Stereotactic Body Radiation Therapy for Liver Lesions. A Single-institution Experience

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Abstract. *Aim: To evaluate survival and toxicity in a cohort of patients treated with stereotactic body radiation therapy (SBRT) for unresectable intrahepatic malignancies. Patients and Methods: From 2007 to 2014, 23 patients with 34 lesions (three primary and 31 metastatic liver tumors) were treated with SBRT. Results: The median follow-up was 9 months (range=1-76) for all patients. Local control was reached in 27 out of 34 (79%) treated lesions, with 1 and 2 years rates of 93% and 73%, respectively. The progression-free survival at 1-year and 2-year was 50% and 25%, respectively. Median overall survival was 16 months (95% confidence interval=8-24 months), with 1-year and 2-year rates of 58% and 41%, respectively. Toxicity was very low consisting mainly of grade 1 and 2 events. Conclusion: SBRT provides good local control for both primary and metastatic liver lesions, with minimal toxicity.*

The liver is a common site of metastases, in particular for lung, breast, and gastrointestinal cancer; and in some patients, this could be the only detectable site of disease (1). Metastasis to the liver often presents early and in these situations, an early diagnosis might allow for intervention that will delay progression. There is a subset of patients presenting with solitary or a limited number of liver lesions for whom apparent cures have been achieved with surgical excision. Patients undergoing surgery for liver metastasis from colorectal cancer (CRC) have 5-year survival rates of 25-40% (2). However, only 10-20% of patients with metastatic CRC are candidates for resection (3). For the majority of patients, chemotherapy represents the only viable treatment option. Advances in chemotherapy have been impressive and the introduction of new chemotherapeutic agents and targeted-therapies over the past decade has resulted in a improvement in outcome for patients with CRC (4). The median survival has improved from 6 months (without treatment) to about 11 months using fluorouracil and leucovorin (5).

The majority of patients with intrahepatic cancer are ineligible for curative resection because of impaired liver function, comorbidities, or multiple, large, or centrally located lesions (6). Patients not suitable for liver resection can benefit from some ablative treatment, such as microwave hyperthermia, radiofrequency ablation, cryosurgery, ethanol injection and transarterial chemoembolization (7).

Historically, radiation therapy (RT) had a limited role in the treatment of liver tumors. The low tolerance of liver tissue to irradiation increases the risk of the radiation-induced liver disease (RILD). According to the radiobiological model, the risk of RILD is proportional to the mean radiation dose delivered to normal liver tissue (8). In contrast to conventional RT, which delivers low-dose fractions to a large volume for a high number of daily fractions, stereotactic body radiation therapy (SBRT) entails precise delivery of a high dose in a single or few fractions, giving an ablative dose to the tumor and sparing normal tissue (9).

Surgical resection of limited lesions in the liver is known to be associated with favorable outcome in well-selected patients, suggesting a clinical benefit in some patients (10). SBRT, if demonstrated to be safe and similarly effective, would be advantageous over surgery, being entirely non-invasive and also deliverable on an outpatient basis, with no requirement for anesthesia (11). In the present study, we retrospectively evaluated the role of SBRT for liver lesions in terms of local control, survival and toxicity.

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Patients and Methods

Patients. The indication for SBRT was determined by a multi-disciplinary tumor board consisting of a hepatologist, a hepatic surgeon, a radiation oncologist, a medical oncologist, and a radiologist. Patients with primary and metastatic liver tumors who were not eligible for surgery or any other local treatment were included in this study. Other inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1, a number of hepatic lesions ≤3, and lesion size of <200 cc. The medical records of 23 patients with 34 liver lesions treated with SBRT between December 2007 and May 2014 were retrospectively reviewed. Patients were included even if their disease was not confined to the liver. The number of treated lesions ranged from one to three (1 lesion: 15 patients, 2 lesions: 5 patients, 3 lesions: 3 patients).

Radiation treatment. All patients underwent computed tomographic (CT) simulation and were immobilized in the supine position. In general, 4D-CT was used to generate the internal target volume. When the target lesion was not readily apparent on the CT images, the planning dataset was registered to a pre-treatment diagnostic magnetic resonance imaging study, using a mutual information algorithm in our in-house treatment planning system, in order to facilitate target delineation (12). The gross tumor volume (GTV) and the internal target volume for free-breathing cases were expanded by a 4-mm radial and 4-mm craniocaudal margin for the planning target volume (PTV). SBRT was planned and delivered using three-dimensional conformal techniques with multiple (typically ≥5 and ≤9), non-opposed, coplanar static ×6 MV beams. Radiation dose was prescribed to the isodose surface covering the 95% of the maximum PTV dose. The majority of patients received either one or three fractions (88.2% and 11.8%, respectively), with 30 Gy in one fraction (38.2%), 23 Gy in one fraction (50%), and 15 Gy in three fractions (11.8%), comprising the most common dose fractionation schemes. Generally, patients received three fractions due to the proximity of organs at risk. The biologically effective dose (BED) (α/β=10 Gy) was 75.9-120 Gy (median=94.2 Gy). The formula for BED10 was used: BED (10 Gy)=nd ($1+d/\alpha/\beta$). Dose limits to the stomach, bowel and spinal cord were Dmax<30 Gy, Dmax<30 Gy and Dmax ≤20 Gy, respectively. Daily image guidance and positioning was performed with cone-beam CT.

Follow-up. Patients were evaluated at 1 and 3 months after completion of SBRT and then every 3 to 6 months thereafter. Follow-up visits typically consisted of a history and physical examination, tumor marker assessment, serum liver enzymes, and imaging with CT, magnetic resonance imaging, or positron-emission tomography. Follow-up imaging was reviewed by a radiation oncologist. Treatment response was assessed for each treated lesion and scored using the Response Evaluation Criteria in Solid Tumors (RECIST) (13). Local recurrence was scored as in-field or marginal failure. New lesions were also documented. Toxicity was evaluated with the radiation therapy oncology group (RTOG) scale. Acute events were defined as adverse events occurring within three months after SBRT. Late toxicities were defined as those occurring three months after RT up to the last follow-up.

Evaluation of response and statistical analysis. The primary end-point was local control (LC), defined as the absence of new or progressive lesions within or at the margin of the PTV. Secondary end-points were progression-free survival (PFS), overall survival (OS), and toxicity. PFS was calculated from the first day of RT and was defined as freedom from any local, distant intrahepatic, or distant extrahepatic progression or death from any cause. OS was measured as the time from the start of RT for the first treated lesion until death or loss to follow-up. LC, PFS, and OS were estimated using the Kaplan–Meier method. Differences between survival curves were analyzed with log-rank test. All statistical analyses were performed using the software package IBM SPSS Statistics for Macintosh, Version 22.0 (IBM Corp., Armonk, NY). A $p \leq 0.05$ was considered statistical significant.

Results

Patient and treatment characteristics. In total, there were 23 patients with 34 lesions treated with SBRT assessable for outcome analysis. The median age at time of enrollment was 68 years (range=46-83 years). The median follow-up time for all lesions was 9 months (range=1-76 months) and 17 months (range=1-76 months) for living patients. Metastatic tumors comprised the majority of lesions (87%), with pancreatic, CRC, breast, lung, gastric primaries and gastrointestinal stromal tumor (GIST) accounting for 9%, 39%, 13%, 9%, 13% and 4% of all lesions, respectively. Hepatocellular carcinoma represented 4% and intrahepatic cholangiocarcinoma 9% of all lesions. Twenty-two out of 23 (96%) patients received one or more chemotherapy cycles before SBRT. Patients' characteristics are presented in Table I.

Clinical outcome. Twenty-seven (79%) treated lesions were locally controlled reaching 1- and 2-year LC rates of 93% and 73%, respectively (Figure 1). With regard to the impact of the lesion size on LC, a significant difference was found. The volume of treated lesion was found to be a predictive factor for LC (median LC not reached (NR) *vs*. 16 months for lesion volume ≤26 cc and >26 cc, respectively; p=0.033) (Figure 2). Dose was not a significant predictor of LC. In our series, lesions which received BED10 >BED100 had a worse LC than those which received BED10 ≤BED100. However, the lesions treated with a BED10 ≤BED100 had a volume smaller than those treated with >BED100. The PFS at 1 and 2 years were 50% and 25%, respectively (Figure 3). The median time to relapse was 9 months (95% confidence interval CI=6-12 months). The OS was 58% and 41% at 1 and 2 years, respectively (Figure 4). The median OS for patients overall was 16 months (95% CI=8-24 months). At the last follow-up, 12 patients (52%) had died. In particular, three patients were affected by primary liver tumors (median OS of 6 months) and nine patients were affected by metastatic liver tumors (median OS of 9 months).

Toxicity. SBRT was well-tolerated by all patients, and none developed a dose-limiting toxicity. All patients completed therapy without treatment breaks. Two patients (9%) experienced acute toxicity: one (4%) patient had grade 1

Table I. *Patient and tumor characteristics*.

	No.	%
Total no. of patients	23	
Total no. of lesions evaluated	34	
Age, years		
Median	68	
Range	46-83	
Primary liver tumors		
Hepatocellular carcinoma	1	4
Intrahepatic cholangiocarcinoma	2	9
Metastatic liver tumors		
Pancreatic primary	2	9
Colorectal primary	9	39
Breast primary	3	13
Lung primary	2	9
Gastric primary	3	13
GIST	1	4
Prior systemic therapy		
Yes	22	96
No	1	4
Lesion volume (cm3)		
Median	26	
Range	2-194	
PS		
0	12	
1	11	
Median biologic equivalent dose (BED10)		
≤100	17	50
>100	17	50

GIST: Gastrointestinal stromal tumor; PS: performance status.

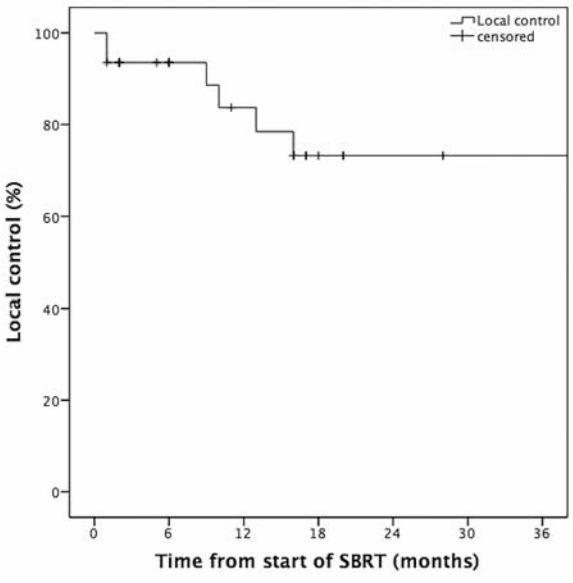

Figure 1. *Kaplan-Meier curves showing local control.*

nausea and one (4%) patient had grade 2 abdominal pain that required analgesic drugs 1 month after treatment. Late toxicities were identified in three patients (13%): one (4%) experienced grade 1 nausea at 4 months from SBRT requiring antiemetics and two patients (9%) developed mild cramping at 4 months after the completion of treatment.

Discussion

SBRT is a highly effective ablative therapy that has been used in the management of many extracranial lesions. Most recently, the phase II RTOG-0236 trial of SBRT for inoperable early stage non-small cell lung cancer led to a tumor control rate of 98% at 3 years (14). SBRT can be applied to other sites employing high RT doses to target volume still respecting normal tissue tolerances. SBRT has been used as non-invasive locoregional treatment for many primary and secondary tumors of the liver, with promising results (1, 15). Several retrospective and prospective studies have investigated the efficacy of SBRT in the treatment of liver metastases from various primary tumor types (16-25). In all studies, the number of lesions was fewer than five and the maximum tumor size was 6 cm (23). Enrolled patients had a good PS (ECOG PS 0-1 or Karfnosky>70), with no or stable extrahepatic disease and adequate hepatic volume and function. Prescription doses, generally ranged from 30 to 60 Gy, while in the phase II trial by Scorsetti *et al*., a prescription dose of 75 Gy in three fractions was employed (25). In two prospective studies, a prescription dose of 18-30 Gy in one fraction was delivered and one phase I trial, individualized radiation doses ranging from 30 to 60 Gy in six fractions was employed (19, 20).

This was a retrospective study of 23 patients with primary or metastatic liver cancer. The median age at the time of treatment was 68 years (range=46-83 years), the patients had a good PS (PS 0-1), a low number of hepatic lesions (≤3), and lesion size of ≤200 cc. Prescription doses generally ranged from 23 to 30 Gy in one fraction, or 15 Gy in three fractions.

In our study, LC was reached in 27 (79%) treated lesions with 1- and 2- year LC rates of 93% and 73%, respectively. Rusthoven *et al*. obtained LC of 95% and 92% at 1 and 2 years, respectively, with 100% 2-year LC for lesions less than 3 cm (21). Scorsetti *et al*., in a phase II study, revealed no significantly increased risk of local recurrence for lesion larger than 3 cm compared to smaller metastases, using an ablative prescription dose of 75 Gy in three fractions (25). In our study, the tumor size was found to significantly predict for LC. LC was better in lesions with a volume ≤26 cc *versus* those with a volume >26 cc (p=0.033). Lee *et al*. suggested that LC depends on a higher prescription dose (19). Survival and LC in our series were not statistically correlated to dose. Results of our series demonstrate a significantly better outcome for

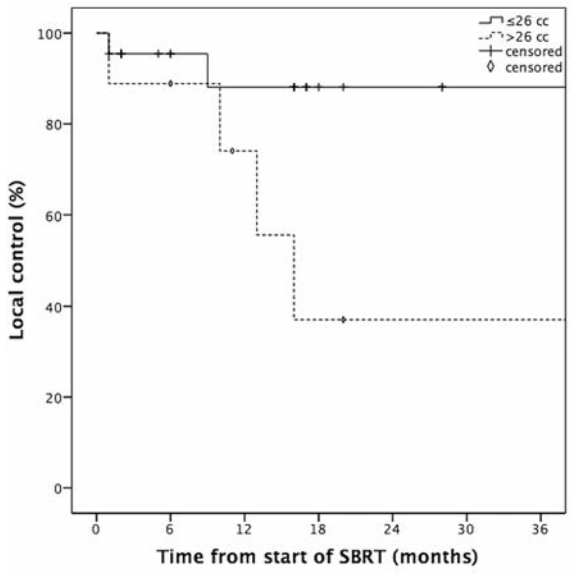

Figure 2. *Kaplan-Meier curves showing local control according to lesion volume.*

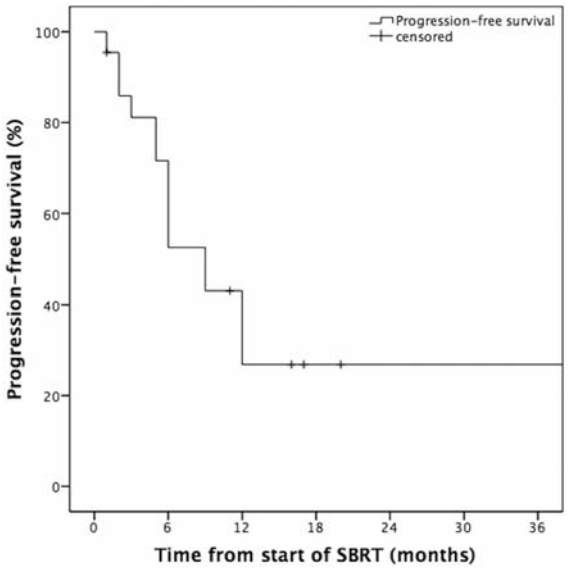

Figure 3. *Kaplan-Meier curves showing progression-free survival.*

patients treated with ≤BED 100 *versus* >BED100. This is in contrast with reports from the literature and is probably due to the small number of patients of our series.

The median OS was 16 months (95% CI=8-24 months), with 1- and 2-year OS rates of 58% and 41%, respectively. Hoyer *et al.* found 1- and 2-year OS rates of 67% and 38%, respectively. In addition, OS was related to the lesion size (≥3.5 cm better than <3.5 cm). In this case, only liver metastases from CRC were analyzed (24). Liu *et al.* recorded a median overall OS for patients of 25.2 months, with 1- and 2-year OS of 81% and 52%, respectively. The survival was higher among patients with metastatic compared to primary lesions (2-year OS of 63% *versus* 29%, p=0.02) (6). In our series, we had a limited number of patients with different types of cancer that implies a bias for correct analysis of the local control and OS. For patients with metastatic liver lesions, the presence of active extrahepatic disease yielded significantly worse survival. In our study and in the literature, we found that despite high control rates, survival was low, likely since almost all patients were medically inoperable, with lower-than-expected OS.

SBRT in our series was well-tolerated, without any case of RILD, suggesting that SBRT may have a favorable toxicity profile. Two patients (9%) experienced grade 1-2 acute upper gastrointestinal (GI) toxicity. Late toxicity was identified in three patients (13%) with grade 1 toxicity (liver and small/large intestine). In a phase I study, Lee *et al.* noted that the risk of serious liver toxicity was low (95% CI=0-5.3%) (19). Similarly, no RILD was observed using a dose constraint allowing no more than 700 ml of uninvolved liver

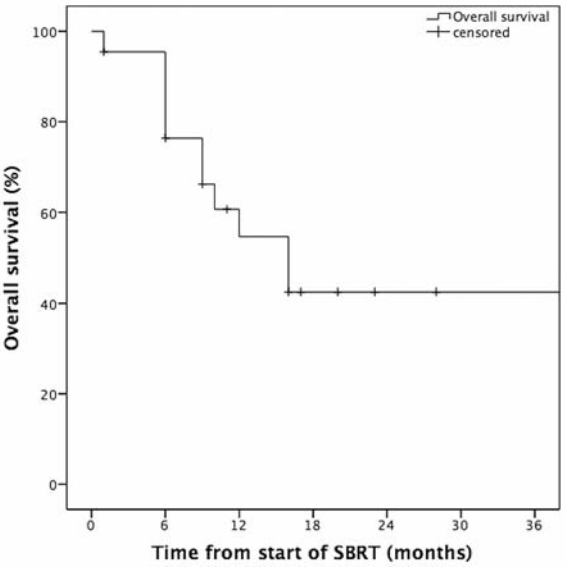

Figure 4. *Kaplan-Meier curves showing overall survival.*

to receive 15 Gy or greater in three fractions in the phase I/II study on 47 patients by Rusthoven *et al.* and in the phase II trial on 61 patients by Scorsetti *et al.* (21, 25).

In this series, we demonstrate that SBRT provides an excellent LC with minimal toxicity for both primary and metastatic liver tumors. Limitations of the study include its retrospective nature, the small number of patients with different types of disease, and variety of pre-SBRT and post-

SBRT systemic and liver-directed therapies. In conclusion, SBRT is a non-invasive, well-tolerated and effective treatment for patients with liver metastases not suitable for surgical resection. Ablative SBRT for liver metastases and primary liver tumor achieves high LC rates at 1 and 2 years. Toxicitiy was very low consisting mainly of grade 1 and 2. Comparative studies are required to better assess this issue.

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