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Clinical Investigation

The Dutch–Belgian Registry of Stereotactic Body Radiation Therapy for Liver Metastases: Clinical Outcomes of 515 Patients and 668 Metastases

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Purpose: Although various studies have reported that stereotactic body radiation therapy (SBRT) for liver metastases has high local control rates and relatively low toxicity, most series included a small number of patients. We aimed to validate these outcomes in a large multi-institution patient cohort treated in accordance with a common protocol.

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The data sets generated and analyzed during this study are owned by the Dutch-Belgian consortium and are not publicly available. Reasonable requests can be submitted and will be considered by the members of the consortium.

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Methods and Materials: A shared web-based registry of patients with liver metastases treated with SBRT was developed by 13 centers (12 in the Netherlands and 1 in Belgium). All the centers had previously agreed on the items to be collected, the fractionation schemes, and the organs-at-risk constraints to be applied. Follow-up was performed at the discretion of the centers. Patient, tumor, and treatment characteristics were entered in the registry. Only liver metastases treated individually as independent targets and with at least 1 radiologic follow-up examination were considered for local control analysis. Toxicity of grade 3 or greater was scored according to the Common Terminology Criteria of Adverse Events (v4.03).
Results: Between January 1, 2013, and July 31, 2019, a total of 515 patients were entered in the web-based registry. The median age was 71 years. In total, 668 liver metastases were registered, and 447 were included for local control analysis. The most common primary tumor origin was colorectal cancer (80.3%), followed by lung cancer (8.9%) and breast cancer (4%). The most-used fractionation scheme was 3x18-20 Gy (36.0%), followed by 8x7.5 Gy (31.8%), 5x11-12 Gy (25.5%), and 12x5 Gy (6.7%). The median follow-up time was 1.1 years for local control and 2.3 years for survival. Actuarial 1-year local control was 87%; 1-year overall survival was 84%. Toxicity of grade 3 or greater was found in 3.9% of the patients.
Conclusions: This multi-institutional study confirms the high rates of local control and limited toxicity in a large patient cohort. Stereotactic body radiation therapy should be considered a valuable part of the multidisciplinary approach to treating liver metastases.

Introduction

A multidisciplinary approach is essential to guarantee the most personalized treatment for patients with liver metastases. Thus, if the best possible treatment or combination of complementary options is to be provided, optimal collaboration is required.

In view of Hellman's proposal that oligometastatic disease is a distinct cancer state between locally confined cancer and systemically metastasized disease, patients with limited metastatic disease may benefit from local directed therapies.[1] With local recurrence rates lower than 10% and 3-year overall survival rates of 72%, surgical resection is considered the gold standard treatment for liver metastases from colorectal cancer.[2,3] In the meantime, percutaneous thermal ablation has evolved as a complement to resection and as a single treatment modality and is now regarded as a potentially curative local treatment option.[2,4,5] After radiofrequency ablation (RFA) for colorectal liver metastases, local tumor-recurrence rates between 4% and 40% have been reported and can sometimes be reduced to 12% by microwave thermosphere ablation.[5] A review of local treatment of breast cancer liver metastases found that overall survival rates 3 years after RFA were between 43% and 70%.[4]

Stereotactic body radiation therapy (SBRT) is generally offered as an ablative and radical local treatment. In a phase 2 randomized trial, the addition of this directed therapy to the standard-of-care palliative treatment appeared to lead to longer overall survival.[6] Long-term outcomes of another phase 2 study also found longer overall survival in a group of non-small cell lung cancer patients randomly assigned to local consolidative therapy followed by standard maintenance or observation (LCT arm) or to standard maintenance therapy or observation (MT/O arm).[7]

Patients with liver metastases referred for SBRT are ineligible for surgery and often are not the most suitable candidates for thermal ablation.[8] Many patients referred for SBRT present with larger lesions than those considered optimal for thermal ablation ($\leq$3 cm) and with tumors for which curative ablation with adequate margins ($\geq$6 mm) is not feasible.[9,10] Several studies on SBRT for liver metastases reported a 3-year local control of 66% to 91% and a 3-year overall survival of 27% to 65%.[11-13] Severe toxicity (grade $\geq$3) was limited, and the treatment appeared to be safe.[14-17] Sporadically, grade 5 toxicity has been described.[12,18]

Most series on SBRT for liver metastases included a limited number of patients, with only 2 articles reporting numbers that were well over 200.[19,20] Both series investigated factors associated with clinical outcomes after SBRT. Mahadevan et al's analysis was conducted between 2005 and 2017 within the international multi-institutional Radiosurgery Society Search (RSSearch) registry,[20] and Andratschke et al's analysis was conducted between 1997 and 2015 within the database of the German Society of Radiation Oncology (DEGRO).[19] Both articles lacked formal inclusion criteria, and information on toxicity was not available from all centers in the RSSearch registry.

The present study aimed to validate the outcomes of SBRT in a large, multi-institutional cohort of patients with liver metastases recently treated according to a common SBRT protocol. To the best of our knowledge, the outcomes we present in this study represent the largest ever published series.

Methods and Materials

Registry

Since 2012, Dutch centers that use SBRT in the treatment of liver tumors have collaborated on the development of guidelines and on sharing clinical and technological experience. In 2013, they adopted a common SBRT protocol for

treating liver metastases and developed a web-based registry that fulfilled the requirements of the General Data Protection Regulations. The system was developed and tested in close collaboration with the chief security officer at Erasmus MC. A consortium agreement designed by the Technology Transfer Office at Erasmus MC was signed by all participating centers in the Netherlands and the center in Belgium.

A description of the registry project and its aim was submitted to the ethical committees of the participating centers (Erasmus MC- MEC 2016-632) and was considered not to be subject to the Medical Research Involving Human Subjects Act. Patient, tumor and treatment characteristics were recorded anonymously.

Planning and fractionation schemes

The clinical target volume was considered to be the same as the gross target volume. No margin was applied to compensate for microscopic tumor extension. By consensus, we agreed on the following fractionation schemes to encompass the periphery of the planning target volume (PTV): 3 × 18 to 20 Gy, 5 × 11 to 12 Gy, 8 × 7.5 Gy, and 12 × 5 Gy. With the exception of the latter (12x5 Gy), all schemes correspond to a biological effective dose$_{10}$ (BED$_{10}$) > 100 Gy, being the BED$_{10}$ of the 12-fraction scheme 90 Gy. The PTV margins and prescription isodose were left to the discretion of the centers.

The planning goal was to cover a high percentage of the PTV (typically at least 95%) with the prescribed dose. There were no limitations for the maximum PTV dose. In principle, for each patient, the scheme with the lowest possible number of fractions (highest BED$_{10}$) not resulting in organs at risk constraint violations was used for treatment (Table EA1).[21-23] However, when the metastasis was close to the central biliary tract or near the large vessels, several institutes preferred more protracted schemes, even though no specific constraints had been defined for these structures.

Endpoints

The frequency and method of follow-up were left to the discretion of the centers and the referring specialists. Local control was assessed per metastasis and by means of computed tomography or magnetic resonance imaging; it was defined as the absence of in-field progression (either regrowth after initial decrease in size or reappearance of the lesion after complete remission).[18,19] In collaboration with the radiologist, this information was collected from radiology reports or by direct inspection of the images. For liver metastases to be eligible for the local-control analysis, a radiologic examination during follow-up was required. Because of the configuration of the registry, only liver metastases treated individually as independent targets (PTVs) were considered for the local-control assessment.

Overall survival was assessed in the Netherlands with the support of the Dutch population register. If needed, information was collected through general practitioners or referral hospitals. The web-based registry did not provide data for assessing any survival endpoints other than overall survival.

Local control and survival time were both calculated on the basis of the day that the last SBRT fraction had been delivered. Toxicity was scored according to the Common Terminology Criteria of Adverse Events (CTC-AE), v4.03. Only events of grade 3 or greater were entered in the registry. Information on toxicity was obtained by consulting hospital files and reports.

Patient eligibility

The treatment had to be delivered according to 1 of the 4 specified fractionation schemes, and at least 1 follow-up time point had to be recorded.

Statistical analysis

The Kaplan Meier estimate was used to measure local control and overall survival. The date of the last known radiology examination was regarded as the last follow-up date for local control. The influence of various prognostic factors on local control and on toxicity (age, fractionation scheme, liver segment, tumor diameter) was investigated using univariate and multivariate (backward stepwise) Cox regression analysis. An extra analysis was also carried out on local control using the method proposed by Geskus[24]; this considered death as a competing risk. The median follow-up time was assessed using the reverse Kaplan Meier method. The calculations were conducted using R statistical software, version 2.13.0.

Results

Between January 1, 2013, and July 31, 2019, a total of 515 patients with 668 metastases were treated and entered into the web-based registry. Patient, tumor, and treatment characteristics are summarized in Table 1. The most frequent primary tumors were colorectal, followed by lung and breast tumors. Most patients were treated for 1 liver metastasis. The treatment was usually delivered in segment 8, and the lowest number of treatments was delivered in segment 3. The preferred fractionation scheme was 3 × 18 to 20 Gy, followed by 8 × 7.5 Gy, 5 × 11 to 12 Gy, and 12 × 5 Gy.

Local control

In total, 447 individually treated metastases in 428 patients (19 patients had 2 metastases) were included in the local-control analysis. The median diameter was 27 mm (range, 8-88 mm). The median follow-up time was 1.1 years (range,

Table 1 Patient and Tumor Characteristics

	Number	%	Median (range)
Age (years)			71 (27-91)
Sex			
Male	319	61.9	
Female	196	38.1	
Pretreatment ECOG			
0	256	49.7	
1	215	41.7	
2	30	5.8	
3	1	0.3	
Not reported	13	2.5	
Number of metastases treated per patient			1 (1-6)
Diagnosis treated metastasis related to diagnosis primary			
Synchronous	150	33.6	
Metachronous	295	66.0	
Missing	2	0.4	
Treatments previous to SBRT*			
None	227	50.8	
Chemotherapy	108	24.2	
RFA/MWA	31	6.9	
Surgery	29	6.5	
Combinations	47	10.5	
SBRT	2	0.4	
Unknown	3	0.7	
Primary histology*			
Colorectal	359	80.4	
Lung	40	9.0	
Breast	18	4.0	
Stomach	2	0.4	
Ovary	2	0.4	
Melanoma	2	0.4	
Other	24	5.4	
Couinaud segment*			
8	134	30.0	
7	72	16.1	
6	51	11.4	
5	37	8.3	
4a,b	60, 24	13.4, 5.4	
3	14	3.1	
2	22	4.9	
1	33	7.4	
Fractionation scheme*			
3 × 18-20 Gy	161	36.0	
5 × 11-12 Gy	114	25.5	
8 × 7.5 Gy	142	31.8	
12 × 5 Gy	30	6.7	

Abbreviation: ECOG = Eastern Cooperative Oncology Group; MWA = microwave ablation;
RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy.
* A total of 447 metastases were included in the local control analysis.

0.1-5.4 years). Local-control rates were 87% at 1 year, 75% at 2 years, and 68% at 3 years (Fig. 1a). There was no significant difference between groups regarding the primary tumor (Fig. 1b) or the 4 fractionation schemes (Fig. 1c). Univariate analysis showed no significant association of age, tumor diameter, fractionation scheme, or location of the metastases in the liver with local control. The combination of factors also was not significant in multivariate analysis (Table 2 and Table 3). When the 447 metastases were stratified in 3 cohorts based on the length of follow-up (<6 months [n = 131], ≥6 to <18 months [n = 180], and ≥18 months [n = 136]), we did not find significant associations among the factors being studied. However, we found significant differences between these 3 groups regarding fractionation scheme ($P = .01$), age ($P = .02$), and tumor diameter ($P = .03$).

Application of the competing risk method showed higher local-control rates than those obtained with the classical approach: 88.4% versus 86.5% at 1 year, 80.3% versus 74.9% at 2 years, and 76.7% versus 68.4% at 3 years (Fig. 1d).

Overall survival

All 515 patients were included in the overall survival analysis. The median follow-up time was 2.3 years (range, 0.1-5.9 years). Overall survival rates were 84% at 1 year, 63% at 2 years, and 44% at 3 years (Fig. 2).

Toxicity

Toxicity was grade 3 or greater in 20 of the 515 patients (3.9%), grade 4 in 2 patients (0.4%), and grade 5 in 1 patient (0.2%). Table 4 presents an overview of the 23 observed toxicity events and grades. Most patients had 1 toxicity event,[18] 1 patient had 2 events, and 1 patient had 3 events.

The patient who developed grade 5 toxicity had been treated with 3x20 Gy for 2 adjacent metastases (relapses after RFA) situated in segments 1 and 4a. The central biliary tract was located within the PTV including the 2 lesions and received a maximum dose of 69.6 Gy. Six months after treatment, the patient developed biliary stenosis. The disease also continued to progress. A biliary stent was placed. The patient died 1 year after treatment. The cause of death was evaluated as probably related to the adverse event.

An episode of stomach perforation, grade 4, occurred 1.5 months after treatment in a patient with 2 metastases, both located at the periphery of the liver in segment 2. Both metastases were treated in 1 target. The radiation therapy plan respected the stomach constraints, but high dose gradients were delivered outside the liver in the direction of the stomach. The patient underwent endoscopic surgery for the stomach perforation.

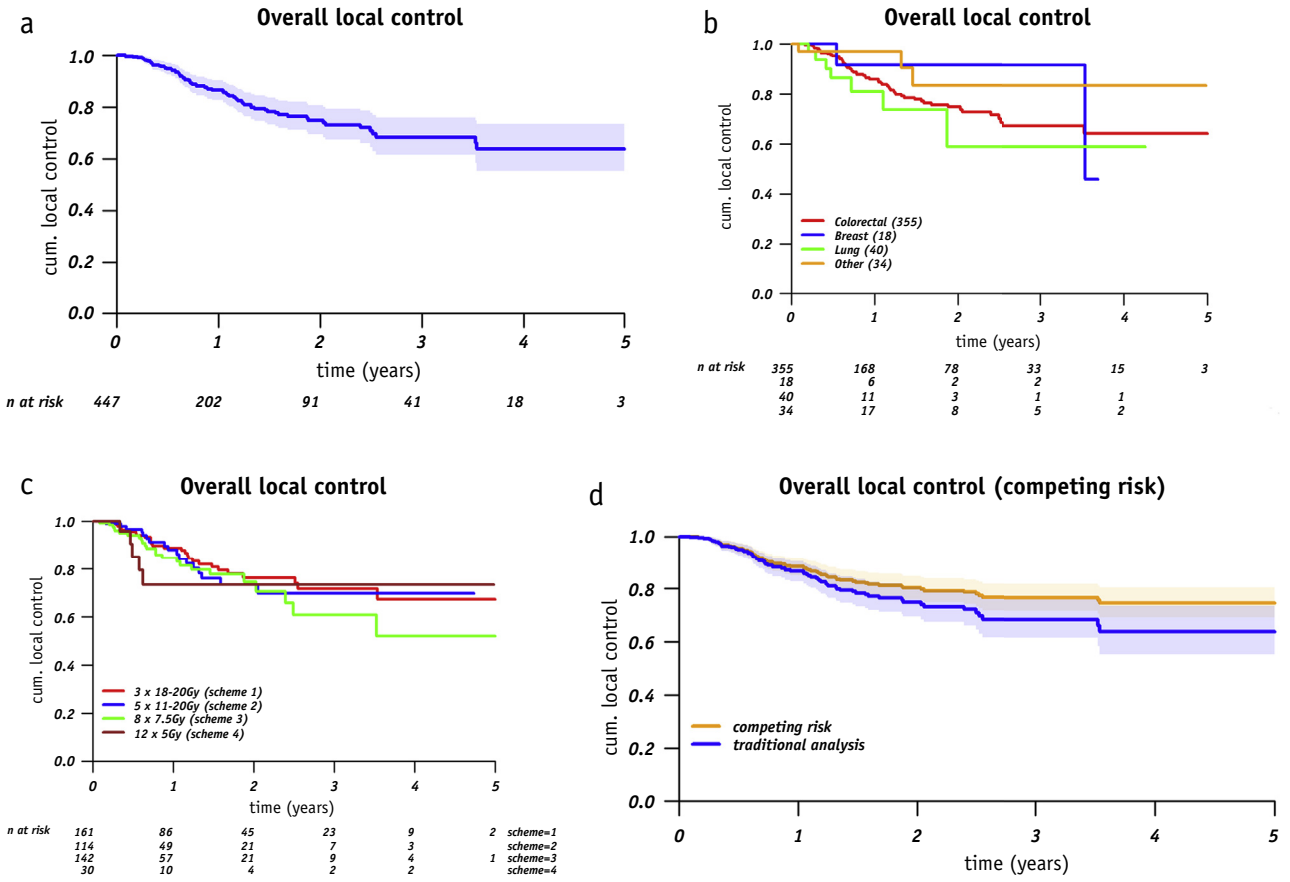

Fig. 1. (a) Overall local control. (b) Overall local control; metastases from different primary tumors. (c) Overall local control; various fractionation schemes applied to treat liver metastases. (d) Overall local control; competing risk method.

Table 2 Univariate Analysis of Impact Factors for Local Control and Toxicity

	Univariate analysis					
	Local control			Toxicity		
Factor	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Scheme						
1 (reference)						
2	1.12	0.61-2.06	.71	1.65	0.62-4.42	.32
3	1.37	0.79-2.38	.26	0.55	0.15-2.10	.38
4	1.50	0.58-3.89	.41	0.79	0.10-6.36	.83
Age	0.99	0.97-1.01	.24	1.03	0.99-1.08	.18
Tumor diameter	1.00	0.98-1.02	.74	1.01	0.98-1.05	.49
Liver segment						
1 (reference)						
2	1.30	0.34-4.85	.70	0.97	0.16-5.82	.97
3	2.76	0.74-10.33	.13	-	0-infinity	1.00
4a	0.54	0.16-1.86	.33	0.17	0.02-1.59	.12
4b	1.52	0.46-4.98	.49	-	0-infinity	1.00
5	0.62	0.15-2.61	.52	0.89	0.18-4.43	.89
6	1.38	0.46-4.13	.56	0.25	0.03-2.37	.23
7	1.45	0.53-3.98	.47	0.13	0.01-1.27	.08
8	0.99	0.37-2.59	.97	0.34	0.08-1.43	.14

Table 3 Multivariate Analysis of Impact Factors for Local Control and Toxicity*

	Multivariate analysis					
	Local control			Toxicity		
Factor	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Scheme						
1 (reference)						
2	1.17	0.63-2.19	.62	2.44	0.76-7.83	.13
3	1.59	0.87-2.91	.13	0.88	0.20-3.81	.87
4	1.34	0.49-3.65	.57	-	0-infinity	1.00
Age	0.99	0.97-1.01	.29	1.03	0.98-1.09	.21
Tumor diameter	1.00	0.98-1.01	.65	1.01	0.98-1.05	.50
Liver segment				NA	NA	NA
1 (reference)						
2	1.32	0.35-4.94	.68			
3	3.72	0.94-14.63	.06			
4a	0.61	0.17-2.13	.44			
4b	1.68	0.51-5.57	.39			
5	0.72	0.17-3.02	.65			
6	1.60	0.51-4.96	.42			
7	1.70	0.59-4.90	.33			
8	1.19	0.44-3.21	.74			

Abbreviation: NA = not assessed.
* The multivariate backward method showed that no factor remained in the model.

An episode of grade 4 gallbladder perforation occurred in a patient with colorectal liver metastases who had been treated with SBRT for a lesion in segment 1 that extended to segments 5 and 8. One month before SBRT, microwave ablation (MWA) had been delivered for a lesion in segment 4 (vicinity of the gallbladder). The PTV extended into the most cranial and medial areas of the gallbladder, reaching a maximum dose of 71.2 Gy and a 6-cc volume receiving ≥44 Gy. Nine months after treatment, perforation of the gallbladder and a possible abscess were detected. Owing to the very limited performance status related to disease progression, conservative treatment was recommended and followed.

Regarding the incidence of severe toxicity, there was no significant difference between the 4 fractionation schemes, although toxicity was slightly higher in the treatments delivered in a lower number of fractions. At 3 years, the rate of severe toxicity was 9%, 22%, 3%, and 2% for the fractionation schemes 3 × 18 to 20 Gy, 5 × 11 to 12 Gy, 8 × 7.5 Gy, and 12 × 5 Gy, respectively. Univariate and multivariate analyses showed that other factors such as age, the tumor diameter, and the location of the metastasis in the liver had no significant association with the development of toxicity of grade 3 or greater (Table 2 and Table 3).

Discussion

This large, multi-institutional study confirmed that local control is high and toxicity is limited after SBRT for liver metastases. To our knowledge, no previously published series has had a larger number of patients.

Since the first publications in the 1990s, several cohort studies—and, more recently, some randomized trials—have investigated the value to patients with limited metastatic disease of integrating SBRT into the treatment framework.[6,7,25-32] Whereas the first studies showed that SBRT controlled oligometastases effectively and that patients could be treated safely at multiple body sites, the more recent randomized trials showed that local directed or consolidative therapy including SBRT was associated with improved survival.

Most reports on SBRT for liver metastases have been published in cohorts of <100 patients; a minority have reported on 100 to 200 patients, and to our knowledge, only 2 series have reported on well over 200

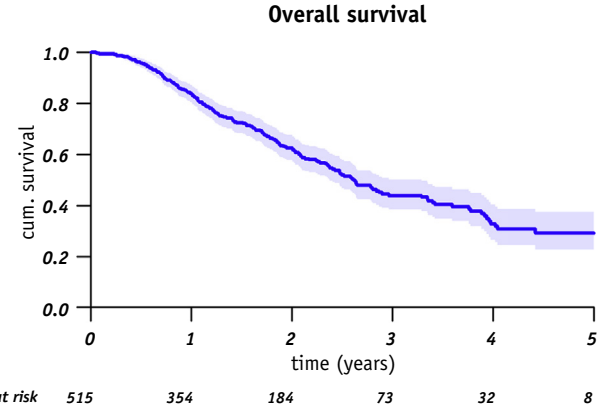

Fig. 2. Overall survival.

Table 4 Toxicity Description (Grade and Type of Event)

CTC-AE grade	CTC-AE event	Primary tumor	Fractionation scheme	Location of metasteses (liver segment)	Maximum diameter, mm
3	Abdominal pain	Colorectal	1	5	27
3	Abdominal pain	Colorectal	1	2	22
3	Bile duct stenosis	Colorectal	1	8	8
3	Bile duct stenosis	Stomach	2	8,4a	Multiple*
3	Bile duct stenosis	Colorectal	2	8	29
3	Chest wall pain	Colorectal	2	6	40
3	Chest wall pain	Breast	4	4a,4b	Multiple*
3	Cholecystitis	Colorectal	2	8	40
3	Cholecystitis	Colorectal	2	4a,4b	Multiple*
3	Fatigue	Lung	1	7	35
3	Fatigue	Colorectal	2	1	35
3	Fibrosis deep connective tissue	Colorectal	2	8	34
3	Flank pain	Other	2	5	41
3	Fracture	Colorectal	1	1	14
4	Gallbladder perforation	Colorectal	3	1	41
4	Gastric perforation	Lung	4	2,2	Multiple*
3	Hematoma	Colorectal	3	4a	14
5	Hepatobiliary disorders	Colorectal	1	1,4a	Multiple*
3	Nausea	Lung	2	8	59
3	Nausea	Colorectal	3	5	20
3	Pneumothorax	Lung	2	8	59
3	Portal vein thrombosis	Colorectal	1	8	8
3	Vomiting	Lung	2	8	59

Abbreviation: CTC-AE = common terminology criteria of adverse events.
* Multiple metastases treated in one target volume.

Table 5 Outcomes After SBRT for Liver Metastases: Selection of Published Literature

Author	Design	Primary tumor	Number of patients/ metastases	Dose fractionation scheme	Local control, 1-3 y, %	Overall survival, 1-3 y, %
Lee et al, 2006[35]	Phase I	Mixed	70/143*	Median 41.8 Gy in 6 fractions	71-NRP	60-30
Andratschke et al, 2015[33]	Retrospective	Mixed	74/91	3-5 × 5-12.5 Gy	74.7-48.3	77-30
Goodman et al, 2016[12]	Retrospective	Mixed	81/106	Median 54 Gy in 3-5 fractions	96-91	89.9-44
Joo et al, 2017[34]	Retrospective	Colorectal	70/103	45-60 Gy in 3-4 fractions	93-68	2y 75
Dawson et al, 2019[14]	Phase I	Mixed	23/NRP	10 × 3.5-5 Gy	NRP	NRP
Clerici et al, 2020[11]	Retrospective	Mixed	202/268	3 × 25 Gy	92-84	79-27
Mahadevan et al, 2018[20]	Retrospective	Mixed	427/568†	Median 45 Gy in 1-5 fractions	80-63	70-30
Andratschke et al, 2018[19]	Retrospective	Mixed	474/623‡	1-13 × 3-37.5 Gy Median 18.5 Gy	76.1-55.7	70-29
Present study, 2020	Prospective	Mixed	515/668§	3 × 18-20 Gy 5 × 11-12 Gy 8 × 7.5 Gy 12 × 5 Gy	87-68	84-44

Abbreviations: NRP = not reported; SBRT = stereotactic body radiation therapy.
* Two patients from the 70 were removed from the study.
† A total of 430 metastases were evaluable for local control.
‡ A total of 607 metastases were evaluable for local control.
§ A total of 447 metastases were evaluable for local control.

patients.[11,13-15,17,19,20,23,33-36] Descriptions and outcomes of a selection of these studies are presented in Table 5. For the selection of articles, priority was given to recent publications and to those including a large number of patients. Our local-control results at 1 year (87%) and 3 years (68%) are within the range of values of the series that had a more limited number of patients, with 1-year local control of 71% to 96% and 3-year local control of 48% to 91%. Our results compared particularly well with those from the registries at 1 year (76%-80%) and 3 years (56%-63%). Taking into account only the series treating patients with more hypofractionated schemes, our results seemed to be inferior at long term (2-3 years).[11,12] Although a $BED_{10} >$ 100 Gy has been associated with a higher chance of local control than a $BED_{10} \leq 100$ Gy, we were not able to detect a significant difference in local control according to this parameter.[20,34,37] Whereas 3 of the fractionation schemes in our series had a $BED_{10} > 100$ Gy, 1 did not, and although the number of patients treated with 12 fractions was not large, this effect may have influenced the outcomes. Our results may also have been influenced by the fact that roughly one-third of our population was treated with a BED_{10} of 108 Gy. Ohri et al showed that after a BED_{10} close to but >100 Gy, the probability of tumor control may be lower than for a BED_{10} of 150 Gy or even ≥200 Gy.[37] Such high doses may be more effective for tumor control but cannot be safely delivered to metastases located in the vicinity of the luminal gastrointestinal structures and probably not to metastases adjacent to the central biliary tract. No direct comparison can be done with other series regarding the location of the metastases in the liver and the possible influence of this factor in our local-control results. Only Meyer et al, in a phase 1 trial, limited the inclusion of patients to those with metastases located outside of the central liver zone.[15] Local control was 100% at a median follow-up of 2.5 years in 14 patients treated with 1 fraction of 35 or 40 Gy.

Besides dose, tumor histology has been reported as a factor that influenced local control.[19] In the DEGRO registry, metastases from colorectal cancer had significantly worse control at 1 year (67%) compared with breast cancer (91%). In our series, no significant difference in local control between primaries was found. A possible explanation may be that the percentage of metastases from non-colorectal cancer was very low (19.8%) compared with the German series (51.9%). Breast cancer as the primary tumor was observed in 4% of our patients, whereas in the DEGRO registry, this percentage reached 13.3%.

Although tumor diameter in our series was not significantly related to local control, some publications showed significantly lower local control with metastases of >3 cm or a volume of >40 cc or ≥75.2 cc.[17,20,35] Although some studies limited the tumor diameter to a cumulative sum of ≤ 6 cm, we and others added no restrictions regarding size.[11,12,19,20,34,35]

Overall survival rates in our series at 1 and 3 years (84% and 44%, respectively) compared well with other series including the 2 registries (Table 5). Differences in overall survival might be influenced by variation in inclusion criteria regarding the extent and severity of the extrahepatic disease accepted in the different studies.[38]

In many series, the reported rates of toxicity of grade 3 or greater have been low, with ranges between 0% and 5%, and fewer authors have reported between 10% to 15%.[11-14,17,19,20,33-36] With a 3.9% rate of toxicity of grade 3 or greater, our series compared well with the findings in the literature.

One episode of grade 5 hepatobiliary toxicity and 3 of grade 3 biliary stenosis were observed in our series. Goodman et al reported hepatic toxicity of grade 3 or greater in 4 patients (4.9%), of grade 3 in 1 patient, and of grade 4 in 2 patients, as well as 1 hepatotoxicity-related death.[12] Total dose was associated with hepatic toxicity of grade 3 or greater. Hoyer et al reported an isolated case of liver failure after treating a patient with 3 fractions of 10 Gy.[18] It is uncertain whether this fatal incident was related to irradiation or to thrombosis. Particular attention should be devoted to toxicity related to the central biliary tree. After single-fraction SBRT in a group of 14 patients, Meyer et al reported 4 biliary stenoses adjacent to the treated tumor.[15] Osmudson and collaborators proposed a surrogate structure for the central biliary tract defined by a 15-mm expansion of the portal vein from the splenic confluence to the first bifurcation of the left and right portal veins.[39] The treatments for primary and metastatic liver tumors were delivered in 1 to 5 fractions. Based on the surrogate structure, dosimetric factors predictive of hepatobiliary toxicity of grade 3 or greater were identified (in 3 fractions: $V_{BED10}33.8 < 21$ cc; $V_{BED10}32 < 24$ cc). There were 2 instances of grade 5 toxicities, 1 in a patient treated for cholangiocarcinoma and 1 in a patient treated for colorectal liver metastasis. Finally, investigators in the NRG-GI001 trial proposed a dose-volume objective to limit the high-dose regions in the central biliary tree to treat patients with cholangiocarcinoma. Although not specifically developed for patients with liver metastases, this objective (0.5 cc ≤ 70 Gy in 15 fractions) may be considered when treating these patients with SBRT. Delivering the treatment in a larger number of fractions may also help to overcome this toxicity, as suggested by Dawson et al.[14]

Gastrointestinal toxicity of grade 4 was found in 1 patient with perforation of the stomach. This effect was most probably dose related. Lee et al reported gastrointestinal toxicity of grade 3 or greater, including gastritis and nausea.[35] Two patients (2.9%) developed late toxicity of grade 3 or greater: 1 developed grade 4 and 1 developed grade 5. In both patients, toxicity was related to the small bowel (bleed and obstruction). Andratschke et al also reported acute gastric toxicity with ulcer bleeding in 1 patient (<1%).[19]

Chest wall pain and fibrous deep connective tissue, grade 3, were observed in 3 patients in our series. In those patients, the liver metastasis was located close to the thoracic/abdominal wall. Dunlap et al studied chest wall

toxicity involving pain and/or rib fracture after SBRT.[40] When possible, the risk of adverse events can be reduced by limiting the dose to the chest wall volume.

Patients who are referred for SBRT are typically not candidates for surgery, RFA, or MWA. Unfortunately, randomized phase 3 trials comparing SBRT with other ablative treatment strategies are lacking. Moreover, as SBRT patients are frequently heavily pretreated, direct comparison between different ablative treatments is difficult. Three retrospective single-institution studies compared SBRT with RFA or MWA for liver metastases.[41-43] Freedom from local progression appeared to favor SBRT to RFA for tumors $\geq$2 cm or to MWA for tumors >3 cm. However, it is difficult to draw firm conclusions from these results.

Our registration study has a few drawbacks. Part of the data were retrospectively registered, as it took some time to build up the online registration tool, and although we agreed on the different fractionation schedules beforehand, dose prescription was left at the discretion of the individual centers, potentially influencing the results. However, this registry reports on the largest number of patients treated with SBRT for liver metastases in daily clinical practice.

In conclusion, this multi-institutional study of liver metastases treated with SBRT in a large patient cohort confirms earlier findings of high rates of local control and limited toxicity. Our achievement highlights the importance of including SBRT in multidisciplinary approaches to liver metastases.

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