Stereotactic body radiotherapy (SBRT) for multiple pulmonary oligometastases: Analysis of number and timing of repeat SBRT as impact factors on treatment safety and efficacy

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Background: Stereotactic body radiotherapy (SBRT) for oligometastatic disease is characterized by an excellent safety profile; however, experiences are mostly based on treatment of one single metastasis. It was the aim of this study to evaluate safety and efficacy of SBRT for multiple pulmonary metastases.
Patients and methods: This study is based on a retrospective database of the DEGRO stereotactic working group, consisting of 637 patients with 858 treatments. Cox regression and logistic regression were used to analyze the association between the number of SBRT treatments or the number and the timing of repeat SBRT courses with overall survival (OS) and the risk of early death.
Results: Out of 637 patients, 145 patients were treated for multiple pulmonary metastases; 88 patients received all SBRT treatments within one month whereas 57 patients were treated with repeat SBRT separated by at least one month. Median OS for the total patient population was 23.5 months and OS was not significantly influenced by the overall number of SBRT treatments or the number and timing of repeat SBRT courses. The risk of early death within 3 and 6 months was not increased in patients treated with multiple SBRT treatments, and no grade 4 or grade 5 toxicity was observed in these patients.
Conclusions: In appropriately selected patients, synchronous SBRT for multiple pulmonary oligometastases and repeat SBRT may have a comparable safety and efficacy profile compared to SBRT for one single oligometastasis.

Oligometastases have first been defined as an intermediate stage between local and systemic disease, where radical local treatment of the primary cancer and all metastatic lesions might have a curative potential [1]. Oligometastatic disease is recognized in the 8th TNM system for non-small cell lung cancer (NSCLC) as stage M1b (a single extrathoracic metastasis) and radical local treatment is recommended, for example in the latest NCCN guidelines. As a consequence, a recent survey among >1000 radiation oncologists revealed that >60% of all survey participants were practicing stereotactic body radiotherapy (SBRT) for oligometastatic disease [2].

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Metastatic tumor load is an established prognostic parameter [3]. However, there is no validated definition of oligometastases. Studies using surgical or locally ablative approaches frequently limited the inclusion criteria to patients with metastases confined to one single organ, but simultaneously allowed a larger number of metastases if radical treatment of all lesions was possible. For example, a maximum of 9 colorectal liver metastases were treated with radiofrequency ablation in the EORTC CLOCC study [4]. This is different to studies using SBRT, where oligometastatic disease is usually defined as maximum 3–5 metastases. However, despite these broad inclusion criteria, the majority of patients have been treated for one single pulmonary or one single liver metastasis only [5–11]. Consequently, there are limited data about safety and efficacy of SBRT for multiple metastases within one organ.

After local oligometastasis control is achieved [10,12], the majority of patients will develop distant progression of the disease. In oligometastatic colorectal liver disease treated with radiofrequency ablation, 60% and 60% of the patients developed intrahepatic and extrahepatic disease progression, respectively [4]. Similar numbers have been reported in oligometastatic NSCLC, where distant progression alone is observed in 64–80% of all patients after radical local treatment [13,14]. The optimal strategy in the situation of distant progression depends on the pattern of disease recurrence. Oligometastatic disease may more likely result in an oligorecurrent progression pattern, which remains amenable to local therapy. However, there exist very limited data about safety and efficacy of repeat SBRT, which is especially relevant in oligorecurrent disease within the same organ due to a potentially increased risk for radiation-induced toxicity.

We therefore performed an analysis of SBRT for >1 pulmonary oligometastases using an international multi-center retrospective database. It is the aim of this study to evaluate whether the total number of treated lesions or timing of repeat treatment courses influences the safety and efficacy profile of SBRT.

Materials and methods

This study was performed on the German Radiation Oncology Society (DEGRO) working group "Stereotactic Radiotherapy" database, a retrospective registry of 715 patients and 967 SBRT treatments for pulmonary oligometastases between May 1997 and July 2014 in 20 German and Swiss hospitals. The database has been used for dose–response modeling analyses [15,16] and is described in detail elsewhere [17]. Leading ethical approval was granted by the University Hospital Heidelberg (S-280/2014).

One SBRT treatment was defined as all SBRT fractions delivered to one pulmonary target and all SBRT treatments performed within a one month interval were defined as one SBRT course. Repeat SBRT was defined as two or more SBRT courses separated by >1 month. The database did not include patients treated with re-irradiation of locally recurrent metastases. Follow-up was measured from the start of the last SBRT treatment within the final SBRT course. Patients with incomplete information on follow-up or overall survival (OS) were removed from the analysis which left 637 patients with 858 SBRT treatments as the baseline dataset for the presented study.

To utilize as many cases as possible for multivariable modeling [18], missing covariates were imputed with multiple imputations by chained equations using the R package 'mice' [19]. A "missing at random" mechanism was assumed being responsible for missing variables, and therefore the following variables were added into the imputation model: Treating institution, primary cancer, histopathology, number of fractions, biologically effective dose (BED) delivered to the isocenter, image guidance technique, pneumonitis grade, follow-up time, OS and early death. Variables were imputed in the order of their number of missing cases. Predictive mean matching, logistic regression and a multinomial logit model were used for imputing continuous, binary and multicategorical variables, respectively [19]. Imputations were checked by inspecting density plots of observed and imputed values. A total of 50 imputation data sets were created, then used to fit the Cox and logistic regression models, and finally regression coefficients were pooled in order to obtain average estimates. Sensitivity analysis using only the complete cases was performed for comparison.

For determining a possible influence of multiple and repeat treatments of pulmonary targets on the efficacy of SBRT, OS was chosen as endpoint and the hazard of death modeled by a Cox regression model. In addition, for determining a possible influence of multiple and repeat treatments of pulmonary targets on the safety of SBRT, a binary outcome "early death" was defined as death from any cause occurring within three months or six months from the start of the last SBRT course, respectively, and in each case its probability was modeled using logistic regression. The three- and six-month endpoints were chosen because radiation induced pneumonitis occurs most frequently within this follow-up time and the risk of death due to cancer progression and comorbidities is expected to be low. The logistic regression model can be written as:

$$y_i = \exp(\beta_0 + \boldsymbol{x_i^T \beta}) \div [1 + \exp(\beta_0 + \boldsymbol{x_i^T \beta})] \quad (1)$$

Here, $y_i = 1$ if early death occurred for patient i and $y_i = 0$ otherwise, and $\boldsymbol{x_i^T}\beta = \sum_{j=1}^{p} x_{ij}\beta_j$ denotes the scalar product between the covariate vector for patient i (consisting of p covariates) and the corresponding vector of regression coefficients $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_p)$.

We differentiated whether more than one lesion was treated with SBRT within one month (synchronous treatment) or more than one month apart (metachronous treatment). Both were used as categorical covariates to evaluate a possible influence on the safety and efficiency of SBRT using univariable logistic and Cox regression as noted above. In addition, multivariable analysis was performed to account for other covariates with a possible influence on early death or OS. The following set of covariates was selected from the available patient-, tumor- and treatment-specific variables based on completeness and clinical judgment: age, gender, baseline Karnofsky performance status (KPS), metastasis diameter, primary tumor status at time of SBRT (controlled/progressive) and number of metastases treated with SBRT (1/>1). The full model was fitted with all predictors simultaneously to obtain accurate odds ratios (ORs) and hazard ratios (HRs) for testing the hypothesis of an association between synchronous and metachronous SBRT and early death or OS in the presence of possible confounders.

Results

Detailed patient and treatment characteristics are shown in Table 1. A total of 145 out of the initial 637 patients (22.8%) were treated with SBRT for multiple lung metastases: 100 patients, 29 patients, 9 patients and 7 patients were treated for 2 metastases, 3 metastases, 4 metastases and >4 metastases respectively. 88 patients had received all 196 SBRT treatments within one month: 72 patients, 14 patients and 1 patient each were simultaneously treated for 2 metastases, 3 metastases, 4 metastases and 6 metastases, respectively. 40 patients were treated for minimum 2 metastases and the interval between the first and second SBRT treatments was minimum one month: the median interval between the first and second SBRT treatments was 5.2 months (range 1.2–69 months). Two patients received a third SBRT course 11.0 and 16.1 months after the second course, and the patient who had received the third course 11.0 months after the second received a fourth SBRT course 5.2 months after the third one. A

Table 1
Patient characteristics at the time of the last SBRT course.

Variable	All patients (N = 637)		Single SBRT (N = 492)		Multiple SBRT (N = 145)		p-value
	N	Summary	N	Summary	N	Summary	
Age [years]*	637	67.1 (10.9–100)	492	67.3 (10.9–90.4)	145	66.4 (15.5–100)	0.06
Gender*	637	Male: 405 (63.6%) Female: 232	492	Male: 320 (65.0%) Female: 172	145	Male: 85 (58.6%) Female: 60	0.19
Baseline KPS*	501	≥90: 259 (51.7%) <90: 242	387	≥90: 198 (51.2%) <90: 189	114	≥90: 61 (53.5%) <90: 53	0.74
Metastasis diameter [cm]*	554	2.0 (0.4–9.0)	421	2.1 (0.5–9.0)	133	1.5 (0.4–8.6)	<0.0001
Primary controlled*	504	Yes: 423 (83.9%) No: 81	395	Yes: 323 (81.8%) No: 72	109	Yes: 100 (91.7%) No: 9	0.02
Solitary metastasis*	561	Yes: 239 (37.5%) No: 322	428	Yes: 229 (53.5%) No: 199	133	Yes: 10 (7.5%) No: 123	<0.0001
Primary cancer	636	Breast Ca: 37 (5.8%) NSCLC: 194 (30.5%) CRC: 139 (21.9%) Kidney cancer: 43 (6.8%) Sarcoma: 48 (7.5%) Esophageal Ca: 17 (2.7%) Melanoma: 18 (2.8%) Other: 140 (22.0%)	491	Breast Ca: 28 (5.7%) NSCLC: 171 (34.8%) CRC: 98 (20.0%) Kidney Ca: 37 (7.5%) Sarcoma: 31 (6.3%) Esophageal Ca: 13 (2.6%) Melanoma: 13 (2.6%) Other: 100 (20.4%)	145	Breast Ca: 9 (6.2%) NSCLC: 23 (15.9%) CRC: 41 (28.3%) Kidney Ca: 6 (4.1%) Sarcoma: 17 (11.7%) Esophageal Ca: 4 (2.8%) Melanoma: 5 (3.4%) Other: 40 (27.6%)	0.001
Histopathology	538	SSC: 117 (21.7%) AC: 252 (46.8%) Sarcoma: 39 (7.2%) Other: 130 (24.2%)	414	SCC: 99 (23.9%) AC: 189 (45.7%) Sarcoma: 25 (6.0%) Other: 101 (24.4%)	124	SCC: 18 (14.5%) AC: 63 (50.8%) Sarcoma: 14 (11.3%) Other: 29 (23.4%)	0.04

Continuos variables are given as median and range, categorical variables as number and percentage. Differences between single and multiple SBRT groups were assessed using the Wilcoxon rank sum test for continuos and Pearson's χ^2 test for categorical variables. The variables marked with "*" were used for multivariable model building. AC: Adeno carcinoma; CRC: Colorectal cancer; SSC: Squamous cell carcinoma.

total of 17 patients were treated for more than one lesion synchronously and were re-treated for progressive metastases >1 month after the first course. Of those, the first synchronous treatments involved two lesions in 13 patients and three lesions in the other 4 patients; the interval to the second SBRT course was median 8.7 months (1.9–23.7 months) (Fig. 1).

Patients treated for multiple metastases were slightly younger (median difference 0.9 years), were treated for significantly smaller pulmonary metastases, and had a higher likelihood of the primary tumor being controlled at the time of the last SBRT treatment (Table 1). Presence of a solitary metastasis at the time of the last SBRT treatment was significantly less frequent in the cohort of patients treated with multiple SBRT. Additionally, the distribution of primary cancer was significantly different with more patients having metastatic colorectal cancer and sarcoma and less patients having NSCLC histology in the multiple SBRT cohort. There were no significant differences with respect to baseline KPS.

Table 2 summarizes patient, tumor and treatment characteristics at the last SBRT treatment separately for patients receiving synchronous SBRT, repeat metachronous SBRT or synchronous SBRT followed by repeat SBRT >1 month later. The number of fractions and BED delivered to the isocenter (using α/β = 15 Gy [20]) within the final SBRT course did not differ between these groups (Fig. 2).

The median follow-up for all 637 patients was 13.0 months (range 0.2–131.9 months) and median OS was 23.5 months (95% CI: 21.4–26.6 months). The actuarial one-, two- and three-year OS rates were 70.8% (95% CI: 67.1–74.8), 49.5% (45.1–54.3) and 33.8% (29.3–39.0) (Fig. 3A). When analyzed from the first SBRT treatment instead of the last, median follow-up was 14.6 months (range 0.2–131.9 months) and median OS was 24.5 months (95% CI: 22.6–27.8 months).

No significant OS differences were observed between patients receiving a single SBRT treatment and those receiving multiple SBRT treatments (p = 0.96 in log-rank test, p = 0.96 in Cox regression) (Fig. 3B). Additionally, the timing of multiple SBRT did not influence OS: we did not observe differences in OS between the 88 patients, who had received all SBRT treatments within one month, the 40 patients, who were treated with repeat metachronous SBRT after a single metastasis treatment and the 17 patients who were treated for more than one lesion in the first SBRT course and were re-treated >1 month after the first course (p = 0.86, log-rank test). Also, neither synchronous (p = 0.60) nor metachronous (p = 0.71) SBRT nor the total number of synchronous (p = 0.997)

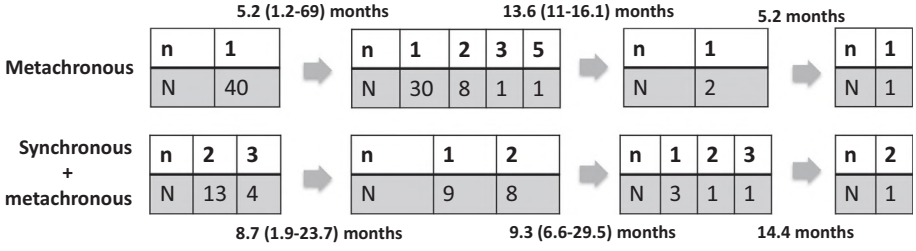

Fig. 1. Timing and treatments of repeat SBRT in the two patient groups receiving metachronous treatments. Each table represents one SBRT course and displays the number of patients (N) that were treated for a total of n metastases within that course.

Table 2
Patient, tumor and treatment characteristics for patients groups receiving repeat SBRT.

Variable	Synchronous SBRT ($N = 88$)		Metachronous SBRT ($N = 40$)		Synchronous followed by metachronous SBRT ($N = 17$)		p-Value
	N	Summary	N	Summary	N	Summary	
Age [years]	88	63.2 (15.5–100)	40	70.5 (23.8–85)	17	67.5 (41.2–82.9)	0.03
Gender	88	Male: 52 (69.1%) Female: 36	40	Male: 23 (57.5%) Female: 17	17	Male: 10 (58.8%) Female: 7	0.99
Baseline KPS	68	≥90: 35 (51.5%) <90: 33	32	≥90: 19 (59.4%) <90: 13	14	≥90: 7 (50.0%) <90: 7	0.73
Overall number of metastases treated	88	2 (2–6) 2: 72 (81.8%) 3: 14 (15.9%) 4: 1 (1.1%) 6: 1	40	2 (2–6) 2: 28 (70.0%) 3: 9 (22.5%) 4: 2 (5.0%) 6: 1 (2.5%)	17	4 (3–8) 3: 6 (35.3%) 4: 6 (35.3%) 5: 2 (11.8%) 6: 1 (5.9%) 7: 1 8: 1	<0.0001
Overall number of SBRT courses	88	1	40	2 (2–4) 2: 38 (95.0%) 3: 1 (2.5%) 4: 1	17	2 (2–4) 2: 12 (70.6%) 3: 4 (23.5%) 4: 1 (5.9%)	<0.0001
Primary controlled	64	Yes: 60 (93.8%) No: 4	35	Yes: 30 (85.7%) No: 5	10	Yes: 10 (100%) No: 0	0.23
Solitary metastasis	84	Yes: 0 (0%) No: 84	35	Yes: 7 (20.0%) No: 28	14	Yes: 3 (21.4%) No: 11	<0.0001
Metastasis diameter [cm]	81	1.5 (0.4–5.9)	35	1.7 (0.6–8.6)	17	1.6 (0.8–3.8)	0.50
BED_{iso} [Gy_{15}]	88	106.1 (30.0–174.8)	40	101.8 (41.7–200.0)	17	107.8 (35.9–177.2)	0.16
Number of fractions	88	3 (1–12)	40	3 (1–10)	17	3 (1–5)	0.33

Differences between groups were assed using the Kruskal–Wallis test for continuous and Pearson's χ^2 test for categorical variables. N: Number of patients.

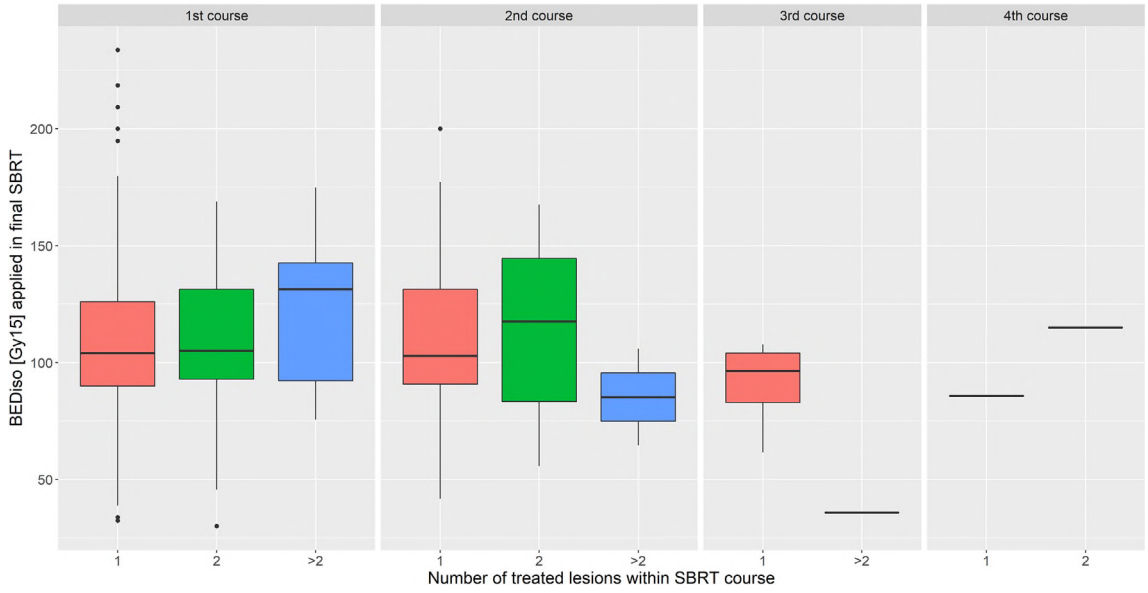

Fig. 2. BED delivered to the isocenter in the last SBRT treatment of the 1st, 2nd, 3rd or 4th SBRT course, respectively. Subgroups are differentiated in color according to the total number of treated lesions.

or metachronous ($p = 0.52$) SBRT treatments was associated with OS in univariable Cox regression among all 637 patients (Supplementary Table 1).

In multivariable Cox regression metastasis size (HR = 1.19, $p = 0.00003$) and "primary controlled" (HR = 0.70, $p = 0.007$) were the most significant predictors of OS, followed by "solitary metastasis" (HR = 0.72, $p = 0.015$) and KPS (HR = 0.77, $p = 0.12$) (Supplementary Table 2). Synchronous (HR = 0.93, $p = 0.71$) and metachronous (HR = 1.10, $p = 0.53$) SBRT was not associated with OS. Very similar results were obtained when replacing the categorical synchronous and metachronous variables with the total number of synchronous and metachronous SBRT courses (results not shown). Similar results were also obtained when restricting the analysis to patients with complete data only (Supplementary Table 2).

Radiation induced pneumonitis grade II and III was reported in 25 and 6 patients, respectively. One male patient developed grade V pneumonitis 112 days after SBRT and died 4 days later; this patient was treated for a single pulmonary metastasis of NSCLC histology and a maximum diameter of 6.7 cm with a dose of 8×6 Gy prescribed to the 80% isodose line. Information on pneumonitis development was lacking for 52 patients.

In total, 34 patients and 78 patients died within 3 months and 6 months after their last SBRT course, respectively. Information on death within these timeframes was missing for 46 and 78 patients

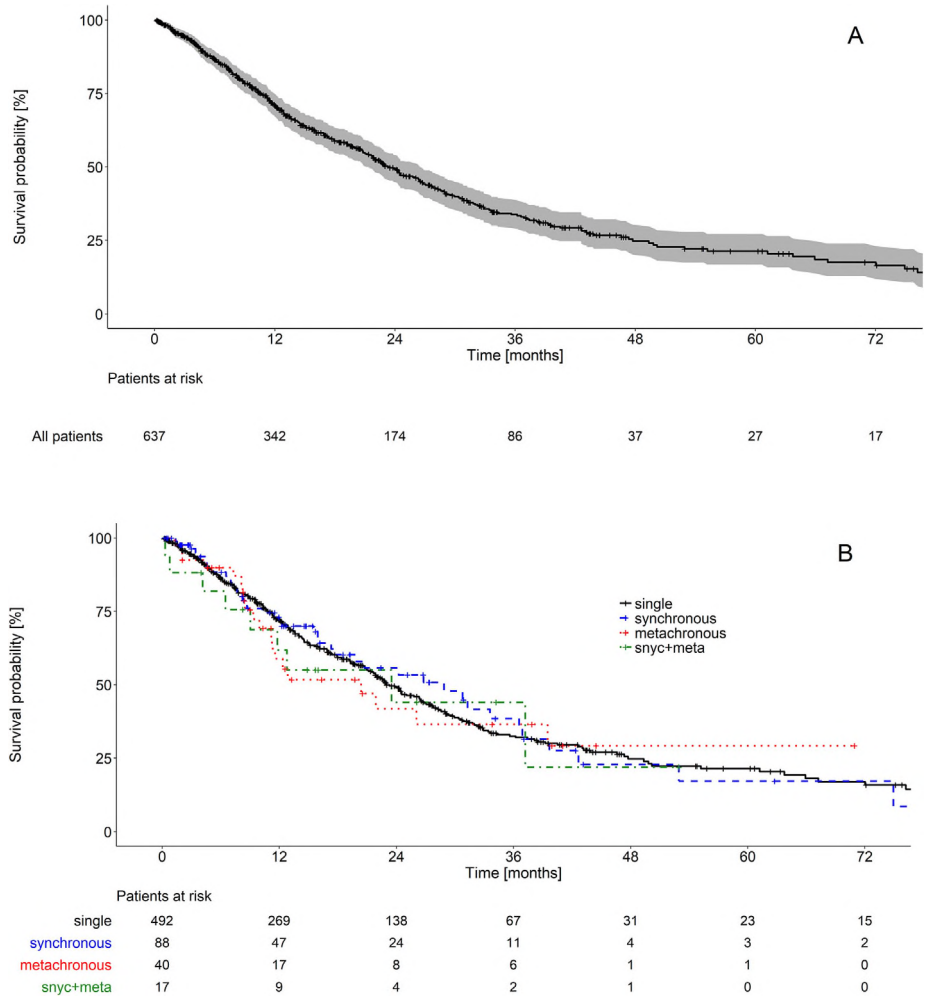

Fig. 3. Kaplan–Meier curves showing the overall survival of (A) the 637 patients used in the analysis and (B) the patients receiving either single, synchronous, metachronous or synchronous followed by metachronous SBRT.

Table 3
Death rates of the different patient groups.

Group	3-Month death count (rate)	*p*-Value	6-Month death count (rate)	*p*-Value
Single SBRT	26 (6.0%)	1	62 (14.4%)	0.7221
Multiple SBRT	8 (6.3%)		16 (12.6%)	
Synchronous SBRT	3 (3.9%)	0.2729	9 (12.0%)	0.6896
Metachronous SBRT	3 (7.7%)		4 (11.1)	
Synchronous followed by metachronous SBRT	2 (11.8%)		3 (18.8%)	

Due to the small number of events in the groups receiving metachronous irradiation, Fisher's exact test instead of Pearson's χ^2 test was used for assessing differences between groups.

that were lost to follow-up, so that the corresponding death rates were 5.8% (34/591) and 14.0% (78/559), respectively. Detailed early death rates are summarized in Table 3. Both 3-month ($p = 1$) and 6-month death rates ($p = 0.722$) of patients receiving single versus multiple SBRT were not significantly different. Additionally, there was no significant difference between the three patient groups receiving repeat SBRT regarding the 3- or 6-month death rates (Table 3).

Neither single SBRT versus multiple ($p = 0.62$) nor single SBRT versus synchronous ($p = 0.60$), or metachronous ($p = 0.88$) SBRT were associated with probability of early death within six months in univariable logistic regression modeling (Supplementary Table 1). Also, no association was found for the total number of synchronous ($p = 0.65$) and metachronous ($p = 0.50$) SBRT treatments or the total number of metastases treated independent of timing ($p = 0.46$). No associations were found either when using death within three months as the end point in univariable analysis (results not shown). In multivariable logistic regression no significant associations were found for synchronous (OR = 0.77, $p = 0.549$) and metachronous (OR = 0.99, $p = 0.974$) SBRT and early death within 6 months (Supplementary Table 2). Regression coefficients for most variables were similar between the imputed and complete sample analyses. Similar results were obtained when using the total number of synchronous and metachronous SBRT courses as predictors of 6-month death (results not shown). Finally, multivariable logistic regression for death within 3 months yielded consistent effect directions (sign of the regression coefficients), but effect estimates were too uncertain to yield any

statistically significant associations due to the small number of events.

Discussion

In our large multicenter analysis of SBRT for pulmonary oligometastatic disease, we identified 145 patients treated for >1 pulmonary target. Most patients were treated for 2 lesions but 45 patients were characterized by a minimum of 3 pulmonary SBRT treatments. Additionally, 57 patients were treated with minimum 2 courses of repeat SBRT. The maximum number of SBRT treatments and courses was 8 ($N = 1$) and 4 ($N = 2$), respectively. Patient selection criteria for multiple SBRT were institutional-specific and not standardized; however, patients treated with multiple SBRT were characterized by good prognostic factors such as younger age, higher proportion of the primary tumor controlled and by a higher proportion of metastases from sarcoma and colorectal cancer and lower proportion of NSCLC histology. Pulmonary metastases in the multiple SBRT cohort were smaller on average but were treated without a dose compromise. Consequently, patients treated with multiple SBRT were carefully selected, reflecting the lack of data in this challenging situation.

The combination of the applied favorable patient selection criteria and radical SBRT without a dose compromise resulted in very similar OS in patients treated for a single pulmonary lesion and patients treated with multiple SBRT: 32.5% vs. 39.2% at 36 months. Additionally, we did not observe that the overall number of pulmonary metastases treated with SBRT or the timing of repeat SBRT – synchronous vs. metachronous vs. synchronous followed by metachronous – had an influence on OS. For correct interpretation of our results, it needs to be considered that OS was calculated from the last treatment within the last course of SBRT.

Regarding safety of SBRT for multiple pulmonary lesions, no case of grade IV or grade V toxicity was observed; only one case of grade V pneumonitis was recorded in a patient who had been irradiated for a single pulmonary lesion. To also consider a potential risk of occult toxicity, we evaluated 3-month and 6-month death rates: most cases of radiation induced pneumonitis are expected during this follow-up and simultaneously the risk of death from comorbidities and cancer progression should be low. We did not find a significant association between 3-month and 6-month death rates and the number of pulmonary metastases treated as well as the timing of repeat SBRT.

Despite most patients fail systemically after radical local treatment for oligometastatic disease, an oligorecurrent pattern of disease progression is observed in a relevant proportion of patients. Decaestecker et al. reported about 50 patients with oligometastatic prostate cancer (mostly bone or lymph node metastases); 32 relapses were observed after radical SBRT, of which 24 (75%) were again oligometastatic [21]. A second radical local treatment was performed in 19 patients, using SBRT in 16 patients and surgery in 3 patients. One patient was treated with a total of 4 SBRT courses. A similar study has been performed by Milano et al., where a very heterogeneous patient cohort was analyzed: 77 patients were treated for oligometastases (64% with 1 or 2 metastases, maximum 5 metastases) at various locations (most frequently liver and lung metastases) of various histologies (most frequently breast cancer and colorectal cancer) [22]. Overall, 56/77 patients failed systemically of which 18 (32%) were oligorecurrent and amendable to repeat radical local treatment. Additionally, the site of first distant recurrence after SBRT for pulmonary oligometastases was again the lung in 73%. This high rate of oligorecurrence is similar to surgical experiences: Butte et al. reported about 952 patients after partial hepatectomy for colorectal liver metastases and a second metastasectomy was possible in 27% of the patients [23].

An oligorecurrent pattern of disease progression offers the possibility of repeat radical local treatment. However, only very limited data are available for repeat SBRT. Valakh et al. reported about repeat pulmonary SBRT of the same recurrent lesion or new lesions in a distance of $\leq$3.5 cm, only 1/9 patient was treated for oligometastatic disease [24]. No grade 4 or 5 toxicity was observed but 33% developed late grade 3 toxicity. Similarly, Kilburn et al. reported about repeat SBRT, where the analysis was limited to patients with an overlap of the 30 Gy isodose lines; the majority of the patients were treated for primary NSCLC [25]. Late toxicity grade 2–3 was observed in 10/33 patients, most frequently chest wall pain. Peulen et al. reported the most comprehensive experience of repeat pulmonary SBRT and limited the analysis to patients with >50% overlap of the PTV; 21/29 patients were treated for pulmonary metastases and three and one patient were treated with three and four SBRT courses [26]. Overall, 8/29 patients developed severe grade 4 or 5 toxicity, and all patients with severe toxicities were re-irradiated for centrally located lesions. Two-year OS was 43% for the entire cohort.

To the best of our knowledge, the study by Milano et al. is still the only report of patients undergoing multiple courses of SBRT for oligometastatic and oligorecurrent disease [27]. A total of 32 patients were treated with repeat SBRT for local failure ($n = 9$) or new lesions ($n = 29$), 10 patients were treated with a minimum 3 SBRT courses, 24 patients for lesions within the same organ; however, the number of repeat pulmonary SBRT was not specified. No case of late toxicity grade $\geq$2 was described. Two and four-year OS were 65% and 33%, and this was not significantly different to a patient cohort from the same institution with only one SBRT course for oligometastatic disease. This experience of similar OS in carefully selected patients treated with repeat SBRT for oligometastatic disease is in good agreement to our results.

The best data are available from surgical series, in particular repeat resection for oligorecurrent colorectal lung or liver metastases: median OS ranged between 53 and 81 months [23,28], and Yokota et al. reported a 3 year OS of 84.1% [29]. This outcome appears not substantially different compared to the first treatment course of oligometastases, again confirming results of our study. However, most studies described that patients were carefully selected, also similar to our own experiences.

Our study suffers from the known limitations of retrospective multi-center registry studies, in particular when analyzing toxicity. We therefore focused on survival, early death and severe toxicity as hard and reliable endpoints of this study. Patient selection criteria for synchronous treatment of multiple metastases and for repeat SBRT are based on institutional-specific policies and guidelines and are not available for analysis; a selection bias for those patients undergoing repeat SBRT with more indolent disease is possible. Similarly, SBRT radiation doses and fractionation were not standardized and were selected according to institutional guidelines. Additionally, detailed data about the location and anatomical relationship of treated metastases and accumulated dose distributions to thoracic organs at risk are not available. Therefore, we are currently planning to collect DICOM RT data of all SBRT treatments to better define our patient cohort dosimetrically. Finally, we also have only insufficient information on the presence and distribution of extrathoracic disease, including intracranial, and use of systemic therapies concurrently with or after SBRT. For these reasons, we are currently updating the clinical database and will perform more in depth analyses on a primary-tumor specific basis. The first study focusing on oligometastatic renal cell cancer has recently been reported [30].

In conclusion, we established the largest series of multiple and repeat pulmonary SBRT for oligometastatic and oligorecurrent disease and neither the overall number of lung metastases nor the timing of repeat SBRT influenced pulmonary toxicity, early death

and overall survival. Synchronous SBRT for multiple pulmonary oligometastases as well as repeat SBRT may therefore be considered in appropriately selected patients. Prospective validation of our findings is however required.

Conflict of interest statement

The authors declare that they have no conflicts of interest relating to the content of this manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.radonc.2018.02.016.

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