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ORIGINAL REPORT

Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Liver Metastases

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ABSTRACT

Purpose
To evaluate the efficacy and tolerability of high-dose stereotactic body radiation therapy (SBRT) for the treatment of patients with one to three hepatic metastases.

Patients and Methods
Patients with one to three hepatic lesions and maximum individual tumor diameters less than 6 cm were enrolled and treated on a multi-institutional, phase I/II clinical trial in which they received SBRT delivered in three fractions. During phase I, the total dose was safely escalated from 36 Gy to 60 Gy. The phase II dose was 60 Gy. The primary end point was local control. Lesions with at least 6 months of radiographic follow-up were considered assessable for local control. Secondary end points were toxicity and survival.

Results
Forty-seven patients with 63 lesions were treated with SBRT. Among them, 69% had received at least one prior systemic therapy regimen for metastatic disease (range, 0 to 5 regimens), and 45% had extrahepatic disease at study entry. Only one patient experienced grade 3 or higher toxicity (2%). Forty-nine discrete lesions were assessable for local control. Median follow-up for assessable lesions was 16 months (range, 6 to 54 months). The median maximal tumor diameter was 2.7 cm (range, 0.4 to 5.8 cm). Local progression occurred in only three lesions at a median of 7.5 months (range, 7 to 13 months) after SBRT. Actuarial in-field local control rates at one and two years after SBRT were 95% and 92%, respectively. Among lesions with maximal diameter of 3 cm or less, 2-year local control was 100%. Median survival was 20.5 months.

Conclusion
This multi-institutional, phase I/II trial demonstrates that high-dose liver SBRT is safe and effective for the treatment of patients with one to three hepatic metastases.

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INTRODUCTION

Stereotactic body radiation therapy (SBRT) involves a brief, intensified regimen of tightly focused external radiotherapy that targets one or more discrete extracranial lesions. The major dose-limiting concern in the use of SBRT for liver tumors is the risk of radiation-induced liver disease (RILD). However, because the liver obeys the parallel architecture model of radiobiology,[1] the risk of RILD is generally proportional to the mean dose of radiation delivered to normal liver tissue.[2] Therefore, it should be possible to safely treat small hepatic lesions with high doses of radiation by using SBRT, provided the mean dose to normal liver can be limited.

Hepatic resection has become an accepted standard therapy for medically and technically operable liver metastases from colorectal cancer (CRC). Several retrospective studies have reported long-term survivorship in selected patients treated with hepatic metastasectomy.[3-5] For example, Fong et al[3] reported a 10-year survival rate of 22% in 1,001 patients with CRC who underwent liver resection for hepatic metastases. Among patients in this series without any unfavorable prognostic features, 5-year survival was 60%. Moreover, local control of hepatic metastases appears to be a key determinant of overall survival. Aloi et al[5] compared radiofrequency ablation (RFA) and resection among patients with solitary CRC hepatic metastases. RFA was associated with a seven-fold increased risk of local failure and a three-fold increased risk of death compared with hepatic resection, despite similar rates of distant intrahepatic and extrahepatic failure in both groups.

University of Heidelberg investigators reported one of the earliest prospective studies to use single-fraction SBRT (dose, 14 to 26 Gy) for the treatment of liver metastases.[6] At a median follow-up of 5.7

months, 43 of 55 lesions remained locally controlled. These investigators recently updated their experience and reported an 18-month local control rate of 66% by using 22 Gy in one fraction.[7]

A dose-control relationship has been described for patients treated with SBRT for liver and lung metastases. In an analysis of 246 lesions treated with three-fraction SBRT, McCammon et al[8] demonstrated significant improvement in local control with increasing dose. The 3-year local control rate in this series was 89.3% for those lesions that received 54 to 60 Gy versus 59% and 8.1% for lesions that received 36 to 53.9 Gy and less than 36 Gy, respectively ($P < .01$). A similar dose-response relationship has been described for SBRT in other sites.[9,10]

On the basis of the relationship between local control and survival in surgical series and the observed dose response with SBRT, we initiated a phase I/II study to evaluate the safety and efficacy of high-dose SBRT in the treatment of liver metastases. We have previously reported the phase I[11] and interim efficacy results.[12] We now report the final results of this multi-institutional, phase I/II trial.

PATIENTS AND METHODS

Eligibility

The protocol was approved by the institutional review board of all participating institutions. Adult patients with one to three hepatic metastases were eligible. Patients with any primary tumor, except germ cell tumor, leukemia, or lymphoma, were eligible. Maximum individual tumor diameter had to be less than 6 cm. No prior radiation therapy to the upper abdomen was allowed. Patients were required to have total bilirubin less than 3 mg/dL, albumin greater than 2.5 g/dL, and normal prothrombin/partial thromboplastin times unless on anticoagulants. Serum liver enzymes had to be less than three times the upper limit of normal. Patients with ascites were excluded. Patients also had to have normal renal function. Patients were not permitted to have chemotherapy within 14 days before or after SBRT. Patients were permitted to have extra-hepatic disease, provided it was low burden and potentially treatable with surgery, ablative radiation therapy, or US Food and Drug Administration–approved first- or second-line systemic therapy regimens. Karnofsky performance status had to be at least 70. All patients signed study-specific informed consent.

Treatment

The SBRT treatment planning and delivery methods used in this trial have been previously described.[11,12] Briefly, patients were immobilized during computed tomography (CT) simulation and were treatment with a customized, external vacuum-type or synthetic body mold. Breathing-related tumor motion was controlled by using active breathing control (ie, controlled breath hold) technique or abdominal compression in most instances. In eight patients, an internal tumor volume (ITV) method was used to define the target volume, in which the gross tumor volume (GTV) included the tumor position in all phases of the normal respiratory cycle. Planning CT images through the liver were usually fused with pre-SBRT diagnostic studies to facilitate target delineation, unless the target lesion could be clearly visualized on planning CT. The GTV was expanded by a 5-mm radial and a 10-mm craniocaudal margin when using ABC and by a 7-mm radial and a 15-mm craniocaudal margin when using abdominal compression to create the planning target volume (PTV). Respiratory movement also was observed under fluoroscopy, and margins were increased when target motion exceeded the planned margins.

SBRT was planned and administered by using dynamic conformal arcs or multiple noncoplanar static beams (using ≥ 7 noncoplanar fields) generated by a linear accelerator with energies of 6 to 15 MV. The dose was prescribed to the isodose line that covered the PTV (80% to 90% isodose line). Stereotactic repositioning was accomplished by using fiducial markers on the body immobilization device or infrared markers on the patients surface (ExactTrac; BrainLab Inc, Westchester, IL). Daily image guidance, by using either orthogonal X-rays or onboard CT imaging, was used to relocalize the target before treatment delivery. SBRT was administered in a three-fraction course to be completed in no more than 14 elapsed days.

In the phase I portion of the trial, dose was escalated from 36 Gy to 60 Gy in three fractions, in increments of 6 Gy, without dose-limiting toxicity. In the phase II component, the dose was 60 Gy in three fractions. Thirteen patients were treated to doses less than 60 Gy, and 36 patients received 60 Gy.

The protocol dose constraints for normal liver (total liver minus cumulative GTV) specified that a minimum volume of 700 mL should receive a total dose less than 15 Gy. From the surgical literature, we know that 75% to 80% of the noncirrhotic liver can be safely resected.[13] If we assume that the average liver is approximately 2,000 mL, then 25% would be 500 mL. Conservatively, we required that 700 mL of normal liver be spared (ie, should receive less than 15 Gy). The basis for the dose constraint used was a conversion from published experiences using conventional fractionation. The entire liver can safely tolerate at least 33 Gy in 22 fractions.[14] The biologically equivalent dose (BED) of this schedule is 49.5 Gy_3, when an α-β ratio of three and no significant repopulation are assumed.[15] A dose of 15 Gy in three fractions would have a normal tissue BED of 40 Gy_3, which is less than the expected tissue tolerance. The percent of total kidney volume (sum of the left and right kidney volumes) to receive a total of 15 Gy had to be less than 35%. The maximum total dose to any point in the spinal cord and stomach/small intestine could not exceed 18 Gy and 30 Gy, respectively.

Study End Points and Statistics

The design of the phase I and phase II components of this trial have been described previously.[11,12] The primary end point for the phase II study was infield local control (LC) in patients with at least 6 months of follow-up imaging post-SBRT. The reason for specifying a minimum of 6 months of follow-up to score LC was to avoid uncertainty associated with early transient radiographic changes within the high-dose region; patients who died without a minimum of 6 months post-SBRT imaging study follow-up were not considered assessable for LC[16] but were analyzed for overall survival (OS).

Follow-up imaging, physical examinations, and toxicity evaluations were obtained at 3-month intervals. LC was assessed at the participating institutions but was confirmed by central review by the coordinating center investigators. Follow-up images were usually compared (by using image fusion software) with the SBRT treatment plan to evaluate LC. New or progressive lesions that developed within or at the margin of the PTV were scored as infield local progression, whereas lesions that developed outside the PTV were scored as distant progression. Secondary end points were toxicity, progression-free survival (PFS), distant PFS (DPFS), and OS.

Actuarial LC and OS curves were generated by using the Kaplan-Meier method.[17] All enrolled patients were included in the calculation of DPFS, PFS, and OS. Only assessable patients were considered in the calculation of LC. The influence of patient, disease, and treatment characteristics on OS were evaluated by using Cox proportional hazards regression.[18] Covariates evaluated in the Cox model included primary tumor site, number of liver metastases, maximum lesion diameter, presence of extrahepatic disease, and treatment with prior systemic therapy for metastatic disease. Bonferroni corrections were used to adjust the multivariate P value to reduce the likelihood of a type I error.[19]

RESULTS

Patients

Between August 2003 and October 2007, 47 patients with 63 liver metastases were enrolled and were treated at seven participating institutions. Forty-nine discrete lesions in 36 patients were assessable for LC. Eleven patients were not assessable for LC: five died before 6 months of follow-up, and two died as a result of progressive systemic disease shortly after 6 months of follow-up without recent liver imaging. Two patients who were treated at Tulane Medical Center (New

Orleans, LA) survived 11.2 and 11.7 months, respectively, after protocol treatment. Their medical records, however, were lost after Hurricane Katrina; consequently, these patients were not assessable for LC, DPFS, or PFS. Two patients were lost to follow-up: one patient had progressive distant hepatic metastases on imaging performed 3 months after SBRT and was subsequently lost to follow-up, and another patient with metastatic gastrointestinal stromal tumor was lost to follow-up at 3.5 months with no evidence of local or distant progression. None of these 11 patients had evidence of local progression at their last follow-up imaging. The median follow-up for assessable patients was 16 months (range, 6 to 54 months). Baseline characteristics for all enrolled patients are listed in Table 1.

Table 1. Baseline Characteristics

Characteristic	No.	%
Total No. of patients	47	
Total No. of lesions evaluated	63	
Age, years		
Median	58.4	
Range	26.6-91.5	
Primary tumor		
CRC	15	31.9
Lung	10	21.3
Breast	4	8.5
Ovarian	3	6.4
Esophageal	3	6.4
HCC	2	4.3
Other	10	21.3
Time since primary tumor diagnosis, months		
Median	22.7	
Range	0-236	
Time since diagnosis of liver metastases, months		
Median	3.4	
Range	0-55	
No. of prior systemic treatment regimens		
Mean	1.7	
Range	0-7	
0	6	12.8
1	18	38.3
2	12	25.5
3	6	12.8
≥ 4	3	6.4
Unknown	2	4.3
Prior local therapy for liver metastases		
Yes	7	14.9
No	40	85.1
Maximum lesion diameter, cm		
Median	2.7	
Range	0.4-6.8	
> 3	25	39.7
≤ 3	38	60.3
Lesion volume, mL		
Median	14.93	
Range	0.75-97.98	
No. of liver lesions*		
1	28	59.6
2	7	14.9
3	12	25.5
Presence of active extrahepatic disease†		
Yes	21	44.7
No	26	55.3
History of brain metastases		
Yes	7	14.9
No	40	85.1

Abbreviation: HCC, hepatocellular carcinoma.
*Denotes number of active metastases only. Previously treated, controlled metastases were not counted (but were included in the category of prior local therapy for liver metastases).
†Extrahepatic disease denotes any untreated primary or metastatic disease and any previously treated primary or metastatic disease that is progressing on serial imaging.

LC

Actuarial LCs at 1 and 2 years were 95% (95% CI, 83.2% to 98.9%) and 92% (95% CI, 76% to 97.4%), respectively. The longest duration of LC was in a patient who had 53 months of follow-up. An SBRT plan for a patient with three treated lesions is shown in Figure 1. Local progression was observed in three of the 49 assessable lesions at a median of 7.5 months (range, 7 to 13 months). The details for the three lesions with local progression are lsited in Table 2.

In a planned subset analysis, 2-year LC for the 38 lesions treated to 60 Gy was 94% (95% CI, 78% to 98.5%). For lesions with maximum diameter of 3 cm or less, 2-year LC was 100% compared with 77% (95% CI, 43% to 92.2%) for lesions greater than 3 cm ($P = .015$, log-rank test). Actuarial LCs for all lesions and for lesions according to size are shown in Figure 2. Multivariate analysis was not performed for LC because of the small number of events.

Post-SBRT Treatment

Among the 36 assessable patients, 26 patients (72%) received systemic therapy after SBRT. Ten patients (28%) received bevacizumab after SBRT, and six patients received bevacizumab as a component of their first post-SBRT regimen.

Survival

Distant progression, including both distant intrahepatic and extrahepatic progression, occurred in 39 patients (83%) at a median of 6 months after SBRT (range, 2 to 53 months). Median DPFS and PFS were both 6.1 months. Distant progression was a component of first progression in all patients. First progression was distant only in 38 patients and was both local and distant in one patient.

At the time of analysis, 27 (57%) of 47 enrolled patients had died. Median and 2-year OS rates were 20.5 months and 30% (95% CI, 15.1% to 47.2%), respectively. Primary tumor site was significantly predictive of survival on both univariate and multivariate analysis. Primary tumors of the lung, ovary, and noncolorectal gastrointestinal malignancies (ie, unfavorable primary sites) were associated with worse survival compared with tumors that originated in other sites. In total, 51% had metastases from unfavorable primary sites. In patients with metastases from unfavorable primaries, median survival was only 12 months. Conversely, median survival in patients with metastatic lesions from favorable primaries—including breast, colorectal, renal, carcinoid, gastrointestinal stromal tumor, and sarcoma—was 32 months ($P < .001$, log-rank test). Among the 23 patients with favorable primary sites, 15 were alive at last follow-up. On Cox analysis, unfavorable primary was the only significant predictor of death (hazard ratio, 9.10; $P < .001$). Actuarial survival rates for all patients and for patients according to primary site are shown in Figure 3.

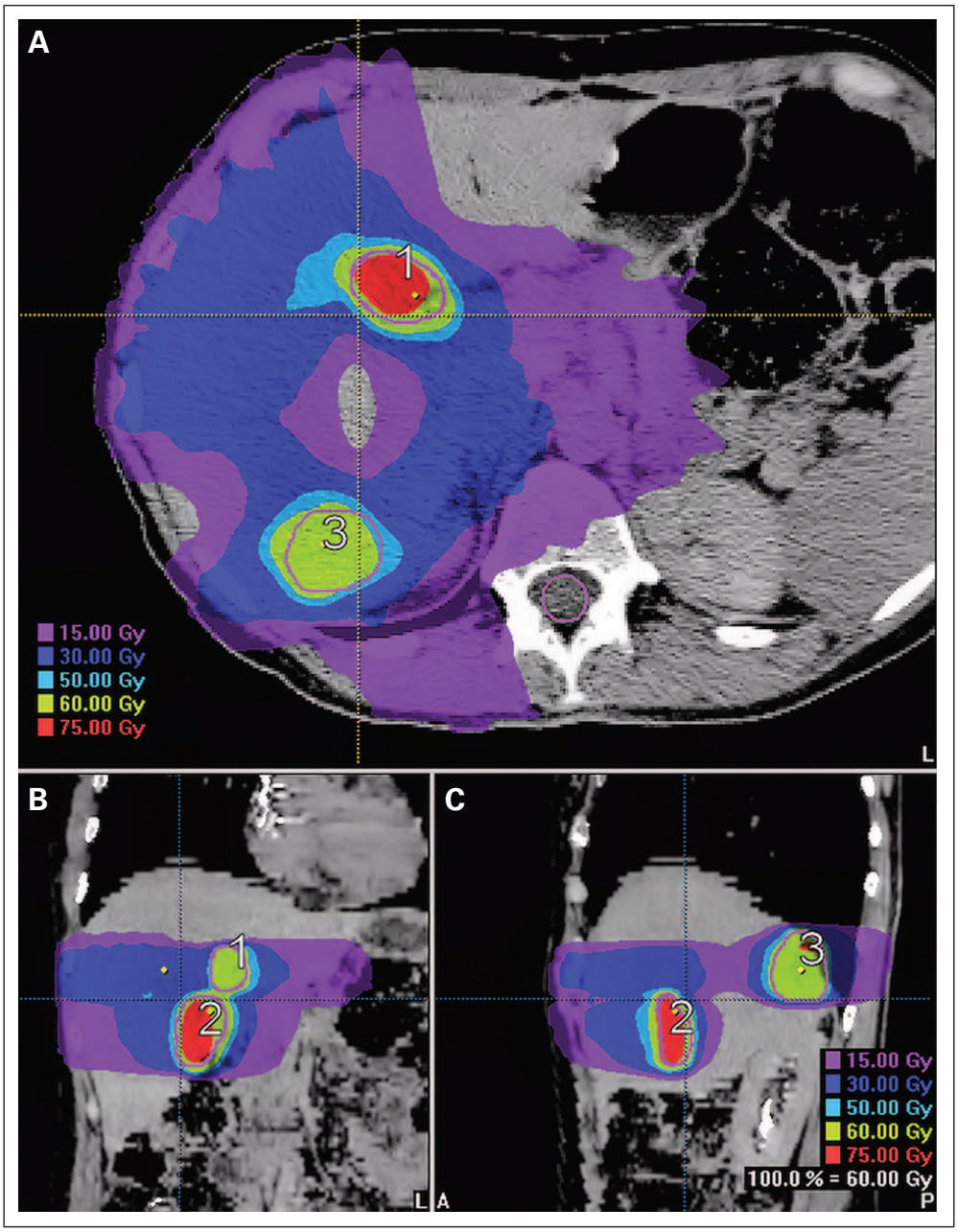

Fig 1. Stereotactic body radiation therapy plan for a patient with three metastases from ovarian cancer. The right superior-medial (lesion 1) and right inferior-medial (2) lesions were treated within a single isocenter. The right posterior-lateral lesion (3) was treated by using a separate isocenter. Prescription dose was 60 Gy in three fractions. Image A is an axial image that shows right posterior-lateral and right superior-medial lesions. Image B is a coronal image that shows the right superior-medial and right inferior-medial lesions. Image C is a sagittal image that shows a coplanar view of the right posterior-lateral and right inferior-medial lesions.

Toxicity

None of the patients who received post-SBRT systemic therapy experienced high-grade radiation toxicity, and none who later received bevacizumab experienced bleeding or thrombotic complications. There have been no instances of grade 4 or 5 toxicity. None of the seven patients who died before becoming assessable for local control had any evidence of treatment-related toxicity. One instance of grade 3 soft tissue toxicity was observed. This patient had an

Table 2. Details for Patients and Lesions With Local (infield) Progression

Primary	Lesion Size (cm)	Dose (Gy)	Time to Local Progression (months)	Salvage Therapy	Total Follow-Up Duration (months)	Current Status
NP	4.3	54	13.4	SBRT 4 Gy ×10 fx	47	AWD
Lung	4.5	60	7.5	Phase I insulin-like growth factor receptor inhibitor	12.3	DOD
Colorectal	3.7	60	6.8	Panitumumab and cetuximab	13.3	DOD

Abbreviations: NP, nasopharynx; SBRT, stereotactic body radiation therapy; fx, fractions; AWD, alive with disease; DOD, dead as a result of disease.

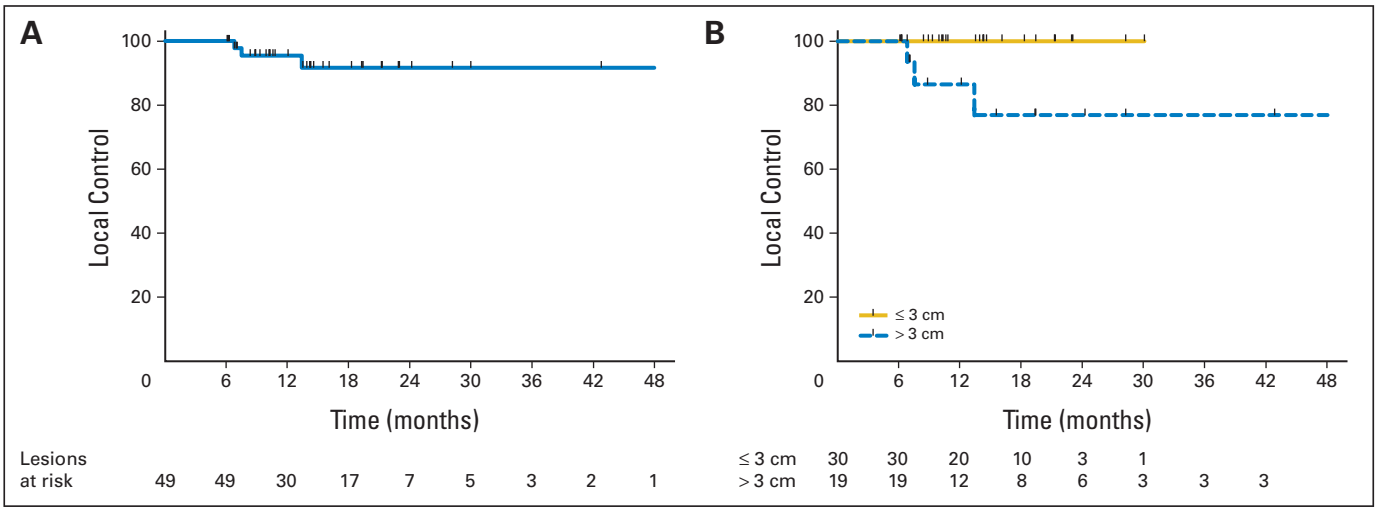

Fig 2. Actuarial local control for (A) all lesions and (B) lesions according to maximal tumor diameter.

inferior-lateral right lobe carcinoid metastases treated to 60 Gy in three fractions by using four coplanar opposing static fields. Approximately 6 months after the completion of treatment, this patient developed skin erythema and pain, which progressed to require narcotic analgesic. Subsequently, the patient developed soft tissue breakdown, which required surgical debridement and a trial of hyberbaric oxygen. On review of the SBRT plan, there was an area in the anterior abdominal wall, near the entry of one of the static beams, that received 48 Gy and that corresponded to the site of soft tissue breakdown. This toxicity was scored as grade 3 in accordance with Common Terminology Criteria of Adverse Events version 3.0.[20] The actuarial rate of any grade $\geq$ 3 toxicity was 2% at last follow-up. Normal liver tissue constraints were met in all patients enrolled, and no instances of RILD have been observed.

DISCUSSION

In this study, we report the final results of a prospective, multiinstitutional, phase I/II trial to demonstrate the safety and efficacy of SBRT for the treatment of patients with one to three hepatic metastases. For the 49 assessable discrete lesions treated, LC at 2 years was 92%. Grade 3 and higher toxicity occurred in only 2% of patients.

Milano et al[21] recently reported the results of a prospective, phase II trial that used SBRT to a dose of 50 Gy in 10 fractions in the treatment of oligometastases, which was defined in that study as five or fewer discrete metastatic lesions. Hepatic metastases were treated in 45% of patients. LC was not reported by site, but 2-year LC for all treated lesions was 67%. LC was higher in the current trial (92%) compared with both the Rochester and Heidelberg series (66%). Although patient selection may contribute to the observed differences, the 2-year survival rate in the Rochester trial was considerably higher than in our trial (50% *v* 30%), which suggests that our patients might, in fact, have had worse prognostic features.

The higher, more intense dose of SBRT used in this series likely contributed to the higher rate of LC observed. The single fraction equivalent dose (SFED) methodology has been proposed by Park et al[22] as a way to compare the relative biologic potency of hypofractionated radiotherapy schedules. This study's SFED of 60 Gy given in three

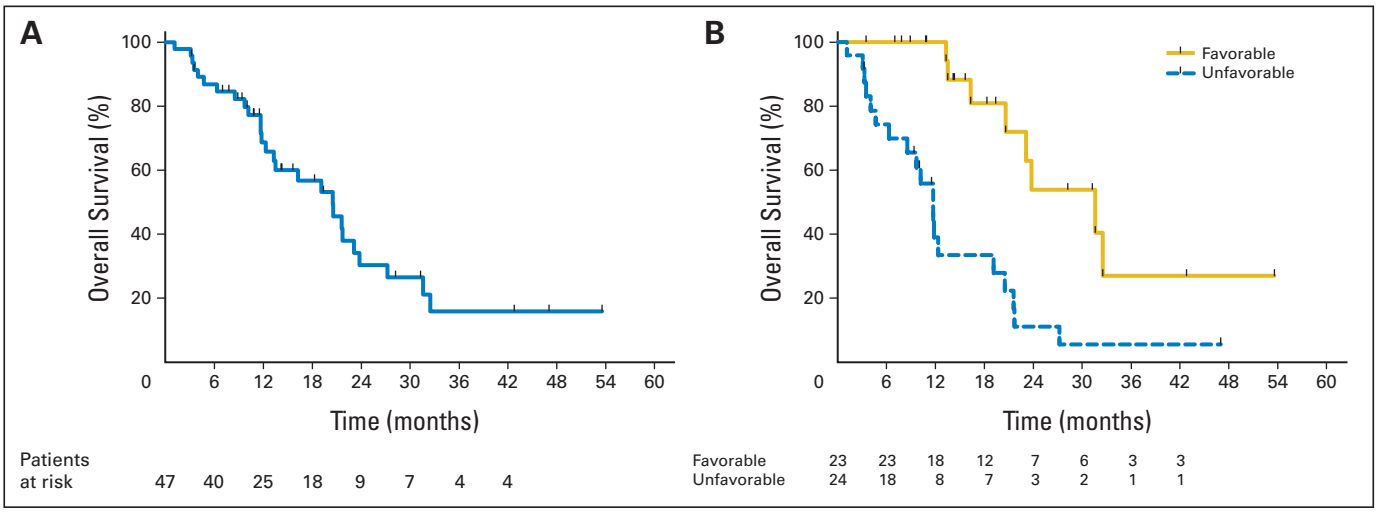

Fig 3. Actuarial survival for (A) all patients and (B) patients according to primary site.

Table 3. Prospective Trials of Stereotactic Body Radiation Therapy for Hepatic Metastases

Study	No. of Lesions	Fractionation	Median Follow-Up	Actuarial Local Control	
				Time	%
Herfarth et al[6]	55	1 × 14 Gy to 1 × 26 Gy	6 months	18 months	67
Hoyer et al[24]	141*	3 × 15 Gy	4.3 years	2 years	79
Milano et al[21]	293†	10 × 5 Gy	41 months‡	2 years	67
Mendez-Romero et al[25]	45	3 × 12.5 Gy§	13 months	2 years	82
Rusthoven et al (this study)	49	3 × 20 Gy	16 months	2 years	92

*Total number of colorectal cancer metastases; 44 liver metastases.
†Total number of lesions treated; 45% of patients were treated for hepatic metastases.
‡In surviving patients.
§Different fractionation (3 × 10 Gy or 5 × 5 Gy) used for patients with hepatocellular carcinoma or with lesions ≥ 4 cm.

fractions is calculated to be 56.4 Gy, which is higher than the SFEDs of 34.3 Gy and 22 to 26 Gy provided by the Rochester and Heidelberg regimens, respectively. Our observation of a high rate of LC when using 60 Gy in three fractions is consistent with the reported LC rate when using the same high dose in medically inoperable non–small-cell lung cancer.[23] A summary of prospective, phase II studies that use SBRT for the treatment of liver metastases is listed in Table 3.

The incidence of grade 3 toxicity was low in the current series. One patient developed grade 3 soft tissue toxicity approximately 6 months after SBRT, which prompted revised skin and soft tissue protocol dose constraints to avoid a hot spot of high-dose within this region. The definition of a recommended SBRT soft tissue dose-volume limitation remains an issue of ongoing investigation. A recent combined analysis of patients treated with thoracic SBRT from the Universities of Virginia and Colorado revealed that the volume of chest wall that receives 30 Gy (V30) was the best predictor of chest wall toxicity.[26] The incidence of severe chest wall toxicity (ie, pain that required narcotic analgesics or rib fracture) increased with increasing V30, and no chest wall toxicity was observed with V30 less than 10 mL.

Survival in this trial was low compared with the rates reported for hepatic resection for liver metastases. In large surgical series, including those primarily in patients with metastatic colorectal cancer, 5-year survival after liver resection ranges between 37% to 71%.[3-5] However, in contrast to these studies, the patients in this trial had poor-risk prognostic features. Sixty-nine percent of patients had received chemotherapy for metastatic disease before study enrollment. Moreover, 45% had extrahepatic disease, and 51% had metastases from unfavorable primaries. Despite the high prevalence of poor-risk prognostic features among patients in this study, SBRT was associated with a high rate of local control. In patients with metastases from favorable primary tumors, mostly colorectal and breast cancer, 2-year LC was 97%, which is comparable to the rates reported for patients with liver metastases from similar primary sites in surgical series.[5]

There are several limitations of this trial. As previously discussed, the median survival for all patients was only 20.5 months, which is most likely related to the unfavorable prognostic features of the patients enrolled. As such, the risk of death as a first event was high in this cohort, and the estimated LC may be artificially exaggerated, because death and local failure are competing events. Among the 23 patients with metastases from favorable primary tumors, however, the median survival was significantly longer (32 months), and the 2-year LC was 97%, which suggests that local control was not substantially influenced by the decreased competing risk of death in this subgroup. Moreover, late toxicity may be under appreciated as a result of limited survival, especially when the higher than conventional fractional dose is considered.

In conclusion, in this multi-institutional, phase I/II trial in patients with one to three discrete liver metastases, SBRT was associated with a high rate of LC and a low incidence of toxicity. These results support the use of high-dose SBRT as an effective and safe, noninvasive therapeutic option in this setting. Differences in baseline prognostic features between patients in this study and those included in most surgical series limit the comparison between SBRT and resection.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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