20] For this reason, the use of high-dose, ablative radiation has increased in the treatment of hepatic tumors[3] and is currently under evaluation in HCC in a phase III trial (NCT01730937) by the Radiation Therapy Oncology Group.

Protons are an attractive radiation modality for larger liver tumors that are not amenable to ablative 5-fraction SBRT. First, the

Table 3. Radiation-Related Toxicities

Toxicity		Grade	
CTCAE Category	CTCAE Term	Any Grade % (No.)	Grade 3 % (No.)
Blood/bone marrow	Liver failure	1 (1)	1 (1)
	Platelets	1 (1)	1 (1)
	Other	5 (4)	
Cardiac general	Any	1 (1)	
Constitutional symptoms	Fatigue (asthenia, lethargy, malaise)	65 (54)	
Dermatology/skin	Hyperpigmentation	12 (10)	
	Rash	61 (51)	
	Other	4 (3)	
GI	Anorexia	25 (17)	
	Ascites (nonmalignant)	1 (1)	1 (1)
	Nausea	30 (25)	
	Ulcer, GI - stomach	1 (1)	1 (1)
	Vomiting	10 (8)	
	Other	20 (18)	
Hemorrhage/bleeding	Any	1 (1)	
Metabolic/laboratory	Bilirubin (hyperbilirubinemia)	1 (1)	1 (1)
	Other	10 (8)	
Musculoskeletal/soft tissue	Any	4 (3)	
Neurology	Any	2 (2)	
Pain	Pain-abdomen NOS	22 (19)	
	Other	13 (11)	
Pulmonary/upper respiratory	Any	5 (4)	

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events (version 3); NOS, not otherwise specified.

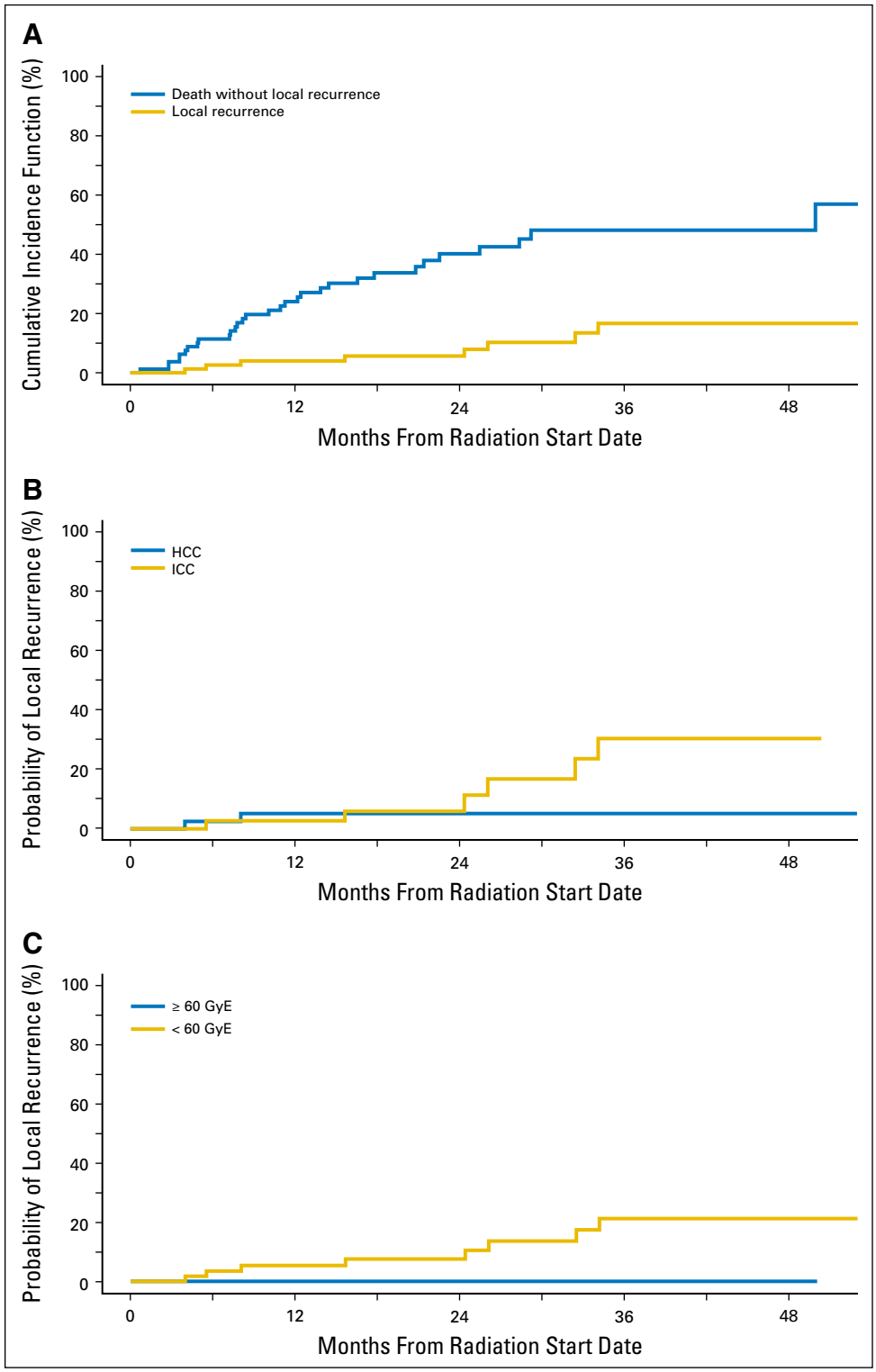

Fig 2. Cumulative incidence functions for local recurrence and death (A); cumulative incidence of local recurrence by disease type (B); and cumulative incidence of local recurrence by radiation dose (C). GyE, Gy equivalent; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma.

lack of exit dose theoretically can offer a higher dose of radiation with an individualized dosing strategy based on MLD, a strategy in which the prescription dose is de-escalated to a safe level for the liver. Second, in tumors in which maximum dosing can be achieved, the uninvolved liver may receive less radiation with protons, thereby potentially decreasing the risk of worsening liver function. In this prospective, multi-institutional study, we demonstrate that 15-fraction, high-dose proton therapy is associated with high rates of LC for both HCC and ICC. Importantly, despite the presence of underlying cirrhosis in most patients treated, we show that protons are well tolerated, with low rates of grade-3 toxicity or worsening hepatic function.

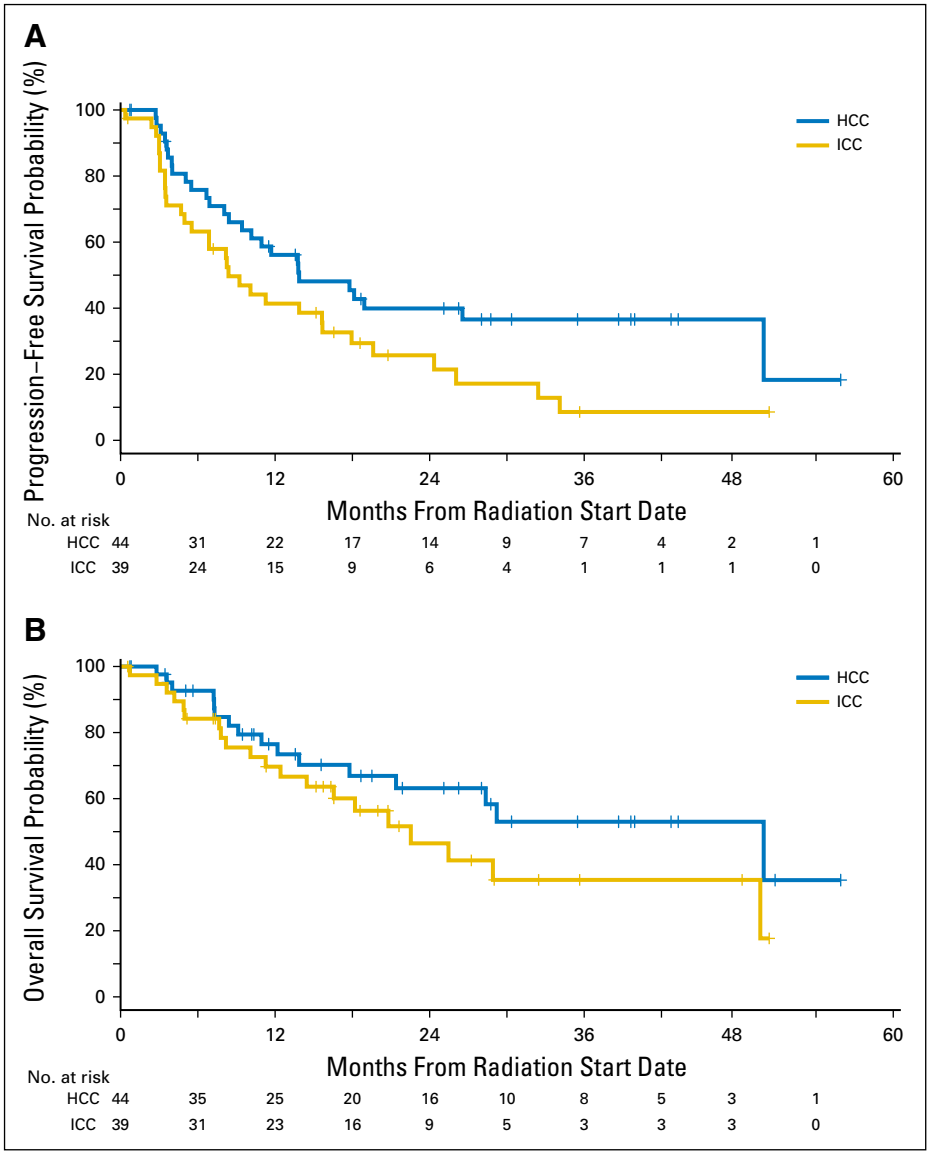

Fig 3. Progression-free survival (A) and overall survival (B) by disease type. HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma.

Protons have been used in HCC with encouraging outcomes. Unlike the SBRT studies, in which between 3 and 6 fractions were given, between 10 and 22 high-dose, hypofractionated treatments have generally been given in the proton studies.[10,11] The results of the current study, with high LC rates and low toxicity rates, are highly concordant with other published proton data in HCC.[10,11] The results of the current study, a LC-2 rate of 94.8% and 2-year OS rate of 63.2%, are similar to other retrospective photon-based SBRT studies.[12,14,15,18,21] However, these studies are imperfect comparisons because they primarily included smaller tumors (median tumor size of approximately 3 cm or smaller) that would be well treated with percutaneous ablation based on tumor size. Patients in this study, with a median tumor size of approximately 6 cm, represent a different population in which the technical challenge of treating patients to curative, rather than palliative, doses is greater because of the increased lesion size.

Table 4. Patterns of Failure

PFS Status	All Patients (N = 83) % (No.)	HCC (n = 44) % (No.)	ICC (n = 39) % (No.)
Alive, no progression	31.3 (26)	40.9[19]	20.5[8]
Distant metastases	45.8 (38)	38.6[18]	53.8[17]
Local failure and distant metastases	3.6[3]	4.5[2]	2.6[1]
Isolated local failure	6.0[5]	0.0 (0)	12.8[5]
Dead of disease, no progression	2.4[2]	0.0 (0)	5.1[2]
Dead of other causes, no progression	10.8[9]	15.9[7]	5.1[2]

Abbreviations: HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; PFS, progression-free survival.

The most robust, comparable, prospective evaluation is the Princess Margaret Hospital (PMH) prospective trial,[4] with SBRT for HCC that form the foundation for the ongoing Radiation Therapy Oncology Group study, which reported a LC-2 rate of < 80% (estimated) and a 2-year OS of 34%. The difference in the results between the current study and PMH report should be interpreted

with caution and cannot be specifically attributed to the modality of protons versus photons. First, PMH accrued patients with a larger median tumor size and volume, a greater percentage of patients with a CLIP score ≥ 2, and a greater percentage of patients with tumor vascular thrombus. Second, the current study, as well as the other proton studies, used a hypofractionated regimen of 15 fractions, rather than the 6-fraction schedule used in the PMH study. Recognizing the limitations of the linear-quadratic model to compare fractionation schedules, it is interesting to note that the highest allowed doses, 67.5 GyE/15 fractions in the current study and 54 Gy/6 fractions in the PMH study are similar in 2-GyE dose (82 Gy *v* 86 Gy, respectively) for tumor effect ($\alpha/\beta = 10$). However, the median doses in the current study (58 Gy/15 fractions) versus the PMH study (36 Gy/6 fractions) are quite different in 2 GyE (67 Gy *v* 48 Gy, respectively). Thus, part of the difference in LC may also be related to the fractionation schedule used.

Another contribution to the difference in OS between the current study and the PMH study may be the impact of protons versus photons on post-treatment hepatic function. Only 3.6% of patients in the overall cohort in the current study had any decrease in CTP class. This compares favorably with the 29% of patients with worsening CTP class at 3 months reported in the PMH study. Worsening CTP class has been associated with a significant decrease in survival.[19] The individualized dosing strategy based on MLD is designed to maintain a low risk of classic RILD, a veno-occlusive syndrome, rather than to preserve long-term hepatic function. However, it remains unknown whether higher MLD that is below a threshold RILD risk is associated with a risk of worsening in CTP class. Again, using the linear-quadratic model to account for fractionation differences, the average MLD (in 2-GyE, $\alpha/\beta = 3$) for HCC patients in this study was lower than in the PMH study (15 Gy *v* 18 Gy). Previous efforts to characterize dose-volume parameters predicting worsening CTP class, as opposed to RILD, remain limited.[22] Because of the numerous potential reasons for differences in outcomes between our study and the PMH study, we are initiating a randomized trial of photons versus protons in patients with unresectable HCC, and patients will be stratified by the use of a 15-fraction versus 5-fraction schedule.

The LC and survival for ICC patients is also encouraging in this study. Unlike HCC, there are limited data regarding the use of radiation therapy for ICC. Retrospective data evaluating conventionally fractionated radiation suggest a median survival of approximately 10 months,[5,6] with a 2-year OS of approximately 10%. Similarly, ICC patients were included in the SBRT study, but the small number of patients with ICC, as opposed to HCC or extrahepatic cholangiocarcinoma, render it impossible to determine efficacy.[13,16,17,23] The median OS of 22.5 months in this study compares favorably with the gemcitabine/cisplatin arm of the Advanced Biliary Cancer-02 trial, which reported a median OS of 11.7 months.[2] Additionally, in contrast to the current study, neither arm had any survivors beyond 32 months in the Advanced Biliary Cancer-02 trial. However, this observation must also be interpreted with caution, because only 27% of patients in the gemcitabine/cisplatin arm had locally advanced disease, and it is unclear what percentage of those patients would have met eligibility for this study. Despite the encouraging signal seen with radiation, it is unclear whether radiation will improve survival in this population of localized, unresectable ICC. For this reason, NRG GI-001 (NCT02200042) has been initiated, in which patients with localized unresectable ICC will receive gemcitabine/cisplatin chemotherapy and will be randomly assigned to additionally receive this 15-fraction radiation schedule (with photons or protons) versus continuing chemotherapy alone.

In conclusion, high-dose, hypofractionated proton beam therapy is safe and associated with high rates of LC and survival for both HCC and ICC. These data provide the strong rationale for a randomized comparison of protons versus photons for HCC and chemotherapy with or without radiation therapy for ICC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Multi-Institutional Phase II Study of High-Dose Hypofractionated Proton Beam Therapy in Patients With Localized, Unresectable Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma

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Appendix

Table A1. Univariate Predictors of Overall Survival by Disease Type

		Disease Type							
		HCC				ICC			
Predictor	Level	No.	HR	95% CI	*P*	No.	HR	95% CI	*P*
Any prior treatment	No *v* yes	44	1.284	0.408 to 4.043	.669	39	1.213	0.473 to 3.106	.688
Clip score	≥ 2 *v* 0-1	44	1.791	0.633 to 5.068	.272				
Dose received	< 60 *v* ≥ 60 GyE	44	2.053	0.659 to 6.390	.215				
ECOG performance status	1-2 *v* 0	44	0.810	0.279 to 2.351	.699	39	1.388	0.526 to 3.664	.508
GTV volume, mL		43	1.001	0.999 to 1.002	.283	39	1.000	0.997 to 1.003	.944
Sum of longest tumor diameters, cm		44	1.126	0.945 to 1.341	.183	39	1.165	0.947 to 1.433	.148
Tumor vascular thrombosis	Yes *v* No	44	2.160	0.753 to 6.198	.152	39	3.615	1.303 to 10.025	.014

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GTV, gross tumor volume; GyE, Gy equivalent; HCC, hepatocellular carcinoma; HR, hazard ratio; ICC, intrahepatic cholangiocarcinoma.