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ORIGINAL REPORT

Phase I Study of Individualized Stereotactic Body Radiotherapy of Liver Metastases

Mark T. Lee, John J. Kim, Robert Dinniwell, James Brierley, Gina Lockwood, Rebecca Wong, Bernard Cummings, Jolie Ringash, Regina V. Tse, Jennifer J. Knox, and Laura A. Dawson

From the Radiation Medicine Program, Departments of Biostatistics and Medical Oncology, Princess Margaret Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada.

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Corresponding author: Laura Dawson, MD, Department of Radiation Oncology, Princess Margaret Hospital, University of Toronto, 610 University Ave, Toronto, Ontario M5G2M9, Canada; e-mail: laura.dawson@rmp.uhn.on.ca.

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ABSTRACT

Purpose
To report on the outcomes of a phase I study of stereotactic body radiotherapy (SBRT) for treatment of liver metastases.

Patients and Methods
Patients with liver metastases that were inoperable or medically unsuitable for resection, and who were not candidates for standard therapies, were eligible for this phase I study of individualized SBRT. Individualized radiation doses were chosen to maintain the same nominal risk of radiation-induced liver disease (RILD) for three estimated risk levels (5%, 10%, and 20%). Additional patients were treated at the maximal study dose (MSD) in an expanded cohort. Median SBRT dose was 41.8 Gy (range, 27.7 to 60 Gy) in six fractions over 2 weeks.

Results
Sixty-eight patients with inoperable colorectal (n = 40), breast (n = 12), or other (n = 16) liver metastases were treated. Median tumor volume was 75.2 mL (range, 1.19 to 3,090 mL). The highest RILD risk level investigated was safe, with no dose-limiting toxicity. Two grade 3 liver enzyme changes occurred, but no RILD or other grade 3 to 5 liver toxicity was seen, for a low estimated risk of serious liver toxicity (95% CI, 0 to 5.3%). Six (9%) acute grade 3 toxicities (two gastritis, two nausea, lethargy, and thrombocytopenia) and one (1%) grade 4 toxicity (thrombocytopenia) were seen. The 1-year local control rate was 71% (95 CI, 58% to 85%). The median overall survival was 17.6 months (95% CI, 10.4 to 38.1 months).

Conclusion
Individualized six-fraction liver metastases SBRT is safe, with sustained local control observed in the majority of patients.

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INTRODUCTION

Liver metastases cause significant morbidity and mortality for patients with colorectal carcinoma (CRC). A total of 25% to 50% of patients with CRC develop liver metastases in their lifetime, with approximately 20% isolated to the liver.[1-5] For patients with liver-confined CRC metastases that are resected completely, 5-year survival rates are 30% to 60%.[6-9] Approximately 25% of patients with liver metastases are suitable for resection, and only 6% of patients with CRC liver metastases in North America ever receive a hepatectomy.[4,10] After resection, 50% of first recurrences occur in the liver.[11] Resection has also been associated with sustained tumor control of non-CRC liver metastases, but appropriate selection criteria of these patients are not clearly defined.[12,13]

Systemic therapies are becoming more effective, but long-term cure is unlikely unless combined with a local therapy. Many local therapies are only effective in small metastases, away from large vessels (ie, radiofrequency ablation), and further studies are warranted on other local therapies.

Radiotherapy for unresectable liver metastases has been limited previously by the potential for radiation-induced liver disease (RILD), which may occur within 3 months after low-dose (30 Gy in 15 fractions) whole-liver radiotherapy. RILD consists of anicteric ascites with an elevation of alkaline phosphatase in relation to the liver transaminases, and it can result in liver failure and death.[14] Advances in radiation planning, motion management, and radiation delivery using image-guided radiotherapy (IGRT) have allowed higher, more conformal doses of radiation to be delivered to liver cancers, improving the probability of tumor control with a lower risk of toxicity.[15,16]

Stereotactic body radiotherapy (SBRT) refers to the precise delivery of high doses of conformal

radiation to extracranial targets using a small number of radiation fractions. Liver SBRT requires conformal radiation planning, liver motion management, and IGRT to ensure the doses are delivered as planned. SBRT has been used previously to treat predominantly small tumors (< 6 cm in diameter), with 1- and 2-year local control rates of 70% to 100% and 57% to 93%, respectively.[17-22] The safety of SBRT for larger liver metastases has not been established. Here we report the outcomes of a phase I study of individualized six-fraction SBRT for unresectable liver metastases of variable sizes.

PATIENTS AND METHODS

Patients

Patients with liver metastases from pathologically confirmed CRC that were inoperable or medically unsuitable for resection were recruited to this research ethics board–approved trial. Patients had to be unsuitable for or refractory to standard treatment. Chemotherapy was not given from 2 weeks before to 4 weeks after SBRT. Extrahepatic disease was permitted only if the largest disease burden was hepatic. Inclusion criteria were Karnofsky performance score ≥ 60, life expectancy more than 3 months, more than 800 mL of uninvolved liver, Child's A liver score, hemoglobin ≥ 90 g/L, neutrophils ≥ 1.5 billion/L, platelets ≥ 80,000 billion/L, bilirubin less than 3× upper limit of limit of normal range (ULN), international normalized ratio less than 1.3 or correctable with vitamin K, AST or ALT less than 6× the ULN, and creatinine less than 200 μmol/L. After 1 year, eligibility criteria were expanded to allow non-CRC metastases and patients with chronic renal failure receiving dialysis to be treated. Patients were excluded if they had active hepatitis, encephalopathy, gross ascites, or were pregnant. There was no maximum liver tumor size or number.

Study Design

This phase I dose-escalation trial was designed to determine the safety and efficacy of individualized six-fraction SBRT of liver metastases. Primary objectives were to determine the maximum-tolerated study dose (MSD) and toxicity. Secondary objectives were to assess the tumor response, local control, progression-free survival, and overall survival.

Radiation Treatment

Patients were immobilized supine in a customized body mold, and simulation involved kV fluoroscopy, computed tomography (CT), and magnetic resonance imaging (MRI) to assess breathing motion and delineate tumors, as previously described.[23,24] Liver breathing motion was reduced with an active breathing control device (Elekta Oncology Systems, Crawley, United Kingdom)[25,26] or abdominal compression for patients with more than 5 mm of liver breathing motion.

The gross tumor volume (GTV) included contrast-enhancing disease visible on an exhale contrast-enhanced CT scan or MRI. The clinical target volume (CTV) was 8 mm around the GTV within the liver to account for possible microscopic disease. A nonuniform expansion for the planning target volume around the GTV (PTV_{GTV}) and CTV (PTV_{CTV}) was based on individual patient tumor motion and reproducibility of immobilization (minimum 5 mm).

All patients were treated with six fractions, conformal SBRT, using three to 10 beam angles, one to four segments per beam, and up to three noncoplanar beams. Radiation dose was prescribed to an isodose covering the PTV_{GTV} with a maximum dose of 140% within the target. The prescribed dose was individualized based on risk of toxicity (Fig 1). The PTV_{CTV} dose was 24 Gy in six fractions over 2 weeks. The initial limit to 0.5 mL of small/large bowel and stomach was 33 Gy (reduced to 30 Gy after 11 patients were treated). Maximum dose limit to the spinal cord plus 5 mm was 27 Gy and to two thirds of combined kidneys was 18 Gy or 10 Gy to 90% of one functioning kidney, in six fractions, over 2 weeks. H2 antagonists or proton pump inhibitors were given to patients receiving ≥ 30 Gy to their stomach.

Daily IGRT was performed using the dome of the diaphragm or the liver as a surrogate for the liver tumor position at treatment. Two-dimensional orthogonal mega-voltage IGRT was used in the first 9 months, and subsequently, three-dimensional kV cone beam CT combined with two-dimensional kV fluoroscopy was used. Repositioning was performed for offsets in liver position more than 3 mm.[23,24]

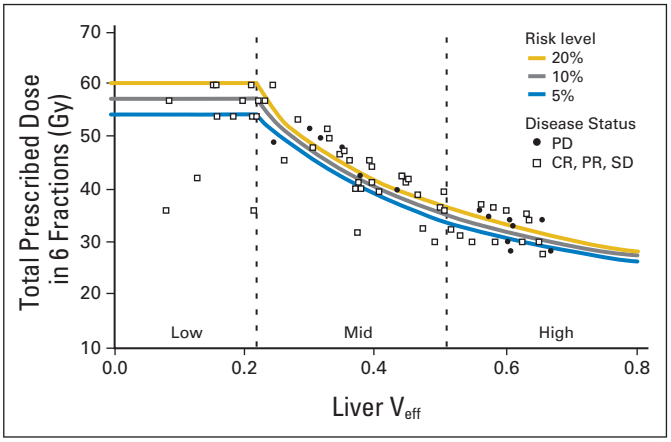

Fig 1. Dose, effective liver volume irradiated (V_{eff}), liver toxicity risk levels, and patient treated tumor Response Evaluation Criteria in Solid Tumor response at last follow-up. Dose was based on the risk level curves shown, with up to 3 Gy more permitted as long as patient calculated risk was maintained and lower doses if required because of nonhepatic limits. PD, progressive disease; CR, complete response; PR, partial response; SD, stable disease.

Radiation Dose Escalation

Patients were stratified based on the effective liver volume (V_{eff}) irradiated, defined as the liver volume minus all GTVs, which, if irradiated uniformly to the treatment dose, would be associated with the same risk of toxicity as the nonuniform dose distribution delivered.[27] RILD risk was estimated using the Lyman-Kutcher-Burman normal tissue complication probability model,[27,28] with model parameters from the University of Michigan experience using 1.5 Gy twice daily.[16] A correction for the dose fractionation of the liver dose volume histograms was made assuming $\alpha/\beta = 2.5$ Gy.[29] For the three strata (low $V_{eff} \leq 0.22$, mid V_{eff} 0.22 to 0.51, and high $V_{eff} > 0.51$ to 0.8), "isotoxic" dose levels were specified, with estimated RILD risks of 5%, 10%, and 20% for the mid and high V_{eff} strata. For the low V_{eff} stratum, dose was escalated from 54 Gy to 57 Gy then to 60 Gy, in six fractions over 2 weeks. The risk of RILD was estimated to be less than 5% for this stratum.

A minimum of three patients at each risk level for each stratum (nine strata total) were observed for at least 3 months without RILD or other dose-limiting toxicity (DLT) before recruitment to the next level. Patients were treated at the current dose level while waiting for toxicity analysis in the first three patients per stratum. Twenty-seven patients were treated in an expanded cohort at the MSD to determine toxicity and efficacy with more confidence.

DLT was defined as common toxicity criteria version 3, grade 4 or 5 gastrointestinal, thrombocytopenia, or hepatic toxicity occurring within 1 month after SBRT and any related grade 4 or 5 liver toxicity or RILD requiring treatment within 3 months of SBRT. The MSD was the dose level at which not more than one patient developed a DLT for each strata.

Assessments

Local response was defined using RECIST (Response Evaluation Criteria in Solid Tumors) to describe the change in the irradiated metastases.[30] Time to local progression was from the first day of SBRT to day of first progressive disease of the irradiated tumor. Patients were observed for local control, even if distant or new liver metastases developed. The local control rate was determined accounting for competing risks of death using a cumulative incidence analysis. Progression-free survival included any intra- or extrahepatic disease progression.

All patients had baseline contrast CT or MRI of the liver, chest, and abdomen. Patients were assessed weekly during treatment, then at 1 month and 3 monthly after SBRT for 1 year, then 6 monthly to 3 years, and

Table 1. Patient Demographics and Treatment Characteristics

Characteristic	Total		Colorectal		Breast		Other	
	No.	%	No.	%	No.	%	No.	%
Demographics								
No. of patients	68		40	59	12	18	16	24
Age, years								
Mean	63		67		57		60	
Range	30-90		39-90		38-76		30-81	
Sex								
Male	32	47	23	58	0	0	9	56
Female	36	53	17	42	12	10	7	44
KPS								
70-80	9	14	8	20	0	0	1	6
90	31	49	19	48	5	42	7	44
100	23	36	11	28	5	42	7	44
Unknown	5	8	2	5	2	17	1	6
Extrahepatic disease at time of treatment								
Total	36	53	18	45	6	50	12	75
Periportal LN	4	6	1	2	1	8	2	12
Abdomen/pelvis	6	8	11	28	3	25	4	25
Metastases: lung, bone	18	26	2	5	1	8	3	19
Other	19	28	8	20	3	25	8	50
Time from initial diagnosis to SBRT, years								
Median	2.5		2.5		3.4		2	
Range	0.4-10.9		0.8-5.6		0.4-10.9		0.9-6.1	
No. of prior liver recurrences								
0	32	47	15	38	8	67	9	56
1	16	24	11	28	2	17	3	19
2	10	15	8	20	0	0	2	12
≥ 3	9	13	6	14	1	8	2	12
Unknown	1	1	0	0	1	8	0	0
Previous treatment								
Surgery	7	10	5	12	0	0	2	12
RFA	8	12	6	15	0	0	2	12
Previous lines of chemotherapy								
0	9	13	6	15	1	8	2	12
1	15	22	9	22	0	0	6	38
2	29	43	18	45	3	25	8	50
≥3	15	22	7	18	8	67	0	0
Tumor								
No. of tumors								
Median	1		2		1		2	
Range	1-8		1-8		1-7		1-5	
GTV, cm^3								
Median	75.2		134.8		12.8		44	
Range	1.2-3,090		6.7-3,090		4.2-573.4		1.2-727.5	
Treatment								
Dose to 95% PTV_{GTV}, Gy								
Median	37.9		35.4		42.2		43.5	
Range	23.7-61.6		23.7-58.7		30.3-60.5		26.6-61.6	
Liver V_{eff}								
Median	0.39		0.44		0.28		0.37	
Range	0.08-0.67		0.13-0.67		0.08-0.56		0.13-0.61	
Mean liver dose, Gy								
Median	16.9		18.3		14.7		15.7	
Range	3-22.7		5.6-22.7		3-21.1		7.9-20.6	
Maximum dose to 700 mL of liver, Gy								
Median	12.7		17.3		8.4		11.7	
Range	0.5-32		1.3-32		0.5-29.9		1.1-19.2	
Maximum dose to 0.5 mL of stomach, Gy								
Median	23.3		23		16.7		26.0	
Range	0-33.4		0-33.4		0.8-31		4.3-30.7	
Maximum dose to 0.5 mL of bowel, Gy								
Median	13.4		14.0		13.9		13.0	
Range	0-35.5		0-35.5		0.5-32		0.8-29.1	

Abbreviations: KPS, Karnofsky performance score; LN, lymph node; SBRT, stereotactic body radiotherapy; RFA, radiofrequency ablation; GTV, gross tumor volume; PTV_{GTV}, planning target volume around the GTV; V_{eff}, effective volume.

annually until year 5. At each follow-up, a liver CT or MRI and blood work were obtained.

RESULTS

Patients

From May 2003 through September 2007, 88 patients were screened, and 70 eligible patients with 143 tumors were treated in the phase I study (n = 43) and expanded MSD cohort (n = 27; Table 1). Two patients were taken off study (one lost to follow-up at 1 month and one with pancreatic cancer who developed obstructive jaundice from progressive disease after receiving two fractions). This left 68 patients with metastases from colorectal (n = 40), breast (n = 12), gallbladder (n = 4), lung (n = 2), anal canal (n = 2), melanoma (n = 2), and other (n = 6) cancers, who are the focus of the study.

The median GTV per patient was 75.2 mL (range, 1.2 to 3,090 mL). The median prescription dose was 41.4 Gy in six fractions (range, 27.7 to 60 Gy). Fifty-nine patients (87%) had refractory disease to one or more lines of standard chemotherapy, and nine patients (13%) were unsuitable for chemotherapy because of patient choice (n = 4) or medical contraindications (n = 5). Ten patients (15%) received further systemic treatment after SBRT for progressive disease, and one patient underwent a liver resection for disease that became resectable 3 months after SBRT.

All risk levels were investigated in the phase I study for all V_{eff} strata, with 13, 35, and 20 patients treated at the low, mid, and high V_{eff} strata, respectively. Forty-two patients were treated at the MSD. Liver was the dose-limiting normal tissue in 48 patients, whereas nonhepatic organs were dose limiting in 20 patients.

Acute/Subacute Toxicity

Overall, treatment was well tolerated, with no RILD, serious liver toxicity, or DLT observed. The estimated risk of serious liver toxicity was low (95% CI, 0 to 5.3%). Acute toxicity was minimal (Table 2). Grade 3 or higher acute toxicity was seen in seven patients (10%). Thrombocytopenia was seen in three patients (transient in two patients [grade 3] and leading to idiopathic thrombocytopenic purpura requiring splenectomy in another patient who took alternative medications during SBRT). Grade 3 liver enzymes were seen in two patients, both who developed extensive hepatic progressive disease. Similarly, four patients with hepatic disease progression had a decline in their liver function 3 months after SBRT (progression of Child's score to B [n = 3] or C [n = 1]).

Subacute liver pain within 3 months of SBRT occurred in six patients (grade 1, transient [n = 3]; grade 2 [n = 3]). Transient gastritis/esophagitis was the most common nonhepatic toxicity seen, occurring in 12 patients (grade 1, n = 5; grade 2, n = 5; grade 3, n = 2), who received a mean dose of 26.6 Gy to 0.5 mL of the stomach (range, 16.9 to 33.1 Gy). Grade 2 colitis was seen in a patient with metastatic pancreatic cancer who had a previous Whipple's operation and prior radiotherapy to celiac axis lymph nodes (54 Gy in 2-Gy fractions 6

Table 2. Biochemical Changes and Acute Toxicity Within 3 Months of Liver SBRT

	Grade							
	1		2		3		4-5	
CTC Toxicity	No.	%	No.	%	No.	%	No.	%
Biochemical changes								
Liver enzymes								
Baseline	27	40	2	3	0	0	0	0
Worst grade	33	49	12	18	2*†	3	0	0
Bilirubin								
Baseline	2	3	1	1	0	0	0	0
Worst grade	3	4	3	4	1†	1	0	0
Albumin								
Baseline	6	9	0	0	0	0	0	0
Worst grade	24	37	0	0	0	0	0	0
Platelets								
Baseline	9	13	0	0	0	0	0	0
Worst grade	25	37	1‡	1	1	1	1‡	1
Acute toxicity								
RILD	0	0	0	0	0	0	0	0
Liver pain	3	4	3	4	0	0	0	0
Chest wall pain	2	3	0	0	0	0	0	0
Skin	0	0	1	1	0	0	0	0
Gastritis/esophagitis	5	7	5	7	2	3	0	0
Colitis	0	0	1	1	0	0	0	0
Lethargy	15	22	12	18	1	1	0	0
Nausea	8	12	4	6	2	3	0	0

Abbreviations: SBRT, stereotactic body radiotherapy; CTC, Common Toxicity Criteria; RILD, radiation-induced liver disease.
*Transaminitis was seen in the presence of outfield intrahepatic disease progression.
†Increased transaminases and hyperbilirubinemia were seen in the presence of intrahepatic disease progression and no biliary dilatation on ultrasound imaging.
‡Thrombocytopenia was seen in two patients taking nonconventional medications; one spontaneously resolved after medications ceased and the other developed idiopathic thrombocytopenic purpura and had renormalization of the platelet count after splenectomy.

months before liver SBRT). The colitis manifested as abdominal discomfort, diarrhea, and a dumping syndrome occurring 1 month after SBRT and lasting for 3 months, at which point the patient developed intra- and extrahepatic disease progression. In this patient, the maximum SBRT dose and estimated cumulative dose (corrected for six fractions) to 0.5 mL of the bowel was 16.1 Gy and 38.3 Gy, respectively.

Late Toxicity

One patient developed a grade 4 duodenal bleed and grade 5 malignant small bowel obstruction 6 months after SBRT, associated with direct tumor invasion of the duodenum and tumor progression. Maximum doses to 0.5 mL of the stomach and duodenum were 32.1 Gy and 33.1 Gy, respectively. Another patient developed a grade 4 small bowel obstruction through an abdominal hernia, which resolved after a laparotomy (maximum dose to 0.5-mL bowel, 14.1 Gy).

Grade 2 nontraumatic rib fractures occurred in two patients, 6 and 23 months after SBRT (maximum dose to 0.5 mL of rib, 51.8 Gy and 66.2 Gy, respectively). Symptomatic improvement occurred over 9 months for both. The second patient also had transient grade 2 chest wall pain 6 months after SBRT. Late grade 2 dyspepsia occurred in one patient at 6 months and persisted for another 6 months (dose to 0.5 mL stomach, 29.5 Gy).

Survival

With a median follow-up of 10.8 months, 31 of 68 patients have died. The median survival was 17.6 months (95% CI, 10.4 to 38.1 months). The 18-month survival rate was 47% (95% CI, 32% to 61%). One-year survival rate for colorectal, breast, and other metastases was 63% (95% CI, 44% to 78%), 79% (95% CI, 36% to 94%), and 38% (95% CI, 14% to 62%), respectively (not statistically significant on univariate analysis; Fig 2). The median progression-free survival was 3.9 months (95% CI, 3.4 to 7 months).

Local Response

In 67 assessable patients at last follow-up, 33 patients (49%) had a sustained objective tumor response according to RECIST (four complete responses, 6%; 29 partial responses, 43%), with stable disease in 20 patients (30%; Fig 3). The median time to maximal response was 6.2 months (95% CI, 5.9 to 7.9 months), and the 12-month local control rate was 71% (95% CI, 58% to 85%; Fig 4). On univariate analysis, local control was improved in smaller-volume tumors ($<$ 75.2 mL; $P = .001$) and with higher delivered dose ($P = .01$). Fifty-six patients developed recurrences. The first site of recurrence was the treated tumor in eight patients (none isolated); 22 patients had isolated hepatic recurrences, and 34 patients (24 with preexisting extrahepatic disease) had extrahepatic recurrences (nine isolated, 23 both hepatic and extrahepatic).

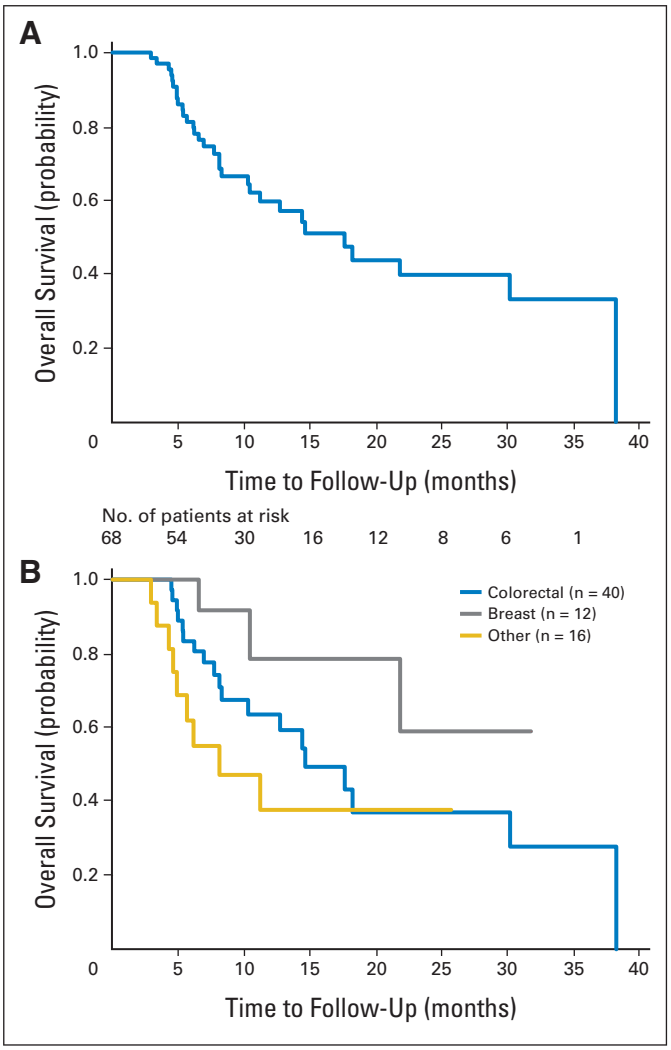

Fig 2. Overall survival of (A) all patients and (B) by diagnosis.

DISCUSSION

This prospective study determined the safety of six-fraction SBRT, using this individualized dose allocation, up to 60 Gy, for patients with unresectable liver metastases that were most often refractory to two or more lines of chemotherapy. The majority of tumors were not suitable for other local therapies, such as radiofrequency ablation, because of tumor size and location. Unique to this study is the irradiation of larger volumes of normal liver compared with most SBRT series (median effective liver volume irradiated, 39%; range, 8% to 67%) as a result of the acceptance of large liver tumors and allowance for individualized dose prescription. A critical volume model has been described previously as a method to preserve liver function after SBRT.[17] This model requires that 700 mL of uninvolved liver receive

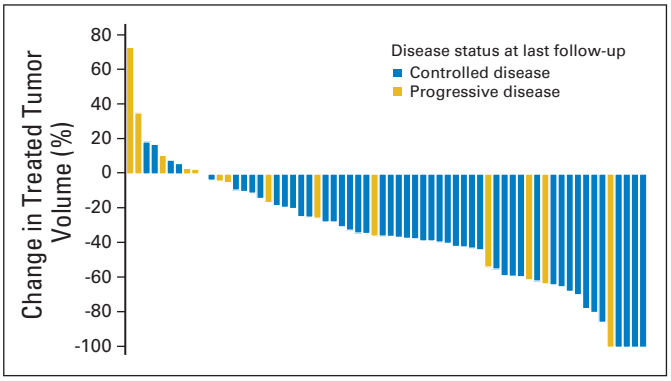

Fig 3. Maximum change in size of treated liver tumor with stereotactic body radiotherapy (n = 67) compared with local control status at the time of last follow-up.

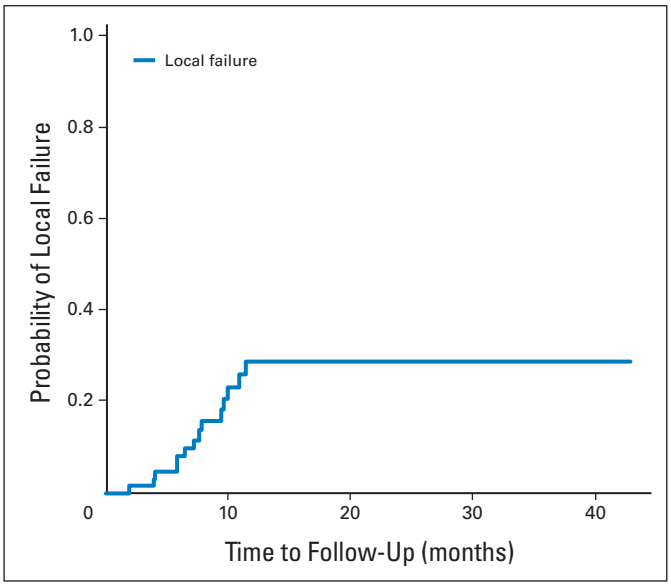

Fig 4. Tumor control rate using cumulative incidence analysis for competing risks of death.

less than 15 Gy in three fractions, which often excludes patients with large metastases or small uninvolved liver volumes from SBRT. In our study population, the mean dose received by 700 mL of uninvolved liver was 14.1 Gy in six fractions, and 35% received more than 19 Gy to 700 mL of liver. Treatment was well tolerated by patients, with no related serious toxicity observed, thus a maximum-tolerated dose of this individualized six-fraction SBRT strategy has not been reached. The estimate of serious liver toxicity risk is low (95% CI, 0 to 5.3%), despite the estimated possibility for rates of up to 20%, based on prior hyperfractionated radiotherapy experience.[29] This discrepancy may partially be explained by the fact that not all patients were treated at the highest risk levels, but may also be due to limitations in the models estimating risk and correcting for differences in dose per fraction. This emphasizes that trials of SBRT are required to determine toxicity estimates, as the risks of SBRT cannot be assumed based on experience from other fractionation schedules.

The risk of luminal gastrointestinal toxicity is likely higher with large dose per fraction SBRT compared with fractionated lower-dose radiation therapy. In our series, luminal gastrointestinal structures often limited the dose that could be delivered safely. With IGRT and strict dose constraints for the luminal gastrointestinal structures, no serious SBRT-related toxicity was seen in the absence of progressive disease. In the latest Michigan series of 128 patients treated with individualized hyperfractionated radiation therapy (1.5 Gy twice daily),[16] upper gastrointestinal bleeding was seen more commonly than liver toxicity (5% *v* 4%). The median survival of 47 patients with CRC metastases was 17.2 months, with progressive disease occurring in 24 (57%) of 45 assessable patients.

The 12-month tumor control of 71% observed in our study is lower than that of other SBRT series, likely as a result of the inclusion of larger tumors. Variability in local control definition may also explain some differences. Despite the inclusion of patients with a poor prognosis, five patients have had no evidence of any progression 2 or more years after SBRT. The 1-year survival rate of 60% is also better than expected in this group of patients. Similar to other studies, tumor control and survival were less for CRC versus breast metastases.

Other SBRT series have generally included patients with smaller tumors (8 mL to 54 mL)[31,32] than the tumors in our study (median volume, 75.2 mL; maximum volume, 3,079 mL). Despite this, rates of serious toxicity are similarly low. Grade 3 or worse liver toxicity has only rarely been reported after SBRT. Similar to our experience, treatment-related pain has been previously seen,[18,19,33-35] although not in most prior experience.[36,37] Pain may occur secondary to liver capsule edema, rib fracture, or nerve injury, and high doses to these tissues should be avoided if possible. To reduce risk of pain and fracture, rib dose in our present studies is now limited to 50.4 Gy in six fractions. The low overall incidence of toxicity in our experience is likely due to the individualization of radiation doses, dose constraints of luminal tissues, and strict adherence to IGRT.

Lower radiation doses were associated with worse survival and local control. Further reductions in the volume of normal tissues irradiated to high doses that may be possible with technological advances in IGRT and motion management strategies to improve accuracy and precision of SBRT may allow higher doses to be delivered and possibly improve outcomes. Pharmacologic manipulation of tumor and normal tissue responses to radiation, and using SBRT earlier in the natural history of cancer progression (eg, before second-line chemotherapy), may also lead to improved outcomes.

Individualized six-fraction liver SBRT, within the dose ranges studied, is safe in liver metastases of various sizes. Phase II and III studies are warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

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Financial support: Laura A. Dawson
Administrative support: Laura A. Dawson
Provision of study materials or patients: John J. Kim, Robert Dinniwell, James Brierley, Rebecca Wong, Bernard Cummings, Jolie Ringash, Laura A. Dawson
Collection and assembly of data: Mark T. Lee, Gina Lockwood, Regina V. Tse, Laura A. Dawson
Data analysis and interpretation: Mark T. Lee, John J. Kim, James Brierley, Gina Lockwood, Jolie Ringash, Laura A. Dawson
Manuscript writing: Mark T. Lee, John J. Kim, Robert Dinniwell, James Brierley, Gina Lockwood, Rebecca Wong, Bernard Cummings, Jolie Ringash, Regina V. Tse, Jennifer J. Knox, Laura A. Dawson
Final approval of manuscript: Mark T. Lee, John J. Kim, Robert Dinniwell, James Brierley, Gina Lockwood, Rebecca Wong, Bernard Cummings, Jolie Ringash, Regina V. Tse, Jennifer J. Knox, Laura A. Dawson

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