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Sequential Phase I and II Trials of Stereotactic Body Radiotherapy for Locally Advanced Hepatocellular Carcinoma

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ABSTRACT

Purpose
To describe outcomes of prospective trials of stereotactic body radiotherapy (SBRT) for hepatocellular carcinoma (HCC).

Patients and Methods
Two trials of SBRT for patients with active HCC unsuitable for standard locoregional therapies were conducted from 2004 to 2010. All patients had Child-Turcotte-Pugh class A disease, with at least 700 mL of non-HCC liver. The SBRT dose range was 24 to 54 Gy in six fractions. Primary end points were toxicity and local control at 1 year (LC1y), defined as no progressive disease (PD) of irradiated HCC by RECIST (Response Evaluation Criteria in Solid Tumors).

Results
A total of 102 patients were evaluable (Trial 1, 2004 to 2007: n = 50; Trial 2, 2007 to 2010: n = 52). Underlying liver disease was hepatitis B in 38% of patients, hepatitis C in 38%, alcohol related in 25%, other in 14%, and none in 7%. Fifty-two percent received prior therapies (no prior sorafenib). TNM stage was III in 66%, and 61% had multiple lesions. Median gross tumor volume was 117.0 mL (range, 1.3 to 1,913.4 mL). Tumor vascular thrombosis (TVT) was present in 55%, and extrahepatic disease was present in 12%. LC1y was 87% (95% CI, 78% to 93%). SBRT dose (hazard ratio [HR] = 0.96; $P = .02$) and being in Trial 2 (HR = 0.38; $P = .03$) were associated with LC1y on univariate analysis. Toxicity ≥ grade 3 was seen in 30% of patients. In seven patients (two with TVT PD), death was possibly related to treatment (1.1 to 7.7 months after SBRT). Median overall survival was 17.0 months (95% CI, 10.4 to 21.3 months), for which only TVT (HR = 2.47; $P = .01$) and being in Trial 2 (HR = 0.49; $P = .01$) were significant on multivariate analysis.

Conclusion
These results provide strong rationale for studying SBRT for HCC in a randomized trial.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the third ranked cause of global cancer mortality.[1] It is one of the most rapidly increasing cancers in terms of incidence and mortality, globally and in North America.[2,3] Fewer than 30% of patients are eligible for currently available curative treatments, namely liver transplant, surgery, and radiofrequency ablation (RFA), as a result of disease stage, poor liver function, or limited resources.[4] Therefore, a significant proportion of patients are incurable, with a 1-year survival rate ranging from 20% to 30%.[5-7] Transarterial chemoembolization (TACE) increases survival primarily in patients without major vascular thrombosis.[8,9] In patients unsuitable for TACE, sorafenib (Nexavar, Bayer Pharma AG, Berlin, Germany) can increase 1-year survival, from 30% with best supportive care to 45%.[5,6] Unfortunately, progression of the treated lesions or elsewhere in the liver is almost invariable for patients treated with TACE or sorafenib.

Over the past two decades, due to advances in computer and imaging technologies, conformal liver irradiation has become a feasible and safe technique for focal HCC, with radiation-induced liver disease (RILD) rates of ≤ 5% in experienced hands.[10] Stereotactic body radiotherapy (SBRT), or stereotactic ablative radiotherapy,[11] refers to the use of a few fractions, generally fewer than 10, of

potent doses of highly conformal radiation therapy with high geometric precision and accuracy. Retrospective studies and two prospective studies have suggested that SBRT can be used safely with local control rates of 75% to 100% at 1 to 2 years, but the number of patients accrued to prospective trials is relatively low.[12-22]

As opposed to most SBRT series focusing on small tumors, an individualized six-fraction SBRT dose-allocation strategy allows large multifocal tumors and HCC with major vascular thrombosis to be treated. This individualized approach was shown to be feasible in 31 HCC patients treated in a phase I study at our institution.[23] Subsequently, the efficacy and toxicity of SBRT were further tested in an expanded phase I/II study (Trial 1) and an immediately subsequent phase II trial (Trial 2), with local control as the primary end point. Patients from both trials were pooled for the present analysis.

PATIENTS AND METHODS

Patients

For both trials, the protocol and patient consent forms were approved by the institutional research ethics board. Patients unsuitable for surgery, TACE, RFA, or alcohol ablation were eligible after discussion in a multidisciplinary tumor board. Diagnosis of HCC was established either with biopsy, characteristic enhancement on two imaging modalities, or characteristic enhancement on one modality with α-fetoprotein elevation more than 200 nmol/L in the context of cirrhosis or hepatitis B. Patients had to be older than 18 years, with a life expectancy more than 12 weeks, at least 700 mL ($\geq$ 800 mL in Trial 1) of uninvolved liver, and Eastern Cooperative Oncology Group performance score $\leq$ 2. Child-Turcotte-Pugh (CTP) A liver scores were required; bilirubin had to be less than 4$\times$ ($<$ 3$\times$ in Trial 1) the upper limit of normal, AST or ALT less than 6$\times$ the upper limit of normal, international normalized ratio less than 1.5 ($<$ 1.3 in Trial 1) except if patients were on oral anticoagulation, hemoglobin $\geq$ 90 g/L, platelets $\geq 50 \times 10^9$/L ($\geq 80 \times 10^9$/L in Trial 1), and neutrophils $\geq 1.0 \times 10^9$/L (no limit in Trial 1), with no clinical ascites, encephalopathy, active hepatitis, or gastric, duodenal, or variceal bleed within 2 months of registration. Prior therapies, other than prior irradiation making SBRT unsafe, were permitted. Tumor vascular thrombosis (TVT) was allowed. In Trial 2, in addition to TVT, no more than five discrete liver tumors were allowed, with a maximal dimension of 15 cm; there were no tumor number or size limits in Trial 1. Extrahepatic disease was permitted in both trials if the greatest burden of disease was hepatic.

Treatment

Logistics of treatment planning and treatment delivery have been described previously.[23-26] In brief, patients were immobilized with a customized vacuum cushion or Med-Tec (Siemens AG, Munich, Germany) board and most often had abdominal compression (51%) or active breathing control (49%) to reduce amplitude of liver motion caused by breathing. Imaging for radiation planning was performed on exhale breathhold multiphasic computed tomography (CT) with or without magnetic resonance imaging (MRI) scans.

Gross tumor volume (GTV) was defined as the arterial enhancing lesions with washout on the venous and/or delayed phase CT and/or MRI. The primary clinical target volume (CTV1) was coincident with the GTV. Optional secondary microscopic clinical target volumes (CTV2) included a 5-mm expansion (8 mm in Trial 1) around the GTV within the liver parenchyma, RFA cavities, or post-TACE volumes adjacent to the GTV. Contrast-enhancing TVT was included as CTV1, and nonenhancing thrombosis was generally included in CTV2. Patient-specific planning target volume (PTV) margins of $\geq$ 5 mm were tailored from the patient's breathing motion and motion management strategy (abdominal compression or breath hold) and were added to CTV1 and CTV2 (PTV1 and PTV2, respectively). Conformal planning was used, with five to 10 coplanar or noncoplanar beams of 6 to 18 MV. Multiple segments per beam angle were permitted, as was automated optimization to develop intensity-modulated plans.

Doses of 30 to 54 Gy (24 to 54 Gy in Trial 1) in six fractions every other day over 2 weeks were delivered to the PTV1. The dose to TVT plus PTV margin could be limited to 30 Gy if required to respect surrounding tissues tolerance. The phase I dose-escalation strategy was previously described.[23] Dose to PTV1 was determined according to an RILD normal tissue complication probability model based on the effective irradiated liver volume (V_{eff}) (Appendix Table A1, online only), with a maximum allowed V_{eff} of 60% (80% in Trial 1). When possible, a dose of 27 Gy (24 Gy in Trial 1) was delivered to PTV2, but coverage of PTV2 was not mandatory. Strict dose constraints were maintained for the surrounding organs at risk (Appendix Table A2, online only).

At each treatment fraction, image-guided radiation therapy was used to position the patient. Cone-beam CT imaging and/or orthogonal fluoroscopy were preferred image-guided radiation therapy technologies.

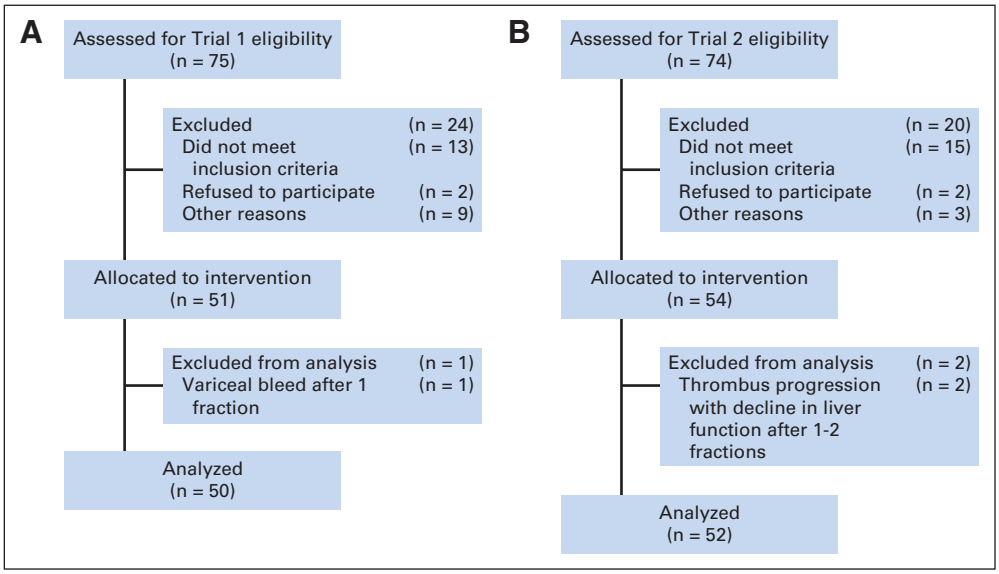

Fig 1. CONSORT diagrams. (A) Trial 1. (B) Trial 2.

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Table 1. Patient and Treatment Characteristics

Variable	Total (102 patients)		Trial 1 (50 patients)		Trial 2 (52 patients)	
	No.	%	No.	%	No.	%
Age, years						
Median	69.4		69.0		71.3	
Range	40.4-90.3		41.6-85.6		40.4-90.3	
Male sex	80	78.4	39	78.0	41	78.8
Ethnicity						
White	54	52.9	26	52.0	28	53.9
Asian	45	44.1	23	46.0	22	42.3
Other	3	2.9	1	2.0	2	3.9
Underlying liver disease*						
Hepatitis B	39	38.2	22	44.0	17	32.7
Hepatitis C	39	38.2	15	30.0	24	46.2
Alcohol related	25	24.5	11	22.0	14	26.9
Other	14	13.7	7	14.0	7	13.5
None	7	6.9	3	6.0	4	7.7
CTP score						
5	73	71.6	37	74.0	36	69.2
6	29	28.4	13	26.0	16	30.8
Baseline median laboratory values						
Bilirubin, μmol/L						
Median	13		14		12	
Range	6-43		7-43		6-40	
Albumin, g/L						
Median	40		40		39	
Range	31-47		32-45		31-47	
INR						
Median	1.08		1.08		1.08	
Range	0.87-1.44		0.93-1.35		0.87-1.44	
AST, U/L						
Median	54		50		56	
Range	17-217		18-217		17-142	
ALT, U/L						
Median	40		38		41	
Range	11-237		14-233		11-237	
Creatinine, μmol/L						
Median	77		89		74	
Range	40-356		40-352		51-356	
Platelets, $\times 10^9$/L						
Median	141		149		133	
Range	55-834		72-834		55-341	
ECOG performance status						
0/1	85	83.3	35	70.0	50	96.2
2	11	10.8	9	18.0	2	3.8
NA	6	5.9	6	12.0	0	0.0
Previous treatments*						
All	53	52.0	27	54.0	26	50.0
Surgery	9	8.8	6	12.0	3	5.8
TACE	22	21.6	9	18.0	13	25.0
RFA	35	34.3	15	30.0	20	38.5
PEI	16	15.7	11	22.0	5	9.6
Other	9	8.8	6	12.0	3	5.8
BCLC stage						
A/B	35	34.3	19	38.0	16	30.8
C	67	65.7	31	62.0	36	69.2
CLIP score						
0-1	50	49.0	20	40.0	30	57.7
2-4	52	51.0	30	60.0	22	42.3

(continued on following page)

Table 1. Patient and Treatment Characteristics (continued)

Variable	Total (102 patients)		Trial 1 (50 patients)		Trial 2 (52 patients)	
	No.	%	No.	%	No.	%
TNM stage†						
I	13	12.8	4	8.0	9	17.3
II	14	13.7	7	14.0	7	13.5
III	67	65.7	35	70.0	32	61.5
IV	8	7.8	4	8.0	4	7.7
Tumor vascular thrombosis	56	54.9	27	54.0	29	55.8
Extrahepatic disease	12	11.8	5	10.0	7	13.5
Baseline AFP, nmol/L						
Median	163		502		113	
Range	< 6-714,500		< 6-714,500		< 6-159,572	
Multiple lesions at baseline	62	60.8	36	72.0	26	50.0
Sum of largest diameters of liver lesions, cm						
Median	9.9		10.5		9.4	
Range	1.8-43.3		1.8-43.3		2.0-18.6	
Size of largest lesion, cm						
Median	7.2		7.2		7.3	
Range	1.4-23.1		1.8-23.1		1.4-17.8	
GTV volume, mL						
Median	117.0		123.1		108.3	
Range	1.3-1,913.4		6.5-1,913.4		1.3-1,385.1	
PTV1 volume, mL						
Median	283.5		297.6		265.6	
Range	10.9-2,467.3		25.6-2,467.3		10.9-1,929.1	
Liver volume, mL‡						
Median	1257.6		1301.4		1204.3	
Range	766.5-3,966.8		856.4-3,966.8		766.5-2,402.6	
Prescription dose, Gy§						
Median	36.0		36.6		33.0	
Range	24.0-54.0		24.0-54.0		27.5-54.0	
Minimum PTV dose, Gy‖						
Median	30.0		23.3		31.9	
Range	1.6-53.8		1.6-47.3		5.2-53.8	
V_{eff}, %¶						
Median	44		47		39	
Range	9-80		16-80		9-73	
Liver mean dose, Gy‡						
Median	15.9		17.1		15.2	
Range	4.3-21.4		7.8-21.4		4.3-18.2	

Abbreviations: AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer staging system[29]; CLIP, Cancer of the Liver Italian Program staging system (0-6 points: 0-2 points given to CTP class A-C and to increasing liver HCC burden, 0-1 point given to AFP and portal vein thrombosis status; a score of ≥ 2 corresponds to an expected median survival of < 19.5 months); CTP, Child-Turcotte-Pugh liver function scale; ECOG, Eastern Cooperative Oncology Group; GTV, gross tumor volume; HCC, hepatocellular carcinoma; INR, international normalized ratio; PEI, percutaneous ethanol injection; PTV1, planning target volume 1; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; V_{eff}, effective irradiated liver volume.

*More than one may apply.

†At time of study registration, as it was not readily available at time of diagnosis.

‡Liver volume minus GTV.

§Prescription dose: when multiple lesions were treated, some may have received a lower dose to meet planning objectives.

‖PTV minus 0.5 mL. On review of the treatment plans at time of analysis, inconsistencies were met, which led to sometimes wide discrepancies between what dose was initially planned and what dose was actually delivered. This resulted in part from imaging quality and from tumor delineation uncertainties and also from changing prescription patterns with time. The standardized dose to PTV is presented here. Detailed dose information is unavailable for the first three patients (data lost after computer system change).

¶V_{eff} methodology to take into account a heterogeneous dose distribution in a structure. See Appendix Table A1 (online only) for scale description.

Evaluation

Patients were assessed weekly during SBRT and, after completion of treatment, at 1 month, every 3 months for the first 12 months, every 6 months to 36 months, and yearly afterwards up to 5 years or until death, regardless of presence of progressive disease. Blood work and liver triphasic CT or MRI were performed at each follow-up. Chest CT was performed at 12 months or more frequently if clinically indicated. Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Dose-limiting toxicity (DLT) was any CTCAE grade 4 or 5 hepatic, thrombocytopenic, or GI toxicity occurring within 1 month of SBRT or RILD requiring treatment in the absence of disease progression within 3 months of SBRT. Tumor response was assessed using RECIST version 1.1.[27] As a result of lack of standardization in the evaluation of TVT response to therapy, TVT response was not included in the response criteria.

Statistics

The primary end points for Trial 1 and Trial 2 were, respectively, toxicity assessment and local control at 1 year; the latter was defined as the absence of

progressive disease within the PTV. Secondary end points were time to liver progression, time to progression, overall survival (all from the date of first SBRT treatment), and quality of life; the latter is the focus of a separate publication. In Trial 1, 50 patients were required to be registered to detect a 15% ± 11% rate of DLT with 90% confidence. In Trial 2, a sample of 30 patients reaching the 1-year follow-up was calculated to detect a local control rate of 60% with SBRT versus 20% without radiotherapy from historical data, with 95% confidence and 90% power. To increase the confidence in toxicity and efficacy estimates after six-fraction SBRT for locally advanced HCC, patients from Trial 1 and 2 were pooled. Wilcoxon rank sum tests were calculated for continuous variables comparisons. Local control at 1 year was estimated using the cumulative incidence function in the presence of death as a competing risk, and multivariate analysis was performed using the Fine and Gray regression model.[28] Time to progression and survival were evaluated with the Kaplan-Meier method and multivariate analysis with the Cox proportional hazards model. SAS version 9.2 TS (SAS Institute, Cary, NC) was used for all analyses, except the competing risks analysis, which was performed using the R package cmprsk in version 2.12.1. Statistical significance was set to $P \leq .05$.

RESULTS

Patients and Treatment

Between February 2004 and April 2010, a total of 149 patients consented (75 in Trial 1, 2004 to 2007, and 74 in Trial 2, 2007 to 2010; see Fig 1 for CONSORT diagram). Forty-four were found ineligible before treatment as a result of disease progression and/or inability to meet planning objectives due to disease burden (n = 24), liver function deterioration (n = 12), consent withdrawal (n = 4), liver transplant eligibility (n = 2), or non-HCC diagnosis (n = 2). In addition, three patients were taken off study after one to two fractions because of progressive TVT causing liver function deterioration (n = 2) and variceal bleed (n = 1). A total of 102 patients were evaluable (50 in Trial 1 and 52 in Trial 2).

Baseline patient characteristics can be found in Table 1. In the whole cohort, 52 patients (51%) had a Cancer of the Liver Italian Program (CLIP)[30] score ≥ 2, 56 (55%) had TVT, and 53 (52%) had experienced disease progression after previous therapies (no sorafenib).

Treatment was completed in 99 (97%) of the 102 patients. Three patients received five of their planned six fractions, secondary to reversible grade 3 liver enzyme elevation (n = 2) and to development of sepsis related to a diabetic foot (n = 1). The median prescription dose was 36 Gy in six fractions. Treatment parameters are shown in Table 1.

Toxicity

Other than the two patients who stopped after five fractions, no significant (≥ grade 3) liver enzyme elevation was observed during

Table 2. Toxicity, CTCAE ≥ Grade 3

Toxicity	Grade 3		Grade 4		Grade 5	
	No.	%	No.	%	No.	%
All	27	26.5	3	2.9	7*	6.9
Fatigue	1	1.0	0	0.0	—	
Biochemical†						
Albumin	0	0.0	0	0.0	0	0.0
AST/ALT	11	10.9	0	0.0	—	
Bilirubin	3	3.0	2	2.0	—	
Creatinine	1	1.0	0	0.0	0	0.0
INR	0	0.0	—		—	
Hematologic†						
Hemoglobin	2	2.0	0	0.0	0	0.0
Leukocytes	1	1.0	0	0.0	0	0.0
Platelets	9	9.0	0	0.0	0	0.0
GI						
Cholangitis	0	0.0	0	0.0	1	1.0
Gastritis/GI bleed	1	1.0	0	0.0	1	1.0
Liver failure	1	1.0	1	1.0	5*	4.9
Nausea/vomiting	1	1.0	0	0.0	0	0.0
Pain (RUQ/chest wall)	1	1.0	0	0.0	—	
Proportion of patients with CTP deterioration, without progressive disease, %						
3 months						
Score			46			
Class			29			
12 months						
Score			17			
Class			6			

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; CTP, Child-Turcotte-Pugh liver function scale; INR, international normalized ratio; RUQ, Right upper quadrant.

*Includes two patients with tumor vascular thrombosis progressive disease probably contributory to liver function deterioration.

†Within first 3 months of treatment; not present at or worsening from baseline.

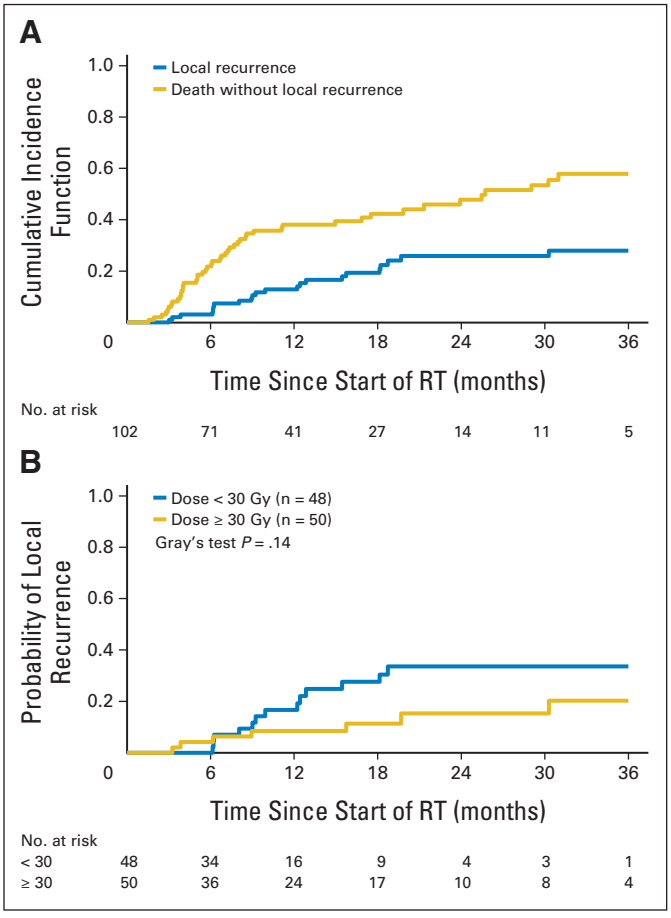

Fig 2. Local recurrence (LR) from time of radiotherapy (RT) start, defined as progression of irradiated disease using RECIST criteria, with death as a competing risk. (A) Overall (1-year LR, 13%; 2-year LR, 26%). (B) By minimum dose to planning target volume minus 0.5 mL, less than 30 Gy versus ≥ 30 Gy (1-year LR, 17% *v* 9%; 2-year LR, 34% *v* 15%).

treatment. No classic RILD was observed. DLT was not reached in Trial 1. In patients without progressive disease, a decline in CTP class was seen in 29% at 3 months and in 6% at 12 months. Table 2 gives a description of the grade 3 or greater toxicity encountered. In seven patients, death was at least possibly related to treatment (1.1 to 7.7 months after SBRT), after exclusion of parenchymal HCC progressive disease per RECIST. Liver failure was involved in five patients, although in two patients, massive TVT progression probably contributed. In another patient, the HCC invaded the common bile duct, which may have contributed to a cholangitis that developed 4 weeks after SBRT. The last patient experienced a fatal duodenal bleed 7.7 months after SBRT and 2 months after reirradiation for a retroperitoneal nodal relapse; the cumulative dose to the duodenum (23 Gy in 16 fractions) was below the 33 Gy in six-fraction limit set in the protocol. There was a significantly higher median liver mean dose in patients who developed grade 5 toxicity compared with those who did not (18.1 Gy *v* 15.4 Gy; $P = .02$).

Response

Local control at 1 year was 87% (95% CI, 78% to 93%; Fig 2). Best response was as follows: complete response in 11 patients (11%), partial response in 44 patients (43%), and stable disease in 45 patients (44%). Factors associated with improved local control are shown in Table 3; none were significant on multivariate analysis. The median time to local recurrence was not reached. α-Fetoprotein response was also observed in the majority of patients early after treatment (Appendix Fig A1, online only).

Overall Survival and Time to Progression

At the time of analysis, 67 patients had died. Median follow-up using the censoring distribution was 31.4 months (95% CI, 24.3 to 36.4 months). Median overall survival was 17.0 months (95% CI, 10.4 to 21.3 months; Fig 3). Significant factors associated with improved overall survival on multivariate analysis were absence of TVT and being on Trial 2 (Table 3). Median time to progression was 6.0 months (95% CI, 3.4 to 6.4 months). Seventy-two patients experienced disease progression in the liver (including local progressions), and 33 developed extrahepatic progression at any time during follow-up.

Although no patients had received sorafenib before SBRT, 18 (17.6%) received it at the time of progression (13 in Trial 2 and five in Trial 1).

DISCUSSION

This large, prospective series of 102 patients with locally advanced HCC confirms that a patient-specific six-fraction regimen of SBRT is feasible, with outcomes better than those of historical controls.[23] However, despite limiting this study to a Child-Turcotte-Pugh A population, SBRT was at least possibly related to death in a minority of patients (two with apparent massive TVT progression). In addition, CTP class deterioration occurred in 29% at 3 months, although this rate was lower by 12 months. The reasons for the late recovery of Child-Turcotte-Pugh are not yet clear. Continued antitumor effect, especially against TVT that may recanalize more than 3 months after radiation,[31] hepatocyte repopulation, or attrition of deceased patients may all have contributed. Liver compensatory hypertrophy has been observed in the months after partial liver irradiation.[32]

This study demonstrated that SBRT has substantial activity against HCC, with a local control rate of 87% at 1 year. Further indication of a treatment effect is the observed dose-response on the univariate analysis. During this study, planning and image guidance technologies evolved, and there was a trend toward less advanced HCC being treated more recently. This could have led to the observed higher tumor doses and reduced liver doses in Trial 2 versus Trial 1. In the present series, radiation dose tended to be inversely proportional to tumor volume because of the dose allocation strategy used, but proximity to radiosensitive GI visceral structures also limited dose in many patients and may explain why tumor volume alone was not significantly associated with local control. In comparison with other

Table 3. Univariate and Multivariate Analysis for Local Control and Overall Survival

	Local Control						Overall Survival					
	UVA			MVA*			UVA			MVA*		
Variable	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
CLIP ≥ 2	1.77	0.79 to 3.95	.17	—		—	1.28	0.79 to 2.08	.32	0.58	0.30 to 1.11	.10
TNM†	0.83	0.64 to 1.09	.18	—		—	1.16	0.97 to 1.39	.11	1.03	0.82 to 1.30	.78
Tumor vascular thrombosis	0.61	0.27 to 1.36	.23	—		—	1.71	1.04 to 2.82	.04	2.47	1.25 to 4.88	.01
ECOG 0-1 *v* 2	2.51	0.34 to 18.70	.37	—		—	0.58	0.27 to 1.22	.15	—		—
Extrahepatic disease	0.27	0.04 to 1.74	.17	—		—	1.36	0.67 to 2.76	.39	—		—
Trial 2 *v* 1	0.38	0.16 to 0.89	.03	0.55	0.18 to 1.63	.28	0.51	0.31 to 0.84	.01	0.49	0.28 to 0.85	.01
Multiple lesions at baseline	1.01	0.46 to 2.22	.97	—		—	1.18	0.72 to 1.95	.51	—		—
Sum of largest diameters of liver lesions	1.06	0.97 to 1.16	.18	—		—	1.04	1.00 to 1.08	.07	—		—
GTV volume	0.96	0.85 to 1.08	.51	—		—	1.06	1.00 to 1.12	.05	1.06	0.99 to 1.13	.09
Minimum dose to PTV1‡	0.96	0.92 to 0.99	.02	0.97	0.92 to 1.01	.16	0.98	0.96 to 1.01	.16	1.00	0.98 to 1.03	.97

Abbreviations: CLIP, Cancer of the Liver Italian Program staging system (0-6 points: 0-2 points given to Child-Turcotte-Pugh class A-C and to increasing liver hepatocellular carcinoma burden, 0-1 point given to α-fetoprotein and portal vein thrombosis status; a score of ≥ 2 corresponds to an expected median survival of < 19.5 months); ECOG, Eastern Cooperative Oncology Group performance status; GTV, gross tumor volume, by 100-mL increments; HR, hazard ratio; MVA, multivariate analysis; PTV1, planning target volume 1 minus 0.5 mL; UVA, univariate analysis.

*Because of the No. of events, only 2 factors could be included in MVA for local control (using death as a competing risk) and 7 factors for overall survival. For overall survival MVA, study and thrombosis remained the only significant factors for two alternative MVA models.

†At time of study registration, as it was not readily available at time of diagnosis.

‡Dose considered as a continuous variable. The HR represents the effect of an increase of 1 Gy.

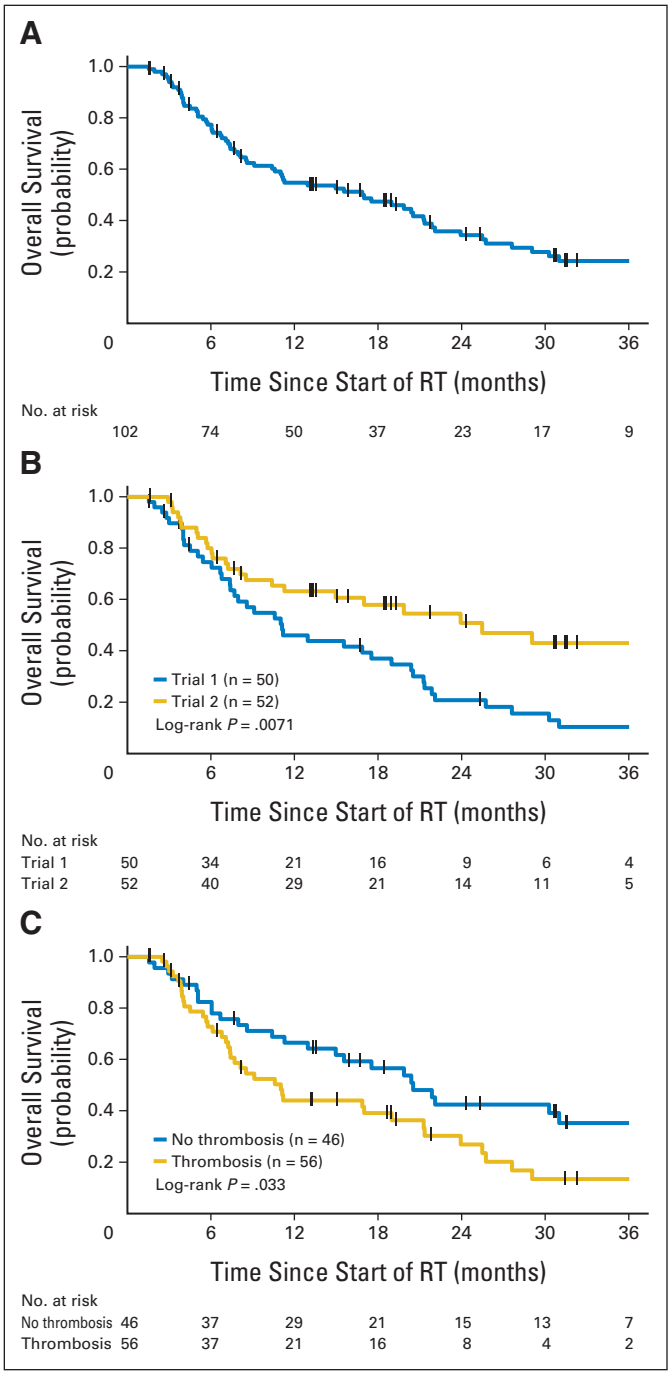

Fig 3. Overall survival (OS) from time of radiotherapy (RT) start. (A) Overall (1-year OS, 55%; 2-year OS, 34%; median OS, 17 months). (B) By Trial 2 versus 1 (1-year OS, 63% *v* 46%; 2-year OS, 51% *v* 21%). (C) By tumor vascular thrombosis presence at baseline (1-year OS, 44% *v* 67%; 2-year OS, 27% *v* 42%).

SBRT series that rarely included lesions larger than 7 cm, the median size of the largest lesion in the present series was 7.2 cm, with tumor volumes ranging from 1.3 to 1,913 mL.

Other prospective trials have reported excellent local control rates after SBRT alone for HCC. Mendez-Romero et al[12] first described the results of delivering 25 to 37.5 Gy in three to five fractions in eight patients with HCC not amenable to other curative modalities. Maximal lesion diameter was 7.2 cm, and 25% had TVT. Two patients experienced local progression in the 25 Gy in five fractions arm, and this dose level was abandoned. All the others had local control, and the 1-year survival rate was 75%. One patient with CTP class B experienced fatal RILD. A trial by Cardenes et al[13] reported on 17 patients with HCC, mostly with CTP class B disease; 18% had TVT, and the maximal lesion size was 6 cm. The dose was 36 to 48 Gy in three fractions, although for patients with CTP class B disease, the dose was reduced to 40 Gy in five fractions after three patients experienced grade 3 to 4 RILD. Local control and survival rates at 1 year were, respectively, 100% and 75%. A later report including 60 patients treated on and off protocol achieved 2-year local control and survival rates of 90% and 67%, respectively; 23 patients had undergone transplantation.[33] Twenty percent of patients had CTP class deterioration by 3 months. Other retrospective series report similar outcomes with doses ranging from 24 to 60 Gy in one to eight fractions.[10]

Despite high local control rates after SBRT, failures in the liver outside the PTV remain a problem, similar to other local therapies, providing rationale for combining regional or systemic treatments with SBRT. Concurrent chemotherapy has been used with conventionally fractionated (1.5 to 3 Gy per fraction) radiotherapy.[34] Another strategy is to combine radiation therapy with TACE.[35,36] A phase I study of SBRT with concurrent sorafenib was conducted.[37] Although it suggested that the combination was feasible using reduced-dose sorafenib, concurrent use is not recommended outside of clinical trials because of the potential for normal tissue sensitization and increased toxicity, especially in patients with a large tumor burden. In a retrospective analysis of 23 patients, a prolongation of the time to progression from 4 months to 10 months was demonstrated when sunitinib (Sutent; Pfizer, New York, NY) maintenance was added to concurrent sunitinib and hypofractionated radiotherapy.[38]

This study's 1-year survival rate of 55% and median survival of 17 months compare favorably with best supportive care and even with sorafenib (18% to 33%/4.2 to 7.9 months and 29% to 44%/6.5 to 10.7 months, respectively[5,6]), the only other potentially available therapy for this patient population. TVT is a clearly established prognostic factor in the literature and in the present series. Compared with other series of SBRT, a larger proportion of patients (55%) had gross vascular invasion in the present cohort, and the overall survival is expectedly lower. The treatment of HCC invading major vessels is a challenge, as it is a contraindication for most other liver-directed therapies. We and others have observed TVT responses after SBRT.[39] That baseline extrahepatic disease does not predict for survival in our trial can probably be explained by the selection of patients whose largest burden of disease was within the liver, often with TVT, rarely with distant metastases.

In addition to the expected prognostic factor of TVT, being in the most recent cohort (Trial 2 *v* Trial 1) was associated with significantly improved survival. This is most likely because of improved patient selection and is possibly related to improvements in diagnostic imaging, target identification, radiation planning, and delivery. Trial 2 included a larger proportion of unifocal HCC of a smaller diameter and patients with better performance status who were possibly more likely to have had access to sorafenib at the time of progression.

In conclusion, in a population of patients for whom curative local treatment options are not available, SBRT can lead to sustained local control, associated with survival rates higher than historical controls, with a low risk of serious toxicity. Disease progression outside the

targeted HCC remains a problem, providing rationale for combining SBRT with regional or systemic therapies. A phase III randomized trial of sorafenib versus SBRT followed by sorafenib for locally advanced HCC is planned (RTOG1112).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. V_{eff} Dose Allocation Strategy for Trial 2

Liver V_{eff} (%)	Dose per Fraction (Gy)
≤ 25	9.0
> 25-30	7.5
> 30-40	6.5
> 40-50	5.5
> 50-60	5.0
> 60	Not suitable for study

NOTE. This table describes the prescribed dose (in 6 fractions), based on the V_{eff} irradiated (liver minus GTV). The V_{eff} determination was previously described[26] using the equation: $V_{eff} = \sum_i \Delta v_i \left(\frac{d_i}{d_{ref}}\right)$ where Δv_i is a volume bin of a differential liver DVH, d_i is the dose to that volume, and d_{ref} is the reference dose, here defined at the isodose line covering the planning target volume around the GTV. Once the dose is determined from these tables, biologic NTCP should be confirmed to be no higher than 10%. The NTCP was based on estimates of RILD toxicity risk calculated using the LKB model (McGinn CJ, et al: J Clin Oncol 16:2246-2252, 1998) that was used to describe the risk of RILD in patients treated with 1.5 Gy twice daily in a previous study from the University of Michigan (Dawson LA, et al: J Clin Oncol 18:2210-2218, 2000). Corrections for differences in dose per fraction were made to the liver DVH, using the linear quadratic formula assuming α/β of 2.5 Gy. The LKB NTCP for RILD toxicity was then calculated using the Michigan parameters (Dawson LA, et al: Int J Radiat Oncol Biol Phys 53:810-821, 2002). If necessary, dose per fraction may be reduced until biologic NTCP is < 10%.

Abbreviations: DVH, dose volume histogram; GTV, gross tumor volume; LKB, Lyman-Kutcher-Burman; NTCP, normal tissue complication probability; RILD, radiation-induced liver disease; $V_{eff,}$ effective liver volume.

*See Tse et al[23] for Trial 1.

Table A2. Trial 2 Normal Tissue Dose Constraints in Six Fractions

Organ	Dose (Gy)
Kidney	Mean < 12
Spinal cord	Maximum < 27
Stomach*	Maximum < 32
Duodenum*	Maximum < 33
Small bowel*	Maximum < 34
Large bowel*	Maximum < 36

NOTE. For liver, see Appendix Table A1; for Trial 1, see Tse et al.[23]

*Organ volume minus 0.5 mL.

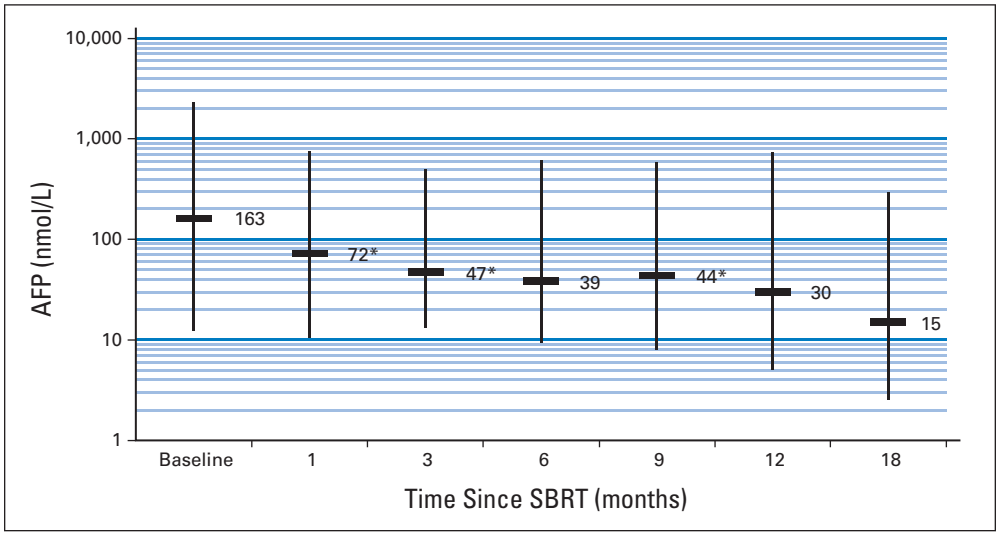

Fig A1. Median serum α-fetoprotein (AFP) with time. (*)$P < .05$ for difference from baseline using Wilcoxon signed-rank test. Thin vertical bars are interquartile ranges. A smaller number of patients at risk with longer follow-up and attrition of deceased patients after nonirradiated liver/distant disease progression warrant caution when interpreting results. SBRT, stereotactic body radiotherapy.