Influence of Institutional Experience and Technological Advances on Outcome of Stereotactic Body Radiation Therapy for Oligometastatic Lung Disease

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Summary

On the basis of a multi-institutional database of 700 patients treated with stereotactic body radiotherapy (SBRT) for lung metastases, this study investigated whether institutional experience and the introduction of technological advances into SBRT improved outcome over time. Overall, technological innovations did not significantly affect outcome. Only the use of pre-SBRT fluorodeoxyglucose positron-emission tomography (FDG-PET) staging was identified as an independent prognostic factor for superior survival. However, local control after pulmonary SBRT was significantly influenced by the individual center's experience.

Purpose: Many technological and methodical advances have made stereotactic body radiotherapy (SBRT) more accurate and more efficient during the last years. This study aims to investigate whether experience in SBRT and technological innovations also translated into improved local control (LC) and overall survival (OS).

Methods and Materials: A database of 700 patients treated with SBRT for lung metastases in 20 German centers between 1997 and 2014 was used for analysis. It was the aim of this study to investigate the impact of fluorodeoxyglucose positron-emission tomography (FDG-PET) staging, biopsy confirmation, image guidance, immobilization, and dose calculation algorithm, as well as the influence of SBRT experience, on LC and OS.

Results: Median follow-up time was 14.3 months (range, 0-131.9 months), with 2-year LC and OS of 81.2% (95% confidence interval [CI] 75.8%-85.7%) and 54.4% (95% CI 50.2%-59.0%), respectively. In multivariate analysis, all treatment technologies except FDG-PET staging did not significantly influence outcome. Patients who received pre-SBRT FDG-PET staging showed superior 1- and 2-year OS of 82.7% (95% CI 77.4%-88.6%) and 64.8% (95% CI 57.5%-73.3%), compared with patients without FDG-PET staging resulting in 1- and 2-year OS rates of 72.8% (95% CI 67.4%-78.8%) and 52.6% (95% CI 46.0%-60.4%), respectively ($P = .012$). Experience with SBRT was identified as the main prognostic factor for LC: institutions with higher SBRT experience (patients treated with SBRT within the last 2 years of the inclusion period) showed superior LC compared with less-experienced centers ($P \leq .001$). Experience with SBRT within the last 2 years was independent from known prognostic factors for LC.

Conclusion: Investigated technological and methodical advancements other than FDG-PET staging before SBRT did not significantly improve outcome in SBRT for pulmonary metastases. In contrast, LC was superior with increasing SBRT experience of the individual center.

Introduction

Stereotactic radiation therapy has a history of several decades. Initially, stereotactic radiation therapy was primarily applied for treating brain lesions (1, 2). In the early 1990s the principles and practice of stereotactic radiation therapy, applying high doses of irradiation to an intracranial lesion in either a single or a few fractions, were transferred to the irradiation of extracranial targets within the body (3). Today, stereotactic body radiation therapy (SBRT) is widely applied in the treatment of medically inoperable patients with early-stage non-small cell lung cancer (NSCLC), as well as patients with oligometastatic disease to the lung. A recent survey among radiation oncologists in 6 European countries and 30 SBRT-experienced institutions showed that 90% to 100% were applying SBRT for pulmonary metastases or early-stage NSCLC, respectively (4). Furthermore, more than 550

radiation oncologists from the United States reported in a survey that the lung was the most common organ treated with SBRT in their centers (5). Several prospective studies about SBRT treatment for both early-stage NSCLC and pulmonary metastases showed highly consistent local control (LC) rates of more than 90%, which is superior to historical outcome after conventionally fractionated radiation therapy (6, 7).

Since the early development and clinical evaluation of SBRT within prospective phase 2 trials, multiple technological and methodical advancements have made SBRT gradually more accurate and efficient. These technologies comprise better staging using fluorodeoxyglucose positron-emission tomography (FDG-PET), respiratory motion detection and motion compensation, accurate and more comfortable patient immobilization, intensity modulated treatment planning, and image-guided tumor targeting (8-11).

However, only very little evidence is available whether these technological advancements translate into improved local tumor control and/or better survival. The working group Stereotactic Radiotherapy of the German Society of Radiation Oncology (DEGRO) recently published a retrospective, multi-institutional study investigating survival and LC of 700 patients treated with SBRT for pulmonary metastases (12). In a second step, a patterns-of-care study analyzing the influence of institutional experience as well as technological and methodical aspects of SBRT was conducted.

Methods and Materials

Patient and treatment characteristics

In 2012 the working group Stereotactic Radiotherapy of the DEGRO asked all German radiation therapy centers to participate in a pooled database of patients treated with SBRT for lung metastases. Stereotactic body radiation therapy of pulmonary metastases from different primary tumors was analyzed in 700 patients treated at 20 centers, which were located in Germany (n = 19) and Switzerland (n = 1), between 1997 and 2014. The analysis was approved by the ethics committee of the University Hospital Heidelberg (S-280/2014). A more detailed description of the database was recently published (12).

Stereotactic body radiation therapy was performed when the following criteria were met: patients with medically inoperable or unresectable pulmonary metastases, or if patients refused operation. Biopsy confirmation was only attained when there was doubt about the metastatic origin of the pulmonary lesion.

Table 1 Patient characteristics

Characteristic	n	%	Median	Minimum	Maximum
Age (y)	700		67.0	6.4	99.9
Sex	700				
Male	449	64.1			
Female	251	35.9			
Pretreatment performance scale (Karnofsky index) (%)	551		90	40	100
Baseline FEV_1 (absolute)	337		1.98	0.49	5.36
Primary tumor histology	698				
NSCLC	210	30.0			
Colorectal cancer	153	21.9			
Sarcoma	51	7.3			
Renal cell carcinoma	48	6.9			
Breast cancer	43	6.2			
Melanoma	24	3.4			
Esophageal cancer	18	2.6			
Others	151	21.7			
Maximum metastasis diameter (cm)	609		2.2	0.4	9.4
No. of metastases	622				
Single	264	42.4			
Multiple	358	57.6			
Metastasis location	589				
Central	126	21.4			
Peripheral	463	78.6			
Time interval between primary tumor diagnosis and SBRT treatment (mo)	670		35.8	0.0	345.5
BED at PTV periphery (Gy)	698		84.4	22.5	180.0
Single fraction dose (PTV encompassing) (Gy)	698		12.5	3.0	33.0
No. of SBRT fractions	699		3	1	13

Abbreviations: BED = biologically effective dose; FEV_1 = forced expiratory volume in 1 second; NSCLC = non–small cell lung cancer; PTV = planning target volume; SBRT = stereotactic body radiation therapy.

All patients were diagnosed with metastatic cancer; patients suffered in median from 1 further metastasis (range, 0-15) in addition to the treated pulmonary lesion (Table 1). However, 92.5% of the patients with further metastases received additional treatment for their metastases (SBRT, conventional radiation therapy, radiofrequency ablation, surgery, or chemotherapy).

Several technological and methodical parameters were investigated regarding their prognostic impact on LC and overall survival (OS): biopsy confirmation, use of FDG-PET scan for staging, immobilization techniques, applied image guidance, and dose calculation algorithm; unfortunately, only insufficient data were available for evaluation of motion management (tracking/gating and utilization of 4-dimensional CT for planning) and methodology of treatment planning (3-dimensional conformal, intensity modulated radiation therapy, volumetric modulated arc therapy). Furthermore, the influence of SBRT experience of each individual institution was evaluated. As each center gained experience in treated patients and years during the analyzed time span 1997-2014, SBRT experience was not analyzed as a stable variable but as a "growing" one. Outcome of each patient was correlated with the individual SBRT experience in patients and years that the respective treating center had gained before. In detail, the variables "SBRT experience in years per institution," "SBRT experience in patients per institution," "SBRT experience in patients treated within the last year," "SBRT experience in patients treated within the last 2 years," and "SBRT experience in patients per institution and year" were considered. For the variables "SBRT experience in patients treated with the last year/or last 2 years" the past year or the past 2 years of the inclusion period were analyzed, respectively.

Local control(LC) was consistently determined as no regrowth within the high-dose area, whereas new lesions within the same lobe were defined as distant metastases. LC and OS were analyzed from the beginning of radiation therapy. Data for LC was only available for 600 patients, whereas OS was analyzed for 700 patients.

Statistical analysis

Univariate Cox models were used for evaluating the impact of the predictors for OS and LC. In a second step, multivariable cox models were performed including all variables with $P \leq .1$ in univariate analysis. To rule out possible confounder variables, we included known prognostic factors for OS and LC in multivariate analysis: Karnofsky performance score, biologically effective dose (BED) as planning target volume (PTV)-encompassing BED, single-fraction (PTV-encompassing) dose, primary tumor histology, metastasis diameter, number of metastases, and time interval between primary tumor diagnosis and SBRT treatment. These prognostic factors were recently published (12).

Receiver operating characteristics (ROC) curves and Youden's index were applied to determine the optimal cutoff for SBRT experience in patients treated within the last 2 years in predicting LC after 1 year. A stepwise variable selection procedure was used for multivariate analysis as recently described (12). Descriptive statistics were performed using Mann-Whitney U tests or χ^2 tests for continuous or categorical data, respectively.

Results

Patterns of care

Whereas 2 institutions started SBRT for pulmonary metastases in 1997, all centers practiced SBRT by the year 2012. In 2012, the last full year covered in this analysis, a total of 102 pulmonary metastases were treated with SBRT (Fig. 1 and Table 1).

Patterns of SBRT practice changed considerably during the analyzed time span (Table 2). The PTV-encompassing dose was continuously increased: whereas pulmonary metastases were treated with a median BED of 81.6 Gy between 1997 and 2003, the PTV-encompassing dose increased to a median BED of 84.4 Gy between 2004 and 2010 and was further escalated to a median BED of 93.0 Gy between 2011 and 2014 ($P \leq .001$).

Between 2004 and 2009, FDG-PET-staging was practiced in 22.3% of the patients and increased to 43.9% of the patients between 2010 and 2014 ($P \leq .001$). A more accurate dose calculation algorithm (type B instead of type A) was applied in 13.4% and 83.6% of the cases during the periods 1997-2006 and 2007-2014, respectively ($P \leq .001$).

The method of patient setup and image guidance changed substantially over time ($P \leq .001$). Whereas between 1997 and 2006 daily pre-SBRT CT simulation outside the treatment room was mainly applied (59.3% of all treatments), daily pre-SBRT in-room CT scans for image guidance were used in 86.1% of the cases between 2013 and 2014.

Univariate and multivariate analysis

Median follow-up time was 14.3 months (range, 0-131.9 months) with 1-year and 2-year LC of 90.9% (95% CI 87.6%-93.5%) and 81.2% (95% CI 75.8%-85.7%), respectively. One-year and 2-year OS were found to be 75.1% (95% CI 72.4%-79.2%) and 54.4% (95% CI 50.2%-59.0%), respectively.

Results of univariate analysis are shown in Table 3. Local control was superior with growing SBRT experience: patients who were treated at more experienced institutions showed better LC. In detail, LC was highly significantly influenced by all SBRT experience variables except for SBRT experience in years per institution ($P \leq .005$). The association of SBRT experience with OS was of borderline significance ($P = .08$). The only significant factor for superior OS was utilization of FDG-PET staging ($P = .002$).

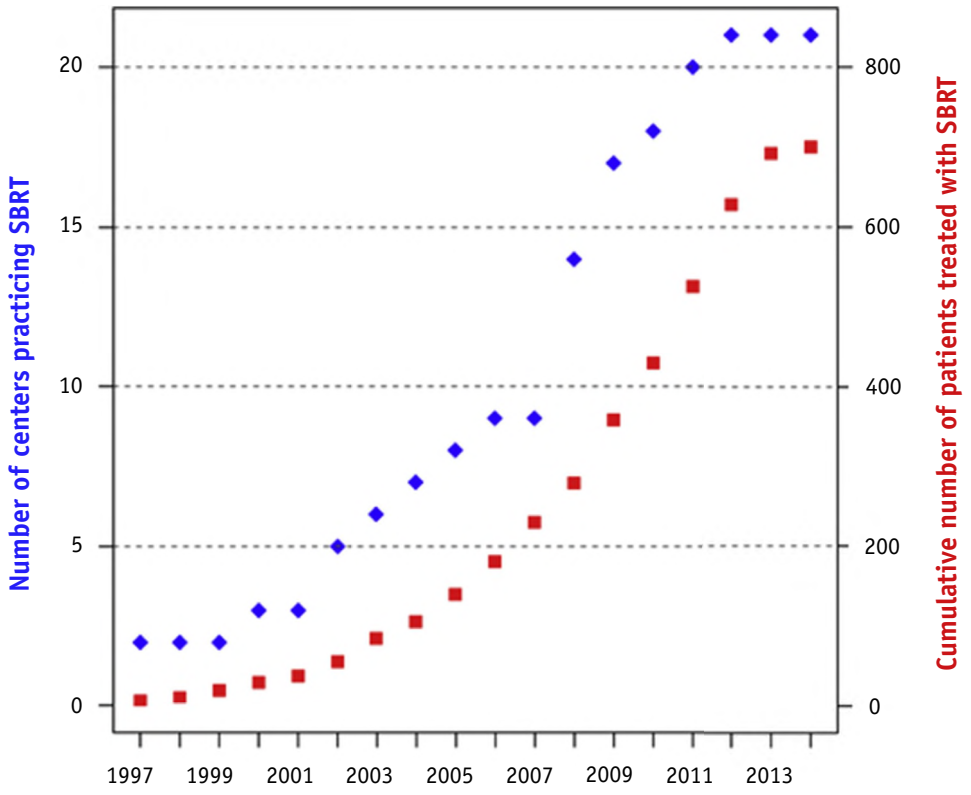

Fig. 1. Patterns of implementation and practice of stereotactic body radiation therapy (SBRT) treatment in 20 centers in and Germany and Switzerland.

As all analyzed SBRT experience variables studied in univariate analysis are highly correlated with each other, we only included "SBRT experience in patients treated within the last 2 years" in multivariate analysis, as this variable was most statistically significant regarding both LC and OS in univariate analysis (Table 3). Furthermore, we performed ROC analysis investigating LC depending on SBRT experience in patients treated within the last 2 years. A cutoff patient number of 4 was calculated. Local control was superior at centers that had performed SBRT for lung metastases in 4 or more patients during the last 2 years ($P<.001$) (Fig. 2).

To test the prognostic relevance of the variable "SBRT experience in patients treated within the last 2 years," we included known prognostic factors for LC and OS for SBRT of pulmonary metastases in multivariate analysis (Table 4), which were recently published by the DEGRO working group "stereotactic radiotherapy" (12). Stereotactic body radiation therapy experience in patients treated within the last 2 years remained as an independent prognostic factor for LC ($P\leq.001$), besides all known prognostic factors. In addition, SBRT experience in patients treated within the last 2 years was not correlated with SBRT dose in BED.

To investigate whether patient selection influenced the impact of SBRT experience on LC, the cutoff patient number of 4 was used to separate experienced from less-experienced centers. Differences in patient characteristics (age, sex, Karnofsky performance score, primary tumor histology, number of metastases, metastasis size, and time interval between primary tumor diagnosis and SBRT, as well as use of FDG-PET staging) were analyzed between experienced and less-experienced centers. Interestingly, we only detected a significant difference in metastasis size ($P=.003$). Median metastasis size at experienced centers was 2.3 cm, whereas less-experienced centers performed SBRT in patients with smaller metastases (1.9 cm) in median.

Regarding OS, SBRT experience was not associated with improved OS in multivariate analysis. All analyzed irradiation technologies except FDG-PET staging did not significantly affect LC and OS in multivariate analysis. However, patients who received pre-SBRT FDG-PET staging showed superior OS ($P=.011$) (Fig. 2). Nearly all known prognostic factors remained independently significant in multivariate analysis (Table 4).

Discussion

A recent international survey asked more than 1000 radiation oncologists from 43 countries about SBRT for extracranial oligometastases and reported that more than 60% used SBRT to treat patients with $\leq$3 extracranial oligometastases. Of those not having used SBRT for oligometastases before, 59% intended to start within the next

Table 2 SBRT treatment characteristics, with analysis for time trends

Characteristic	n	%	Median	Minimum	Maximum	Time trend
Biopsy confirmation of metastases						$P=.408$
No	486	69.4				
Yes	155	22.1				
Unknown	59	8.4				
Staging FDG-PET						$P\leq.001$
No	277	39.6				
Yes	230	32.9				
Unknown	193	27.5				
Dose calculation algorithm						$P\leq.001$
Type A	183	26.1				
Type B	403	57.6				
Unknown	114	16.3				
Patient setup and image guidance						$P\leq.001$
Stereotactic setup	83	11.9				
Resimulation outside treatment room	154	22.0				
In-room IGRT	459	65.6				
Unknown	4	0.5				
Immobilization devices						$P\leq.001$
Vacuum cushions	533	76.1				
Wingstep/mammaboard	42	6.0				
None	55	7.9				
Unknown	70	10.0				
BED at PTV periphery (Gy)	698		84.4	22.5	180.0	$P\leq.001$
SBRT experience in years per institution			5.1	1.2	16.4	
SBRT experience in patients per institution			23	4	109	
SBRT experience in patients treated within the last year of the inclusion period			4.5	0	18.5	
SBRT experience in patients treated within the last 2 years of the inclusion period			5	0	23	
SBRT experience in patients per institution and year			4.5	0.6	19.2	

Abbreviations: FDG-PET = fluorodeoxyglucose positron-emission tomography; IGRT = image guided radiation therapy. Other abbreviations as in Table 1.

2 to 3 years (13). As there is increasing interest in pulmonary SBRT, the DEGRO working group "Stereotactic Radiotherapy" raised the question whether technological equipment and institutional experience in SBRT may affect outcome.

Up to now variation in equipment, technology, and techniques has not been linked to local control probability and survival after SBRT (14, 15). In agreement, we did not detect a significant effect of nearly all investigated irradiation technologies on outcome: biopsy confirmation of metastatic disease, immobilization techniques, image guidance, and dose calculation algorithm. One reason for this might be that the introduction of these modern technologies was accompanied by a parallel escalation of irradiation dose. A distinct dose-response relationship for local tumor control for pulmonary SBRT is well known (16-19): for optimized LC of pulmonary SBRT, a biological effective dose of $\geq$100 Gy is recommended (8, 20, 21). Hence, implementation of more advanced technologies might have contributed to improved outcomes of SBRT by having allowed a continuous dose escalation within the DEGRO community. Technological and methodical advancements in pulmonary SBRT during the last years were probably a prerequisite for the fast and broad implementation of SBRT in our radio-oncologic communities. Whether safe dose escalation and broad adoption of SBRT might have been possible without the investigated technologies remains unclear and cannot be answered in this analysis.

However, we detected a prognostic impact of pre-SBRT FDG-PET staging on OS. Patients who received FDG-PET staging before SBRT treatment showed significantly improved 1-year and 2-year OS of 82.7% (95% CI 77.4%-88.6%) and 64.8% (95% CI 57.5%-73.3%), respectively, whereas patients without sufficient staging had 1-year and 2-year OS rates of 72.8% (95% CI 67.4%-78.8%) and 52.6% (95% CI 46.0%-60.4%), respectively ($p=0.012$) (Fig. 2A). The significant effect of FDG-PET staging on OS is most likely explained by better patient selection. Patients with multiple metastases identified by FDG-PET were probably more likely subjected to systemic treatment rather than local SBRT. This finding is supported by surgical data; Congedo et al (22) illustrated that the utilization of preoperative staging with PET-CT was an independent prognostic factor for outcome of oligometastatic NSCLC patients. Additional pre-SBRT PET-CT staging might be

Table 3 Univariate analysis of factors influencing OS and LC

Factor	OS			LF		
	HR	95% CI	*P*	HR	95% CI	*P*
Biopsy confirmation of metastases	1.020	(0.779-1.337)	.884	0.986	(0.558-1.724)	.961
Staging FDG PET-CT (CT ref.)	0.635	(0.478-0.842)	.002	0.446	(0.256-0.778)	.004
Dose calculation algorithm (type A ref.)	1.058	(0.824-1.359)	.659	0.373	(0.220-0.633)	≤.001
Patient setup and image guidance (stereotactic setup ref.)			.237			.023
IGRT outside	0.770	(0.562-1.055)		1.303	(0.549-3.095)	
IGRT inside	0.768	(0.545-1.082)		2.374	(0.989-5.698)	
Immobilization devices (vacuum cushion ref.)			.129			.731
Wingstep/mammaboard	0.701	(0.224-2.200)		1.092	(0.149-7.983)	
No immobilization	1.404	(0.991-1.989)		2.362	(0.854-6.538)	
SBRT experience in y per institution	0.986	(0.957-1.015)	.343	0.973	(0.908-1.044)	.447
SBRT experience in patients per institution	0.996	(0.991-1.001)	.115	0.980	(0.966-0.994)	.005
SBRT experience in patients treated within the last year	0.985	(0.962-1.008)	.195	0.856	(0.798-0.919)	≤.001
SBRT experience in patients treated within the last 2 years	0.976	(0.950-1.003)	.081	0.844	(0.781-0.912)	≤.001
SBRT experience in patients per institution and year	0.976	(0.949-1.004)	.095	0.857	(0.790-0.929)	≤.001

Abbreviations: CI = confidence interval; HR = hazard ratio; LC = local control; LF = local failure; OS = overall survival; ref. = reference. Other abbreviations as in Tables 1 and 2.

The variables biopsy confirmation of metastases, staging FDG-PET, dose calculation algorithm, patient setup and image guidance, immobilization devices, and motion management were analyzed as categorical variables; the remaining variables were taken as continuous variables for analysis.

recommended to identify candidates for SBRT in patients with lung oligometastases.

A recent survey about contemporary SBRT practice in 45 centers in 6 European countries reported that the majority of radiation oncologists thought that SBRT should be primarily performed in experienced/high-volume centers (4). However, up to now there are few data about the influence of SBRT treatment experience on outcome, because many studies are single-center studies with small patient numbers. Analyzing SBRT for pulmonary metastases in 700 patients treated at 20 centers, we detected a learning curve for SBRT practice. Local control was significantly superior with increasing SBRT experience of the treating center. Centers had inferior LC when SBRT was implemented and improved their outcome with increasing SBRT experience. For defining the influence of SBRT experience in detail, we analyzed several subvariables regarding SBRT experience (Table 3). Interestingly, SBRT experience in patients per institution and SBRT experience in patients per institution and year affected outcome to a lower degree than recent treatment experience within the last 2 years (Tables 3 and 4). This may be explained by the rapid adoption of new

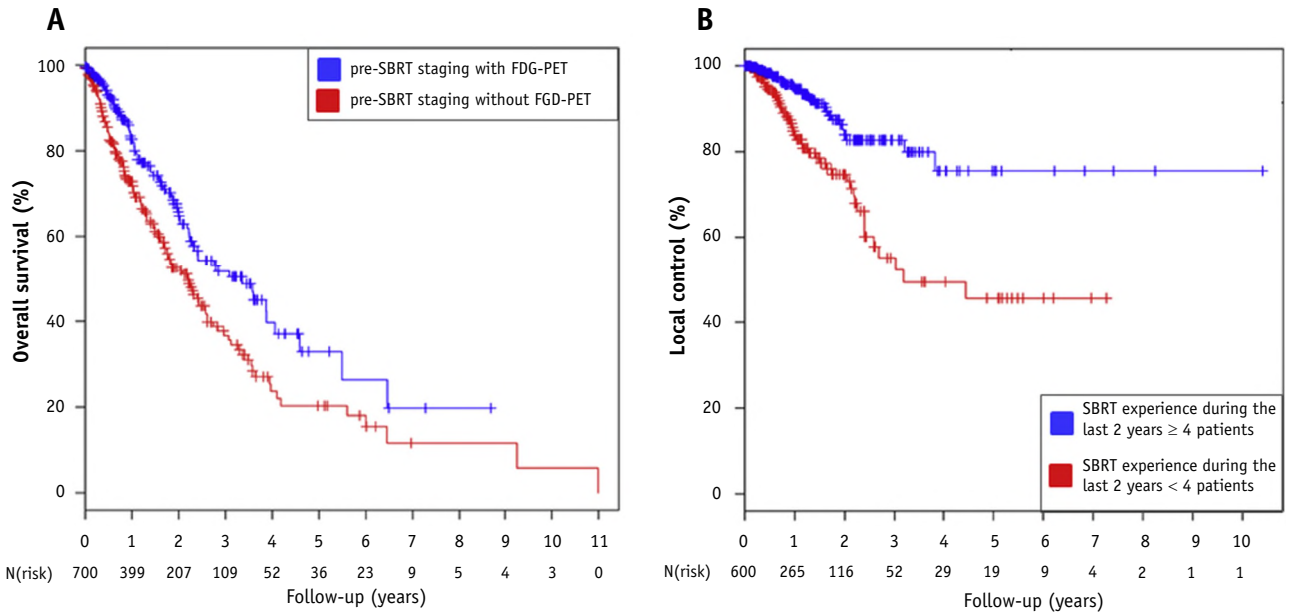

Fig. 2. (A) Patients showed significantly superior overall survival if fluorodeoxyglucose positron-emission tomography (FDG-PET) was performed before stereotactic body radiation therapy (SBRT) ($P = .012$). (B) Local control was significantly superior if centers had treated at minimum 4 patients during the last 2 years ($P < .001$).

Table 4 Multivariate analysis of factors influencing OS and LC

Factor	OS			LF		
	HR	95% CI	*P*	HR	95% CI	*P*
Staging FDG-PET-CT (CT ref.)	0.660	(0.487-0.895)	.011	0.613	(0.358-1.051)	.076
SBRT experience patients treated within the last 2 years				0.844	(0.779-0.913)	≤.001
Pretreatment performance scale (Karnofsky Index) (%)	0.975	(0.962-0.988)	≤.001			
Total BED (Gy)				0.985	(0.973-0.996)	.011
Single fraction dose (Gy)				1.040	(1.005-1.076)	.024
Primary tumor histology (NSCLC ref.)			.003			
Breast cancer	0.987	(0.605-1.610)				
Colorectal cancer	0.758	(0.531-1.083)				
Renal cell carcinoma	0.639	(0.399-1.026)				
Sarcoma	1.060	(0.656-1.711)				
Esophageal cancer	0.999	(0.481-2.076)				
Melanoma	2.644	(1.381-5.062)				
Others	1.278	(0.933-1.750)				
Maximum metastasis diameter (cm)	1.101	(1.022-1.187)	.015			
No. of metastases (multiple ref.)	0.759	(0.593-0.971)	.033			
Interval between primary tumor diagnosis and SBRT treatment (mo)	0.991	(0.981-1.000)	.055			

Abbreviations as in Tables 1-3.

The variables staging FDG-PET, primary tumor histology, and number of metastases were analyzed as categorical variables, whereas all remaining variables were taken as continuous variables for analysis.

technologies and methodologies in SBRT. SBRT might have changed so quickly, especially within the first years after implementation, that past experience with collected old technologies and equipment loses relevance by time.

To rule out that further factors affected the influence of SBRT experience on outcome, we included known prognostic indicators for LC and OS in multivariate analysis. Interestingly, higher SBRT experience in patients treated within the last 2 years was identified as an independent prognostic factor for superior LC. Stereotactic body radiation therapy experience in patients treated within the last 2 years was not correlated with known prognostic factors like SBRT dose in BED in multivariate analysis. Hence, the significant influence of SBRT experience on LC could not be explained by utilization of higher SBRT dose in BED.

A cutoff patient number of 4 was identified in ROC analysis. Patients who were treated at centers that had performed SBRT in 4 or more patients within the last 2 years showed superior 1-year and 2-year LC of 94.6% (95% CI 91.8%-97.6%) and 83.9% (95% CI 77.8%-90.6%), whereas patients treated at less-experienced centers only had 1-year and 2-year LC rates of 83.8% (95% CI 78.0%-90.2%) and 74.6% (95% CI 67.1%-83.3%), respectively ($P<.001$) (Fig. 2B). This cutoff in experience is considered rather small and should be a realistic minimum goal in all centers with an active oligometastatic SBRT program.

Additionally, we examined whether better patient selection could also be a reason for the significant influence of SBRT experience on outcome. Centers with higher SBRT experience were compared with centers with lower experience in terms of patient and tumor characteristics. Interestingly, there was only a significant difference in metastasis size ($P=.003$). However, patients with larger metastases were treated at more-experienced centers. Therefore, higher SBRT experience could not mainly be explained by better patient selection.

Several factors could explain this favorable learning curve: availability of SBRT practice guidelines, long history of SBRT within the DEGRO society and its active SBRT working group, availability of national and international SBRT teaching courses, and the possibility of "off-line" training and teaching as opposed to "on-line" training on real patients, which is required in surgical disciplines. However, it needs to be considered that only experience in SBRT for lung metastases was analyzed in this study. Stereotactic body radiation therapy for primary NSCLC or liver tumors, which is similar from a technical perspective, could have contributed to gaining SBRT experience, but this information was not available.

Evidence of a learning curve with larger SBRT experience has also been observed in a recently published study by Koshy et al (23), which showed improved OS but not LC (not analyzed) when SBRT for inoperable stage I NSCLC was performed at experienced/high-volume facilities. In detail, Koshy et al suggested that OS was superior at high-volume centers offering a larger range of clinical services, including multidisciplinary lung tumor boards as well as a greater physician expertise in treating early-stage inoperable lung cancer (23). Surgical series support the importance of experience and showed analogously improved survival after resection of lung cancer in high-volume hospitals (24, 25).

However, SBRT experience in patients treated within the last 2 years was not identified as an independent prognostic factor for OS in our analysis. This might be caused by the fact that survival after SBRT for pulmonary metastases is known to be strongly influenced by pretreatment prognostic factors. Navarria et al (26) recently published a meta-analysis of several studies, searching for appropriate candidates for SBRT for lung oligometastases. They reported the ideal candidate to show favorable primary tumor histology, a long disease-free interval, control of the primary tumor, and small lesions, as well as a limited number of lesions. Notably, predictors of LC did not translate into predictors of survival in this study and many others regarding SBRT for pulmonary metastases (27-29). Hence, thorough candidate selection remains the most important predictor for survival after SBRT for lung oligometastases. Furthermore, future studies should also focus on more detailed toxicity and quality of life analyses.

Some limitations of this study need to be addressed and were mainly caused by the fact of a multicenter retrospective analysis. Long-time follow-up data did not exist for all patients, leading to a rather short median follow-up time of 14 months (range, 0-131.9 months). In this study the term "oligometastatic disease" was applied for patients with pulmonary metastases from different primary tumors, leading to a wide range of life expectancies. This rather heterogeneous group might have impaired outcome analysis. Subgroup analyses for the main tumor entities are planned.

Due to the retrospective and multicenter character of the study, there was increased uncertainty in the local control endpoint. Differentiation between benign radiographic changes and local recurrence after SBRT is challenging because many patients develop fibrosis in the treated lung region (30, 31). In our study there was no central review for LC. As precise guidelines regarding follow-up visits after pulmonary SBRT are still missing in Germany, frequency of follow-up visits and imaging varied. However, LC was consistently defined as no regrowth at the high-dose area by each center. New lesions in the same lobe outside the high-dose area were consistently taken as distant metastases. Additionally, the estimated values for LC after 2 years have to be interpreted considering the 2-year survival of 54.4% (95% CI 50.2%-59.0%).

Not all technical aspects of SBRT treatment could be investigated as the number of variables was limited. Data were missing for the utilization of 4D-CT and intensity modulated treatment planning. More advanced motion management techniques such as tracking or gating were not analyzed because less than 10% of the patients were treated with either method.

Conclusions

Overall, advanced treatment technologies did not significantly influence outcome after pulmonary SBRT. Only patients who received pre-SBRT FDG-PET staging showed significantly improved OS. In contrast, SBRT treatment experience was identified as an independent prognostic factor: SBRT treatment at a more-experienced center was associated with superior LC.

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