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Clinical Evaluation

Stereotactic body radiotherapy for primary and metastatic liver tumors — the Mayo Clinic experience

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Introduction: To better understand the efficacy of liver SBRT we reviewed our prospectively collected institutional SBRT database.

Methods: Between May 2008 and March 2013, 80 patients with 104 liver lesions received SBRT. The Kaplan-Meier method estimated local control (LC), overall survival (OS). Cox proportional hazards regression models identified factors associated with LC and OS.

Results: The median follow-up for living patients was 38.6 months. Patients had primary (n=17) or metastatic (n=63) tumors. The median tumor size was 2.7 cm (range, 0.6-14.0). The 1 and 4 year rates of LC were 89.4% and 88%, respectively. Colorectal (CRC) metastasis was associated with lower rates of LC (p=0.013). OS at 1 and 4 years was 78% and 25%, respectively. Patients with CRC metastases had higher rates of OS (p=0.03). The occurrence of severe acute and late toxicity was 3.8% and 6.3%, respectively.

Conclusions: SBRT should be studied in prospective clinical trials compared with other liver-directed treatment modalities.

Keywords: stereotactic body radiotherapy, radiation therapy, liver metastasis, liver tumor, local control, radiation-induced liver disease

1. INTRODUCTION

More than fifty-percent of patients with metastatic cancer develop liver metastases during the course of their disease (Buchler et al. 2002). Some tumor types have a high propensity for metastatic spread to the liver, such as colorectal cancer (CRC). Without any treatment, the estimated 5-year overall (OS) with liver metastasis from CRC is less than five percent (Grothey et al. 2004; Norstein and Silen 1997; Stangl et al. 1994). Survival rates for patients with liver metastasis from CRC have significantly improved with advances in segmental liver resection and improved systemic therapy. In select CRC patients with liver metastases undergoing

potentially curative resection, five-year survival rates are 30-60% with acceptable morbidity and mortality. (Choti et al. 2002; Jarnagin et al. 2002; Simmonds et al. 2006; Wei et al. 2006) Unfortunately only small subsets of patients with metastatic disease are considered candidates for surgical resection (Al-Asfoor and Fedorowicz 2007).

As an alternative to metastasectomy, local ablative therapies with radiofrequency ablation (RFA) and cryoablation are becoming more commonly utilized given the minimally invasive nature of the procedure and promising results. Prospective data are limited but retrospective data have shown local control (LC) rates greater than 80% with cryoablation or RFA, depending on the tumor size and proximity to large vessels(Bilchik et al. 2000; Flanders and Gervais 2010; Tanis et al. 2014; Wood et al. 2000). A single prospective study evaluating unresectable CRC metastases limited to the liver suggests higher survival rates and less disturbance of quality of life with local ablation compared to chemotherapy alone(Ruers et al. 2007). Two clinical trials by the European Organization for Research and Treatment of Cancer (EORTC) in patients with metastatic CRC compared surgery and RFA for liver metastasis and found similar rates of LC between the two modalities(Tanis et al. 2014). Similar to surgical series, most data are limited to patients with CRC.

Experiences with radiation treatment of liver metastases began with several Radiation Therapy Oncology Group (RTOG) trials evaluating the use of whole liver radiation for palliation of symptomatic tumors(Turek-Maischeider and Kazem 1975; Borgelt et al. 1981; Leibel et al. 1987). Further studies with partial liver dose escalation were safely conducted leading to the development of stereotactic body radiotherapy (SBRT) for treatment of liver metastases (Ben-Josef 2005; Dawson et al. 2000; Dawson et al. 2002). Several institutions have reported liver SBRT outcomes with a variety of primary histologies and SBRT dose schedules with 1-year LC rates ranging from 67% to 100%(Berber et al. 2013; Chang et al. 2011; Herfarth et al. 2001; Hoyer et al. 2006; Mendez Romero et al. 2006; Wulf et al. 2006). A phase I/II liver SBRT dose escalation trial was conducted and safely achieved a maximal dose of 60 Gy in 3 fractions with no dose limiting toxicity(Schefter et al. 2005). After a median follow up of 15 months, the two-year local control (LC) was 92% for all patients and 100% for tumors less than 3 cm(Rusthoven, Kavanagh, Cardenes, et al. 2009). SBRT results for primary hepatic lesions have also been reported with high rates of LC for cholangiocarcinoma and hepatocellular carcinoma (HCC) (Bujold et al. 2013; Kopek et al. 2010). With growing interest and more frequent use of SBRT for liver tumors, we report our institutional experience with SBRT of primary and metastatic tumors involving the liver.

2. METHODS AND MATERIALS

2.1. Patients

This study was approved by our institutional review board. Our prospectively collected SBRT database was queried for all patients who received SBRT for liver tumors between May 2008 and March 2013. All patients underwent a complete history, physical examination, and imaging with computed tomography (CT), positron emission tomography (PET), and/or magnetic resonance imaging (MRI) of the abdomen. All patients had normal liver function and ECOG performance status of 1 or greater. Patients with primary liver tumors had a Child-Pugh class of A. Patients with prior resection, local ablative therapy, chemotherapy or active non-hepatic disease were included.

2.2. SBRT Technique

In most cases, gold fiducial markers were percutaneously placed near the tumor for tumor localization with orthogonal kV radiographs or cone-beam CT imaging. Simulation and immobilization were performed using the Body-Fix whole-body immobilization system (Medical Intelligence, Schwabmunchen, Germany). Fiducial marker and/or tumor motion was assessed using fluoroscopy and/or four-dimensional CT (4DCT) imaging with Varian real-time position management (Palo Alto, CA). For tumors with motion > 1 cm, abdominal compression or breath-hold technique were typically used. A gross tumor volume (GTV) included all visualized tumor as seen on CT, MRI or PET imaging. Internal target volume (ITV) was created, accounting for tumor motion as seen on the 4DCT for patients treated with free breathing or tumor variability on multiple (typically 3) breath hold CT scans. The clinical tumor volume (CTV) was defined as GTV or ITV. A planning target volume (PTV) with a 5 mm margin was created from the CTV to account for setup error and could be increased to up to 10 mm at the discretion of the treating physician (primarily based on the reliability of breath hold CT scans). The total dose and dose per fraction were at the discretion of the treating radiation oncologist. Organs at risk (OAR) include the stomach, small bowel, large bowel, spinal cord, chest wall and esophagus with dose constraints dependent on the total number of fractions as previously reported and consistent with American Association of Physicists in Medicine Task Group 101 guidelines (Barney et al. 2012; Benedict et al. 2010). The treatment goal was to cover 95% of the PTV with the prescription dose. Initially, three-dimensional conformal radiation plans with 9-12 co-planar static fields were used. More recently, intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT)

planning was utilized. There was no association between radiation dose and planning technique utilized. Radiation plans were created using the Eclipse (Varian Medical Systems, Palo Alto, CA) treatment planning software. Cone beam CT image guidance was utilized for localization of tumor targeting and position of organs at risk. Dose-volume histograms (DVH) were created for each patient for statistical analysis.

3. TOXICITY AND FOLLOW UP

Patient follow up schedule was at the discretion of the treating physician and typically began approximately 2-3 months after completion of SBRT and included subsequent CT, MRI or PET scan every 3-6 months. In most cases, the initial imaging modality utilized was MR or PET imaging with CT imaging typically used after establishment of tumor control for distant tumor surveillance. Tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Local failure (LF) was defined as failure within 1 cm of the primary tumor. Regional failure was defined as failure within the liver further than 1 cm from the treated tumor. Distant failure was defined as progression of previous extra-hepatic metastasis or new lesions outside of the liver. Toxicity was scored using National Cancer Institute (NCI) Common Terminal Criteria for Adverse Events (CTCAE) version 3.0 including the highest grade at any time point during patient treatment or follow up. Acute and late toxicities were defined as within and after 3 months following SBRT, respectively.

4. STATISTICS

Rates of LC, OS and progression free survival (PFS) were estimated using the Kaplan-Meier method. LC control was defined as absence of local progression and measured from the last date of SBRT to the date of local progression, death or last follow up. OS was measured from the last date of SBRT to patient death or last follow up. PFS was defined as absence of local, regional, or distant progression or death and measured from the last SBRT date to the date of last documented follow up, any form of progression, or any cause of death. For patients with multiple liver tumors treated with SBRT (simultaneously or sequentially), LC was calculated for each lesion from the time of treatment, while OS was calculated for each patient from the time of first SBRT treatment. Univariate analysis was used to identify predictors of OS or LC using the Cox proportional hazard model. Multivariate analysis was performed using the backward selection method incorporating prognostic factors with p value < 0.2. A P-value < 0.05 was considered statistically significant. JMP software (SAS analytics) version 10.0.0 was used for statistical analysis. For evaluation and normalization of radiation dose and fractionation biologic effective dose (BED) 10 Gy was calculated using the following equation:] (n= number of fractions, d=dose per fraction, was 10 for early responding tissue) and was used to assess tumor response. Because BED calculation may not perform optimally for large dose per fraction, single fraction effective dose (SFED) calculations were also used with the following equation to evaluate patient toxicity: (D=total dose, n=number of fractions, D_q represents the radiosensitivity of the tissue for which 2.1 was used (Jirtle et al. 1982)).

5. RESULTS

5.1. Patient Characteristics

Eighty patients with 104 primary and secondary tumors were analyzed. Median follow up for living patients was 38.6 months (range, 3-59). At the time of analysis, 47 patients were deceased (59%). Baseline patient and treatment characteristics are listed in Tables 1 and 2. For patients with liver metastases treated with SBRT, the most common primary site was colorectal adenocarcinoma (n=19, 24%), melanoma (n=15, 19%), and non-small cell lung cancer (n=6, 8%). Most patients had prior chemotherapy (n=61, 76%) with 21% of patients receiving at least second-line chemotherapy. Fifteen patients (20%) had prior hepatic resection. Eighteen patients (22.5%) had prior local treatment including percutaneous and open RFA. Eight patients (10%) received multiple courses of local liver therapy including surgery, RFA, and radioembolization. For 13% of lesions, SBRT was administered for LF after surgery or other local ablative therapy. Thirty-one percent (n=25) of patients had active non-hepatic metastatic disease at the time of treatment. The most frequent dose schedules were 60 Gy in 3 fractions (n=29, 28%), 60 Gy in 5 fractions (n=29, 28%), and 50 Gy in 5 fractions (n=22, 21%). The median BED10Gy and SFED for all treatments were 132 Gy (range, 66-180 Gy) and 51.6 Gy (range, 28-55.8 Gy) (Table 2).

6. LOCAL AND REGIONAL CONTROL

Local control is shown in Figure 1. The 1 and 4 year rates of LC were 89.4%, and 88%, respectively (Figure 1). Ten LFs were observed with one occurring at four months and the remaining between 12 and 23 months. RECIST graded response after SBRT was complete response in

Table 1. Patient Characteristics

	Overall
Age, median years (range)	62.8 (37.9-92.1)
Gender, n (%)	
Male	49 (47.1)
Female	55 (52.9)
Number Lesions Treated, n (%)	
1	64 (80.8)
2	10 (12.5)
≥3	6 (7.5)
Mean tumor size, cm (SD)	3.1 (2.0)
Primary Tumor Site, n (%)	
Primary Liver Tumor	17 (21.2)
Metastatic Liver Tumor	63 (78.8)
Colorectal	19 (23.7)
Melanoma	15 (18.8)
Bile Duct	16 (20.0)
Lung	6 (7.5)
Pancreas	5 (6.3)
Other	19(23.7)
Recurrent residual lesion, n (%)	
Recurrent or Residual	13 (12.5)
De novo	91 (87.5)
Chemotherapy prior to SBRT, n (%)	
Yes	80 (76.9)
No	24 (23.1)
Active Non-hepatic disease, n (%)	
Yes	74 (71.2)
No	30 (28.8)

Table 2. Treatment Characteristics

	Overall
GTV volume (cc), median (range)	18.2 (0.3-767.5)
PTV volume (cc), median (range)	67.1 (8.6-1135.0)
Total Dose (cGy), median (range)	6000 (2800-6000)
Total Dose (cGy), n (%)	
5000	28 (26.9)
6000	58 (55.7)
Other	18 (17.3)
Number of fractions, n (%)	
1	3 (2.9)
3	42 (40.4)
4	1 (1.0)
5	58 (55.8)
Dose fraction (cGy), median (range)	1200 (750-2800)
BED 10 (Gy), median (range)	132 (65.6-180)
SFED (Gy), median (SD)	51.6 (28-55.8)
Tumor motion control, n (%)	
Breath hold	28 (26.9)
4D-Abdominal Compression	63 (60.6)
4D-Free Breathing	13 (12.5)
Treatment Planning, n (%)	
IMRT	13 (12.5)
VMAT	39 (37.5)
3D Conformal	52 (50.0)

*GTV=gross tumor volume; PTV=planning target volume; BED=biologically effective dose; SFED=single fraction equivalent dose; IMRT=intensity-modulated radiation therapy; VMAT=volumetric modulated arc therapy;

35% of patients (n=37), partial response in 51% of patients (n=53), stable disease in 11% (n=11) and progressive disease in 3% (n=3) of patients. LF was more frequent in the colorectal group (n=6) with a significant decrease in LC compared to the overall group. The 1, 2, and 4 year rates of LC for patients with CRC versus those with different histology were 76 vs 94%, 71% vs 94% and 71% vs 94%, respectively (p=0.006) (Figure 1). Tumor size greater than 3 cm was associated with decreased LC which was not statistically significant (HR=2.5; 95% CI 2.5-0.67, p=0.17). On univariate analysis, gender, size, $BED_{10Gy,}$ SFED, and tumor immobilization technique did not significantly predict for LC (Table 3). Regional progression in the liver was seen in 55% of patients and systemic progression was seen in 53% of patients. Median time to liver and systemic progression was 11 and 15 months, respectively.

7. OVERALL AND PROGRESSION FREE SURVIVAL

Median OS for the entire group was 19 months following SBRT. Kaplan Meier estimates of OS at 1, 2, and 4 years are 78%, 44%, and 25%, respectively (Figure 2). Median PFS was 7.8 months for the entire group. PFS at 1, 2, and

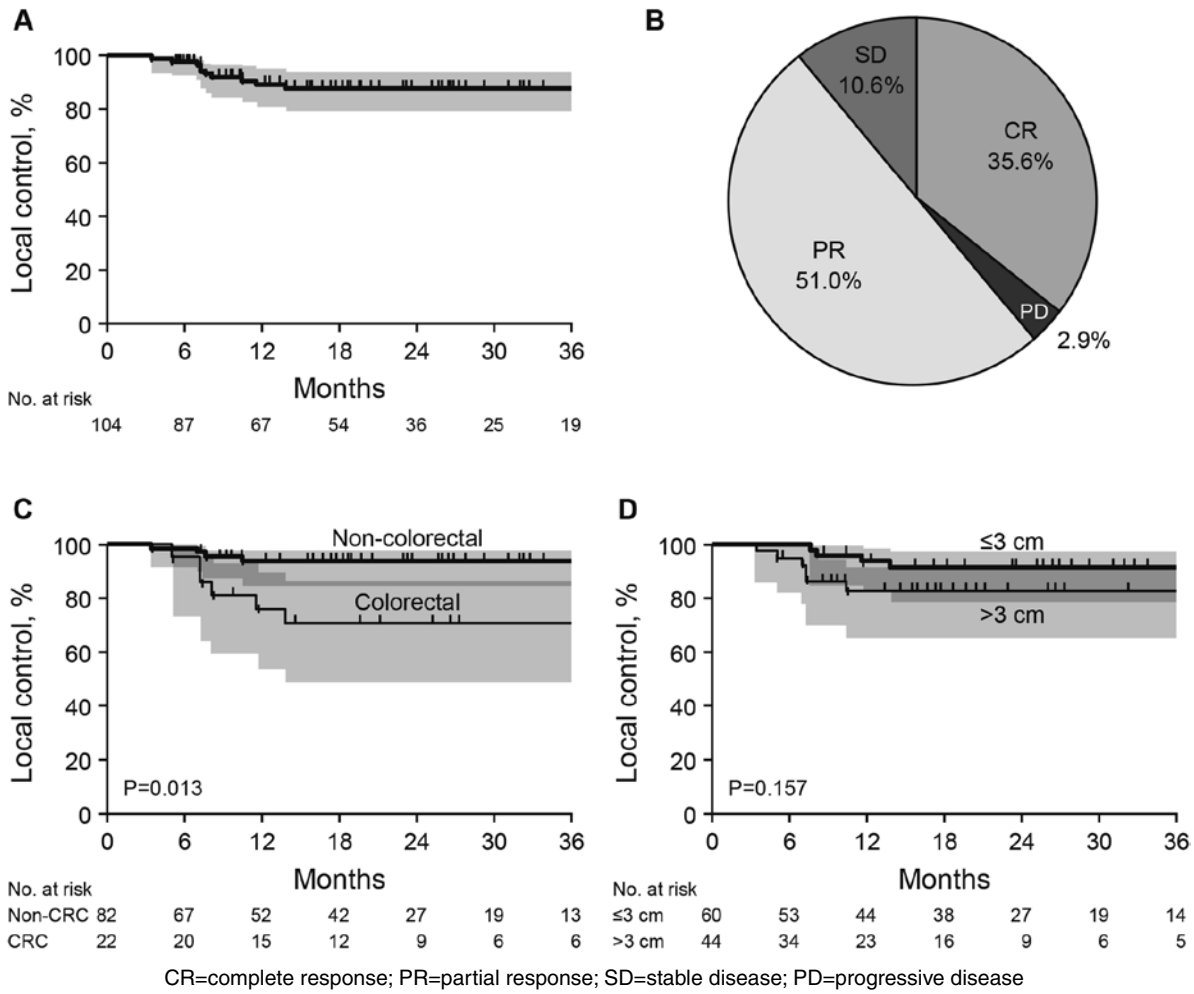

Figure 1. A. Local control for all patients. B. Tumor response based on RECIST criteria C. Local control for patients with colorectal cancer vs. all others. D. Local control for patients with tumor > or ≤ 3cm. CRC=colorectal cancer

4 years was 32%, 12%, and 11%, respectively (Figure 2). Patients with non-CRC primary had lower OS compared to patients with CRC primary with a median survival of 18 vs. 59 months (p=0.014, HR 2.73; 95% CI 1.2-6.1) (Figure 2). No difference in PFS was observed between the various histologies. Multivariate analysis showed patients with CRC had higher OS compared to all other subgroups (p=0.02, HR 0.51; 95% CI 0.25-.97) (Table 4).

8. TOXICITY

Acute gastrointestinal (GI) toxicity ≥ grade 2 occurred in 33% (n=27) of patients with the majority representing grade 2 nausea and emesis (n=24). The rate of grade ≥ 3 acute toxicity was 3.8% including two patients with grade 3 gastric ulcers and one patient with a grade 4 gastric perforation and subsequent sepsis (Table 5). In the three patients with gastric ulceration or perforation, the mean SFED for stomach D_{1cc} and D_{max} was 21 Gy and 30.8 Gy compared to 10.4 Gy and 13.5Gy for patients without, respectively. There was no acute non-GI toxicity greater than grade 2. Two of the 3 patients with acute gastric ulceration or perforation received Bevacizumab within 4 weeks before SBRT.

Late toxicity was most frequently low grade and included grade 1 to 2 chest wall pain (n=6) and grade 1-2 abdominal pain (n=9). The rate of late grade 3 to 5 late toxicity was 6.3% (n=5) including grade 3 biliary stenosis (n=1), grade 4 perforated stomach ulcer (n=1), grade 4 perforated duodenal ulcer (n=2), and grade 5 fulminant liver failure (n=1) (Table 5). For patients with grade 3 and 5 liver toxicity the SFED for

Table 3. Variable association with Local Recurrence-Free Survival

				Univariate Cox Models	
	Lesions	# Local Failure	2 year LC	P-value	Hazard Ratio (95% C.I.)
Overall	104	10	88.0%(81.2-95.3)	--	--
Site				0.013	
Non-CRC	82	4	93.8%(88.1-99.9)		1.0(reference)
CRC	22	6	70.8%(53.6-93.5)		4.9(1.4-19.4)
Size (cm)				0.17	
≤ 3	60	4	91.6%(84.1-99.8)		1.0(reference)
> 3	44	6	82.7%(70.8-96.5)		2.5(0.7-9.3)
Number of Lesions					
1	49	5	87.1%(72.3-94.6)		1.0(reference)
2	22	4	79.1%(55.6-91.9)		1.5 (0.36-5.5)
≥3	33	1	96.3%(77.9-99.5)	0.18	0.3 (0.01-1.6)
BED10 (Gy)				0.35	
≤100	31	5	76.9%(60.8-97.2)		1.0(reference)
>100	73	5	91.9%(85.5-99.0)		0.4(0.11-1.3)
SFED					
<50	46	6	83.1%(67.0-92.2)		1.0(reference)
≥50	58	4	92.0%(80.5-97.0)	0.35	0.55(0.14-1.9)

* The overall test of association of site with local recurrence-free survival is p=0.10.
†CRC=colorectal; LC=local control; BED=biologically effective dose; SFED=single fraction equivalent dose

mean liver (liver subtract GTV) and liver D33cc was 11.3 Gy and 16.9 Gy compared to 6.5 Gy and 8.2 Gy for patients with < grade 3 or no toxicity, respectively. The volume of liver receiving 15 Gy or less was 564 cc and 1051 cc for patients with grade 3 and 5 liver toxicity, respectively. Both patients had a Child-Pugh score of 5 prior to SBRT with normal synthetic liver function. The patient with late stomach perforation had a raw $D_{1\,cc}$ and SFED D_{1cc} and D_{max} of 36 Gy, 32.6 Gy and 40.7 Gy compared to 16.3 Gy, 10.6 Gy and 13.8 Gy for those without, respectively. The duodenal mean raw D_{1cc} and SFED D_{1cc} and D_{max} for the two patients with late duodenal perforation was 15.7 Gy, 9.4 Gy and 13 Gy compared to 11.4 Gy, 5.8 Gy and 11 Gy without perforation, respectively. The patient with later gastric perforation and 1 of the 2 patients with late small bowel perforation received Bevacizumab within 1-4 weeks of SBRT. The patient with grade 5 liver failure had a history of steatohepatitis, bone marrow transplant and chemoembolization prior to SBRT, but no further liver-directed therapy after SBRT. Eighteen months following liver SBRT the patient developed new cirrhosis, portal hypertension and ascites without evidence of liver cancer or hepatomegaly. Alkaline phosphatase, aspartate transaminase, alanine transaminase and total bilirubin were mildly elevated. This progressed rapidly and the patients expired secondary to massive hemorrhage due to disseminated intravascular coagulation.

9. DISCUSSION

Consistent with previous reports, our study demonstrates excellent LC with liver SBRT as local ablative therapy for liver tumors. Previous studies reported LC rates of 67% to 100% at one year with varying radiation dose schedules (Berber et al. 2013; Chang et al. 2011; Herfarth et al. 2001; Hoyer et al. 2006; Mendez Romero et al. 2006; Wulf et al. 2006). Wulf *et al.* demonstrated a non-significant difference in LC based on dose with a 12 month LC of 100% in a high-dose group (37.5Gy/3 or 26 Gy/1) compared to 86% in the low-dose group (30Gy/3 or 28Gy/4) (Wulf et al. 2006). Further evaluation by Chang et al found rates of LC in colorectal metastasis were impacted by total dose, dose per fraction, and BED (Chang et al. 2011). Rusthoven *et al.*

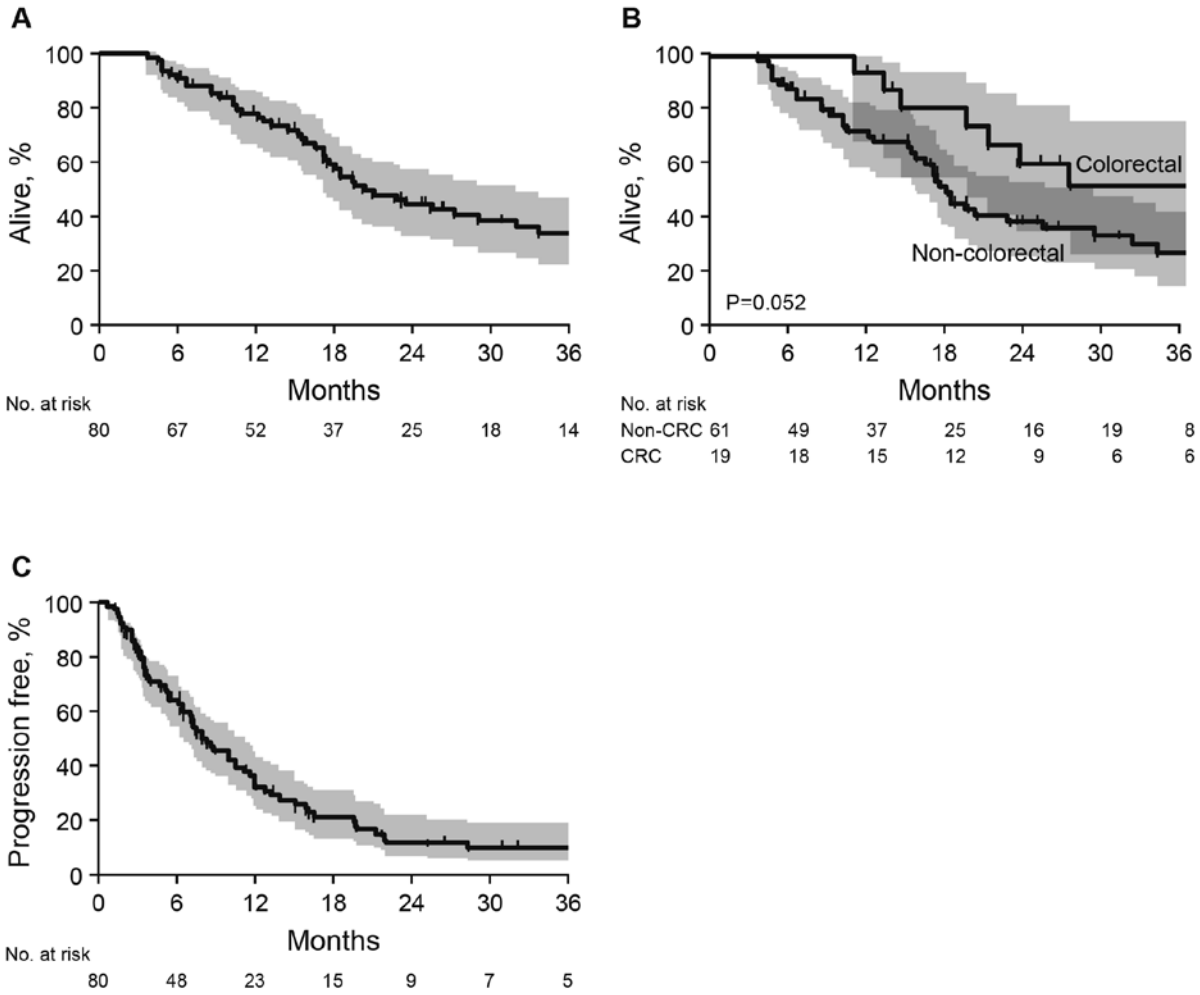

Figure 2. A. Overall survival for all patients from the completion of SBRT. B. Overall survival comparing patients with colorectal cancer primary compared to all others. C. Progression free survival following SBRT for the entire group.

reported a phase I/II dose escalation trial and found 1- and 2-year LC rates of 95% and 92%, respectively, when using doses of 60 Gy in 3 fractions(Rusthoven, Kavanagh, Burri, et al. 2009). Tumors less than 3 cm had a LC rate of 100%. We did not observe a correlation between LC and BED, SFED or tumor size; although tumors less than 3 cm and patients treated with BED_{10Gy} > 100 had a non-statistically significant improvement in LC. This is most likely a reflection of the small sample size and limited number of events. On univariate analysis, LC was decreased for patients with CRC compared to other histologies, similar to previous reports (Chang et al. 2011; Wulf et al. 2006).

While no direct comparison has been made, SBRT compares well with studies evaluating ablative therapy with interventional radiology techniques. Relative contraindications for interventional ablative therapies include tumor size and proximity to large vessels and vital structures (Bilchik et al. 2000; Bilchik, Wood, and Allegra 2001; Joosten et al. 2005; Wood et al. 2000; Mulier et al. 2005). A meta-analysis of 95 studies including 5,224 liver tumors treated with percutaneous and intraoperative RFA showed local recurrence rates of 4-16% for tumors < 3cm, 22-26% for tumors 3-5 cm, and 50-60% for tumors >5 cm in size, respectively. LC with surgery and RFA appear similar as shown in a retrospective review of the EORTC 40004 and 40983 clinical trials. Tanis *et al.* compared LC of RFA vs. surgery in patients with liver lesions < 4 cm in size and no extrahepatic disease. Similar actuarial rates of LF were observed, 6% vs. 5.5%, respectively; with worse LF of 21.4% for tumors 3-4 cm treated with RFA (Tanis et al. 2014). SBRT is an attractive modality as it is less invasive and has fewer restrictions in tumor size and proximity to large vessels. Currently, the International Liver Tumor Group

Table 4. Variable association with Overall Survival

					Univariate Cox Models		Multiple Variable Cox	
	Patients (N)	Deaths (N)	Median OS (yrs.)	2 yr. OS	P-value	HR (95% C.I.)	P-value	HR (95% C.I.)
Overall	80	45	1.7	44.4%(33.8-58.4)	--	--	--	--
Gender								
Male	41	23	1.5	39.6%(25.7-60.9)		1.2(0.6-2.1)		
Female	39	22	1.7	49.3%(34.9-69.8)	0.58	1.0(reference)	--	--
Age								
> 60	50	33	1.5	35.0%(23.2-52.9)		1.8(0.97-3.7)		1.9 (1.03-4.0)
≤ 60	30	12	3.3	62.4%(45.4-85.8)	0.06	1.0(reference)	0.04	1.0(reference)
Non-liver met								
No	25	15	1.9	42.7%(25.7-70.9)		0.8(0.4-1.4)		
Yes	55	30	1.7	45.3%(32.7-62.6)	0.41	1.0(reference)	--	--
Site								
Non-CRC	61	37	1.5	39.3%(27.8-55.6)		2.2(1.05-5.0)		2.3 (1.2-5.3)
CRC	19	8	4.9	60.8%(40.6-91.2)	0.04	1.0(reference)	0.02	1.0(reference)
Lesion Type								
Recurrent	10	8	2.3	42.8%(31.0-57.6)		1.3(0.5-3.2)		
De Novo	70	37	1.7	57%(32.6- 100.0)	0.56	1.0(reference)	--	--
Number of Lesions								
1	45	26	1.5	33.4%(19.9-50.3)		1.0(reference)		
2	13	9	1.9	48.1%(22.1-75.1)		1.03 (0.5-2.1)		
≥3	22	10	2.8	63.9%(40.9-81.9)	0.34	0.6 (0.3-1.2)	--	--

*The overall test of association of site with Overall Survival is p=0.10. †CRC=colorectal; OS=overall survival; mets=metastasis

is evaluating liver SBRT versus RFA for CRC liver metastasis in a randomized clinical trial.

Many surgical series with segmental hepatectomy for metastatic CRC report impressive median survival greater than 50 months. In the EORTC 40983 trial, 364 patients with metastatic CRC, 4 or less liver metastases, and no extrahepatic disease were randomized to hepatic resection with or without chemotherapy (Nordlinger et al. 2013). Median survival in the surgery alone arm was 54.3 months and 5-year OS was 47.8%. Information regarding non-CRC metastatic liver tumors is less established. Our data, along with a growing body of evidence, suggest liver SBRT as an excellent alternative for patients who are not optimal surgical candidates. The median OS for patients with CRC metastasis in the present study was 59 months, similar to surgical series. In addition, most patients in our series received several lines of chemotherapy prior to SBRT, had previous liver resections or other ablative techniques, and had extrahepatic disease.

Most patients in our series tolerated treatment well with severe acute and late toxicity ≥ grade 4 of 4% and 6%, respectively. This is comparable to RFA reports of severe complications ranging from 6 to 9% (Wong et al. 2010). The most frequent serious complication in our series was gastrointestinal perforation. Bevacizumab, a known risk factor for bowel perforation, was used within 7-60 days of SBRT treatment in three of the four patients with perforation (Hapani, Chu, and Wu 2009; Barney et al. 2013). While low grade toxicity is primarily reported in most SBRT series, more severe toxicity such as bowel ulceration, perforation or stenosis as a result of SBRT has been documented (Hoyer et al. 2006; Kopek et al. 2010). RTOG 0438 used a small bowel and stomach constraint of 37 Gy as maximum dose for 1 cc of both organs. The initial reported toxicity includes 2 of 26 patients with grade 3 GI toxicity including enteritis and colonic hemorrhage(Katz et al. 2012). In patients with cholangiocarcinoma, Kopek *et al.* reported a higher mean D_{max} in patients with > grade 2 ulceration (37.4 Gy) compared to patients with < grade 2 toxicity (25.3 Gy) and thus recommend < 1 cc of duodenum to receive 21 Gy or more in 3 fractions. The International Liver Tumor Group developed a randomized clinical trial comparing liver SBRT and

Table 5. Severe Acute and Late Toxicity

Organ	Timing	Grade	Type	OAR, Dmax Gy (SFED)	OAR, D9cc Gy (SFED)	OAR, D1cc Gy (SFED)	Rx Dose/ Fraction	SBRT Technique	Primary Tumor	Other
Stomach	Acute	4	Gastric perforation and sepsis	36.2 (27.8)	21.4 (13)	28.3 (19.9)	60 Gy/5	3D CRT	Melanoma	Bevacizumab within 4 weeks before SBRT
		3	Gastric Ulcer	39 (30.6)	19 (10.6)	29.7 (21.3)	60 Gy/5	VMAT	Bile Duct	
		3	Gastric Ulcer	35.1 (30.9)	19.7 (15.5)	25.9 (21.7)	60 Gy/3	3D CRT	Melanoma	Bevacizumab within 3 weeks before SBRT
	Late	4	Gastric Perforation	44.9 (40.7)	26.2 (22)	36.8 (32.6)	60 Gy/3	3D CRT	Ovary	Bevacizumab within 1 week after SBRT
	Timing	Grade	Type	OAR, Dmax Gy (SFED)	OAR, D9cc Gy (SFED)	OAR, D1cc Gy (SFED)	Rx Dose/ Fraction	SBRT Technique	Primary Tumor	Other
Small Bowel	Late	4	Bowel Perforation	21.6 (13.2)	9.1 (0.7)	17.6 (9.2)	50 Gy/5	3D CRT	Breast	
		4	Bowel Perforation	16.9 (12.7)	5.9 (1.7)	13.8 (9.6)	60 Gy/3	3D CRT	Melanoma	Bevacizumab within 4 weeks before and 3 months after SBRT
	Timing	Grade	Type	Liver-GTV Dmax Gy (SFED)	Liver-GTV D33 cc [Gy] (SFED)	Liver-GTV mean dose Gy (SFED)	Rx Dose/ Fraction	SBRT Technique	Primary Tumor	Other
Hepatobiliary	Late	3	Biliary Stenosis	56.8 (48.4)	28.5 (20.1)	22.6 (14.2)	50 Gy/5	3D CRT	Bile Duct	
		5	Liver Failure	65.1 (56.7)	22.1 (13.7)	16.9 (8.5)	60 Gy/5	VMAT	Bile Duct	Prior chemoembolization and bone marrow transplant

†OAR=organ at risk; Dmax=maximum dose; SFED= single fraction effective dose; Rx=prescription; SBRT=stereotactic body radiotherapy; 3D CRT=3D conformal radiotherapy; VMAT=volumetric modulated arc therapy

RFA for CRC liver metastasis. In this protocol, the $D_{1\ cc}$ of the esophagus, stomach, duodenum, and bowel was set at 21 Gy. In the present study, stomach perforation was more frequent than small bowel (n=4 vs. n=2). All patients with stomach perforation had a $D_{1\ cc} > 21$ Gy (range, 26-36.8 Gy) but no patients with small bowel perforation exceeded $D_{1\ cc} > 21$ Gy (17.6 and 13.9 Gy). While there is no standard dose constraint for organs at risk, effort should be made to minimize the stomach and bowel dose as much as possible, especially in patients who have received or may receive bevacizumab therapy in the future. Specialized radiation planning techniques such as static field or volumetric IMRT may be a means to minimize high dose radiation to OAR. Though in our study, rates of severe toxicity were numerically greater in patients receiving 3D CRT planned SBRT, there was no statistically significant difference between the planning techniques utilized. Each SBRT plan should be individualized based on patient anatomy to find the best delivery technique to deliver effective dose to tumor and minimize OAR irradiation.

In our series, 2 patients (2.5%) experienced grade ≥ 3 liver toxicity following SBRT, including 1 patient with grade 5 fulminant liver failure 18 months following treatment. While the exact etiology of the liver failure is uncertain, SBRT was likely a contributing factor. Rusthoven *et al.* maintained at least 700 cc of normal liver receiving less than 15 Gy and reported a grade ≥ 3 toxicity rate of 2% with no grade 4 or 5 toxicity or RILD (Rusthoven, Kavanagh, Burri, et al. 2009). Other groups have reported incidence liver toxicity including Chang *et al.,* who reported a 3% rate of grade ≥ 3 acute and late asymptomatic elevated liver enzymes with no cases of RILD. Mendez Romero *et al.* reported four cases of RILD in patients with metastatic disease or HCC with one grade 5 toxicity in a patient with HCC. Bujold *et al.* reported grade ≥ 3 toxicity of 36.3% including 7 patients with grade 5 toxicities in patients treated for HCC (Bujold et al. 2013). It is well recognized that patients with liver metastasis have a higher liver tolerance to radiation therapy than patients with HCC (Dawson et al. 2002; Pan et al. 2010). The higher rate of toxicity seen in HCC patients is likely reflective of baseline hepatic dysfunction and poor expected survival in patients with hepatic cirrhosis. As such, care should be taken in patients with abnormal liver function and liver disease.

The present study is a single institutional retrospective review and as such contains all the limitations and biases associated with retrospective studies. The patient population is diverse with a variety of primary tumors and past treatments which could impact radiosensitivity and response to treatment. Further, treatment dose and schedule and follow up was at the discretion of the treating physician. It is likely that other unknown biases may impact the outcomes reported in the study. As such, this data should be considered hypothesis generating. Further evaluation and studies into the efficacy of liver SBRT and in comparison to other local control modalities would be best evaluated on randomized, clinical studies.

10. CONCLUSIONS

In this study, we demonstrated that SBRT treatment for liver metastasis and primary liver tumors is an effective and safe treatment. Survival and LC of patients treated with SBRT is comparable to reported series of surgery and minimally invasive techniques such as RFA. With LC rate in excess of 88% and acceptable toxicity, SBRT is a reasonable option for management of liver tumors and may be included in the multidisciplinary discussion about the management of patients with liver tumors.

Authors' disclosure of potential conflicts of interest

The authors reported no conflict of interest.

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