Safety and Efficacy of Stereotactic Body Radiotherapy for Stage I Non–Small-Cell Lung Cancer in Routine Clinical Practice

A Patterns-of-Care and Outcome Analysis

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Introduction: To evaluate safety and efficacy of stereotactic body radiotherapy (SBRT) for stage I non–small-cell lung cancer (NSCLC) in a patterns-of-care and patterns-of-outcome analysis.

Methods: The working group "Extracranial Stereotactic Radiotherapy" of the German Society for Radiation Oncology performed a retrospective multicenter analysis of practice and outcome after SBRT for stage I NSCLC. Sixteen German and Austrian centers with experience in pulmonary SBRT were asked to participate.

Results: Data of 582 patients treated at 13 institutions between 1998 and 2011 were collected; all institutions, except one, were academic hospitals. A time trend to more advanced radiotherapy technologies and escalated irradiation doses was observed, but patient characteristics (age, performance status, pulmonary function) remained stable over time. Interinstitutional variability was substantial in all treatment characteristics but not in patient characteristics. After an average follow-up of 21 months, 3-year freedom from local progression (FFLP) and overall survival (OS) were 79.6% and 47.1%, respectively. The biological effective dose was the most significant factor influencing FFLP and OS: after more than 106 Gy biological effective dose as planning target volume encompassing dose (N = 164), 3-year FFLP and OS were 92.5% and 62.2%, respectively. No evidence of a learning curve or improvement of results with larger SBRT experience and implementation of new radiotherapy technologies was observed.

Conclusion: SBRT for stage I NSCLC was safe and effective in this multi-institutional, academic environment, despite considerable interinstitutional variability and time trends in SBRT practice. Radiotherapy dose was identified as a major treatment factor influencing local tumor control and OS.

Key Words: Stereotactic body radiotherapy, Non–small-cell lung cancer, Patterns-of-care.

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Stereotactic body radiotherapy (SBRT) is considered the treatment of choice for early-stage non–small-cell lung cancer (NSCLC) if patients are inoperable because of medical comorbidities. Several prospective phase II trials reported consistently high rates of local tumor control of 84% to 98%,[1–6] which is substantially better compared with historical data using conventional radiotherapy.[7] A meta-analysis suggested that this improved local tumor control by SBRT transfers into an improved overall survival (OS).[8] In addition, two population-based analyses reported improved OS in the elderly patients by the introduction of SBRT.[9,10] Despite this intensified local treatment, toxicity has been reduced by the use of modern radiotherapy technologies, which focus the irradiation to small volumes. This high accuracy of SBRT for best possible sparing of lung tissue is of particular importance in the fragile patient population frequently suffering from severe pulmonary comorbidities.

On the basis of these promising results, SBRT for early-stage NSCLC was quickly adopted in the radiotherapy

community: a national survey in the United States reported that 57% of all responding physicians practiced SBRT for lung cancer in 2010,[11] and a similar survey in Italy reported SBRT practice in 41% of all responding radiotherapy centers in 2009.[12] However, there exist concerns about this rapid and widespread implementation of SBRT.

Despite consistent clinical outcome, the methodology of SBRT varied substantially, for example, all prospective trials used different fractionations and total irradiation doses. Furthermore, multiple novel technologies have been developed in the recent years, addressing various aspects of SBRT, although their potential impact on clinical outcome is unknown. This lack of standardization bears the risk of jeopardizing the results achieved so far when SBRT is practiced outside of specialized centers or well-defined study protocols.

Another issue of concern is the limited OS of patients treated with SBRT for NSCLC because of the high competing risk of death from their comorbidities. All prospective studies and the majority of the retrospective studies only included small patient numbers, which makes analysis of long-term safety and efficacy difficult.

After Sweden and Japan pioneered work in SBRT, Germany and Austria started with the practice of SBRT in 1998. A working group, Extracranial Stereotactic Radiotherapy, was established in 2004 within the German Society for Radiation Oncology (DEGRO) for development of national guidelines, and coordinated education about implementation and practice of SBRT. In 2011, a patterns-of-care and outcome analysis was initiated within this working group to investigate implementation, practice, and outcome—safety and efficacy—after SBRT for stage I NSCLC in Germany and Austria.

MATERIALS AND METHODS

In 2011, the initiative to this analysis was started within the working group Extracranial Stereotactic Radiotherapy of the DEGRO. Inclusion criterion for participation in this analysis was experience in pulmonary SBRT (primary and secondary tumors), with minimum 20 patients treated until 2011. All centers with SBRT practice documented in the working group Extracranial Stereotactic Radiotherapy were asked in written form for participation in this analysis. In addition, responding centers were asked about other potential centers with experience in SBRT, which were also invited.

It was the aim of this study to analyze safety (30- and 60-day mortality; radiation-induced pneumonitis) and efficacy (OS and freedom from local progression [FFLP]) of SBRT, for stage I NSCLC. FFLP was defined as regrowth of the tumor in the treated area; recurrences distant to the primary lesion in the same lobe were not classified as local failure but as distant metastases. There was no central definition of local progression in terms of computed tomography (CT) morphological criteria, fluoro-deoxy-glucose positron emission tomography (FDG-PET) imaging, or biopsy confirmation.

A database in Excel format was generated consisting of 35 items, patient characteristics (age, sex, performance status, pretreatment pulmonary function), tumor characteristics (biopsy status, histopathology, tumor stage, maximum tumor diameter, staging FDG-PET), treatment characteristics (immobilization, image guidance, single-fraction dose at isocenter [maximum dose in PTV]) and PTV-encompassing dose (minimum PTV dose), dose inhomogeneity within PTV (PTV-encompassing dose/maximum PTV dose), number of treatment fractions (dose calculation algorithm), and outcome characteristics (FFLP, regional recurrence, distant recurrence, death, radiation-induced pneumonitis).

Inclusion criteria for this analysis were clinical or histopathological diagnosis of stage I NSCLC; clinical diagnosis based on CT ± FDG-PET imaging was also allowed. SBRT was not defined by the number of treatment fractions (e.g., ≤5 fractions) but by a combination of the target volume concept (primary tumor only without elective nodal irradiation), conformal treatment planning (3Dimensional conformal, intensity-modulated radiation therapy, volumetric modulated arc therapy), and stereotactic or image-guided patient setup. The participating centers were asked to include in the database all patients treated at their institution fulfilling the criteria above. If in-house databases existed for this patient cohort, the complete follow-up of the patients was to be provided. For centers without in-house databases, the latest information from clinical follow-up was to be documented.

To correlate irradiation doses with clinical results, biological effective doses (BED) were calculated: an α/β-ratio of 10 Gy was assumed for the pulmonary tumor and BED was calculated using the linear-quadratic model:

BED Gy = dose/fraction × fraction number (1+ fraction dose/α/ß)

Statistical analyses were performed with Statistica X (Statsoft, Tulsa, OK), and all statistical tests were two-sided. A p value of 0.05 or less was considered statistically significant. The Pearson χ^2 or Fisher's exact test and Kruskal-Wallis analysis of variance were used to compare categorical and continuous variables between groups, respectively. Receiver operating characteristics (ROC) curves were used to test prognostic factors (tumor size, irradiation dose) in predicting outcome, with their performances measured based on the area under the ROC curve. Estimated likelihood of events was calculated using the Kaplan–Meier method with start of follow-up on the last day of SBRT treatment. The log-rank test was used to compare differences between curves in univariate analysis. Multivariate analysis (MVA) was performed using Cox proportional hazard method with backward exclusion of nonsignificant variables; all variables that were statistically significant in the univariate analysis were included in the MVA.

RESULTS

Patterns-of-Care

Sixteen academic and nonacademic centers were contacted, of which 13 agreed to participate in this analysis. Reasons for refusal were, *too small patient numbers* (n = 2) and *lack of resources to complete follow-up* (n = 1). All participating centers were located in Germany (n = 11) and Austria (n = 2), and all, except for one German center, were academic hospitals. Data of 642 patients were collected; 60 patients were excluded because of cN+ or cM+ disease, resulting in 582 eligible patients.

Figure 1 shows introduction of SBRT over time: two institutions started SBRT for stage I NSCLC in 1998, and all 13 institutions practiced SBRT by the year 2008. In 2010, the last full year covered in this analysis, 95 patients in total were treated with SBRT. The median number of patients per institution was 39 (range, 8–110), and the median number of patients per institution and year was five (range, 1–29). Patient and treatment characteristics are summarized in Table 1.

Time trends in patient characteristics were analyzed and are summarized in Table 1. No time trend was observed for patient age, pretreatment performance status, pretreatment pulmonary function, and maximum tumor diameter. Histopathological confirmation was frequent (84.5%) but decreased over time with biopsy rates of 89.3% and 77.6% in 1998–2008 and 2009–2011, respectively ($p = 0.0003$). Use of FDG-PET for staging increased continuously over time: FDG-PET staging was first performed in 2000, and was practiced in 52% to 57% of the patients between 2003 and 2006, in 71% to 81% between 2007 and 2009, and in more than 90% of the patients from 2010 onward ($p < 0.0001$).

Patterns of SBRT practice changed substantially over time. The PTV-encompassing dose was increased continuously and reached a plateau of 94 Gy±26 Gy BED on average in 2006 to 2011 ($p < 0.0001$) (Fig. 2).

Single-fraction radiosurgery was performed at five centers, but 89 of 106 radiosurgical treatments were performed at two institutions. The PTV-encompassing dose was increased from 20.4 ± 2.0 Gy to 24.9 ± 2.9 Gy in the time intervals 1998–2003 and 2004–2011, respectively. Dose inhomogeneity remained constant at 80% (PTV-encompassing dose/maximum PTV dose).

In fractionated SBRT, the average single-fraction dose and dose inhomogeneity remained rather constant, whereas, the number of treatment fractions increased over time. The most frequently used fractionation schemas were 3 × 12.5 Gy prescribed to the 60% to 65% isodose line ($n = 147$) and 3 × 15 Gy prescribed to the 65% isodose line ($n = 107$). Only six patients were treated with more than 10 fractions. All except three institutions used a minimum of two risk-adapted fractionation schemas with the number of fractions and single-fraction doses adjusted to tumor size and location.

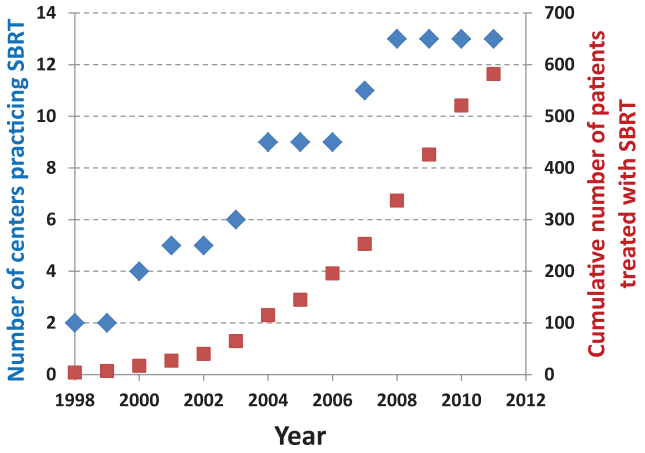

FIGURE 1. Patterns of implementation and practice of SBRT in 13 centers in Germany and Austria. SBRT, stereotactic body radiotherapy.

A more accurate dose calculation algorithm (type B instead of type A)[13] was used in 25% and 52% of the patients between 1998–2006 and 2007–2011, respectively ($p < 0.0001$). The method of patient setup and image guidance changed rapidly over time. SBRT with stereotactic patient setup (no image guidance for direct visualization of the pulmonary target) was practiced in 70 patients only: this was the most frequently practiced method until 2001 (56% of all treatments) and was last performed in 2009. Daily pre-SBRT CT resimulation outside the treatment room started in 1998 and was the predominant image-guided radiotherapy (IGRT) technology between 2002 and 2006 (57% of all treatments). In-room IGRT started in 2002 and was the leading IGRT technology from 2007; daily pre-SBRT in-room image guidance was used in 92% of all treatments in 2011. Intrafractional patient-immobilization devices like the stereotactic bodyframe or customized vacuum cushions were used on all patients.

No significant interinstitutional variability was observed for patient age, pretreatment pulmonary function, and maximum tumor diameter but for pretreatment performance status, histopathological confirmation, and use of FDG-PET staging (all $p < 0.01$) (Table 1). SBRT practice varied significantly in terms of radiotherapy dose, fractionation, dose calculation algorithm, and IGRT technology (all $p < 0.001$).

Patterns-of-Outcome

Average follow-up for all patients was 21.4 months and the maximum was 144 months; follow-up was more than 3 years for 108 patients. Three-year FFLP was 79.6% for all 582 patients (Fig. 3); the pattern of disease recurrence was distant with 3-year freedom from distant metastasis and regional metastasis of 63.4% and 75.4%, respectively. Three-year OS was 47.1% (Fig. 4). Three patients (0.5%) died within 30 days after SBRT and 10 (1.7%) within 60 days

Results of Univariate Analyses for Factors Influencing FFLP and OS

Table 2 shows that FFLP was most significantly influenced by the PTV-encompassing dose in BED, dose inhomogeneity within the PTV, and technology for patient setup and IGRT (all $p < 0.01$). The cutoff dose of 106 Gy BED was calculated in ROC analysis, and FFLP reached a plateau of 92.5% after SBRT with 106 Gy BED or more. In addition, tumor stage, histopathology, and number of SBRT procedures per year and institution affected FFLP significantly (all $p < 0.05$). A significant dose–effect relationship regarding FFLP was observed for stage IA ($p = 0.01$) and stage IB ($p = 0.05$), resulting in identical 3-year FFLP of 92.6% and 92.2% for stage IA and stage IB, respectively, after irradiation with more than 106 Gy BED.

Most significant factors influencing OS were pretreatment performance status and PTV-encompassing dose in BED (all $p < 0.001$). Additional parameters affecting OS were tumor stage, dose calculation algorithm (all $p < 0.01$), pretreatment forced expiratory volume in 1 second, histopathology, and number of SBRT procedures per year and institution (all $p < 0.05$).

TABLE 1. Patient and Treatment Characteristics with Analyses for Time Trends and Inter-Institutional Variability

	No. of Patients	%	Median	Minimum	Maximum	Time Trend	Interinstitutional Variability
Age (yr)	582		72.2	30.9	92.4	0.07	NS
Sex						0.43	$p < 0.001$
Male	405	69.6					
Female	177	30.4					
Baseline Karnofsky Index	540		80	40	100	0.40	$p < 0.001$
Baseline FEV_1 (%)	446		58	16	129	0.97	0.50
Biopsy confirmation of NSCLC						$p < 0.001$	$p < 0.001$
No	90	15.5					
Yes	492	84.5					
Clinical stage						0.01	$p < 0.001$
IA	327	56.2					
IB	236	40.5					
I	19	3.3					
Staging FDG-PET						$p < 0.001$	$p < 0.001$
No	142	24.4					
Yes	415	71.3					
Unknown	25	4.3					
Histology						0.08	$p < 0.001$
Adeno Ca	231	39.7					
SCC	195	33.5					
Other	55	9.5					
Unknown or no biopsy	101	1.9					
Maximum tumor diameter (cm)	347		2.5	0.8	4.9	0.34	0.51
Dose calculation algorithm						$p < 0.001$	$p < 0.001$
Type A	265	45.5					
Type B	249	42.8					
Unknown	68	11.7					
Number of SBRT fractions	582		3	1	20	0.02	$p < 0.001$
Single-fraction dose PTV-encompassing (Gy)	582		12.5	2.9	33.0	$p < 0.001$	p<0.001
Total dose PTV-encompassing (Gy)	582		37.5	12.0	64.0	$p < 0.001$	$p < 0.001$
Dose inhomogeneity (PTV-encompassing dose/ maximum PTV dose) (%)	582		65	60	100	$p < 0.001$	$p < 0.001$
Total BED PTV-encompassing (Gy)	582		84.4	38.3	180.0	$p < 0.001$	$p < 0.001$
Patient setup and IGRT						$p < 0.001$	$p < 0.001$
Stereotactic setup	70	12.0					
Resimulation outside teratment room	165	28.4					
In-room IGRT	347	59.6					

FEV_1, forced expiratory volume in 1 second; NSCLC, non–small-cell lung cancer; FDG-PET, fluoro-deoxy-glucose positron emission tomography; SCC, squamous cell carcinoma; Adeno Ca, adenocarcinoma; SBRT, stereotactic body radiotherapy; PTV, planning target volume; BED, biological effective dose; IGRT, image-guided radiotherapy.

Similar to FFLP, the irradiation dose significantly influenced OS in both stage IA ($p = 0.01$) and IB ($p = 0.02$). Whereas OS was significantly different between stage IA and stage IB in the low-dose cohort (3a OS 47.8% versus 34.8%; $p = 0.03$), this difference was not significant in the high-dose cohort (3a OS 64% versus 58.3%; $p = 0.25$).

Results of the MVA are shown in Table 3. The most important factor influencing clinical outcome was the PTV-encompassing dose: irradiation doses of 106 Gy BED or more were associated with better OS (hazard ratio [HR] = 0.62) and FFLP (HR = 0.39).

Grade of toxicity was not available for one institution and patients from that institution were excluded from toxicity analysis. Radiation-induced pneumonitis grade 2 or higher was observed in 38 of 512 patients (7.4%) and grade 5 pneumonitis was documented in two patients (0.4%).

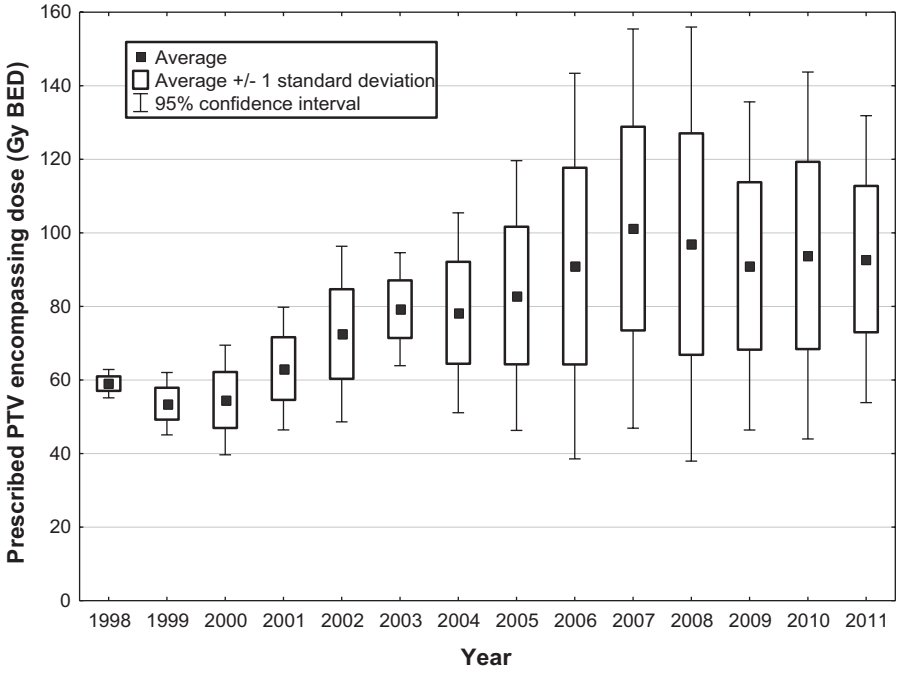

FIGURE 2. Time trend of irradiation dose in stereotactic body radiotherapy. BED, biological effective dose; PTV, planning target volume.

DISCUSSION

SBRT was introduced in Germany and Austria in 1998, a few years after this concept had been first described in Japan and Sweden.[14,15] As a consequence, this represents one of the largest data sets, with 582 stage I NSCLC patients treated at 13 centers between 1998 and 2011.

SBRT was safe in this multi-institutional environment: 30- and 60-day mortality rates were low at 0.5% and 1.7%, respectively, and only two cases of grade 5 toxicity were observed. However, efficacy of SBRT seems worse in our analysis compared with that in published prospective phase II studies and large retrospective analyses: 3-year FFLP was 79.6% and 3-year OS was 47.1%. However, the strongest predictor for FFLP and OS in univariate analysis and MVA was the PTV-encompassing irradiation dose, which has been continuously escalated with time and reached a plateau at 94 Gy BED on average from 2006. After treatment with irradiation doses of 106 Gy BED or more (patients $n = 164$; institutions $n = 7$) 3-year FFLP was 92.5% and 3-year OS was 62.2%. Recurrence rates are now in good agreement with the published prospective trials and OS seems even favorable. A dose–effect relationship for local tumor control is well documented[16–20] and has been described for OS by several studies.[18,19,21,22] These results indicate that intensified SBRT with the consequence of improved local tumor control transfers into improved OS.

Substantially higher doses of three fractions of 18 to 20 Gy (151–180 Gy BED) are usually used in SBRT based on the phase I study by McGarry et al.[23] However, a recent

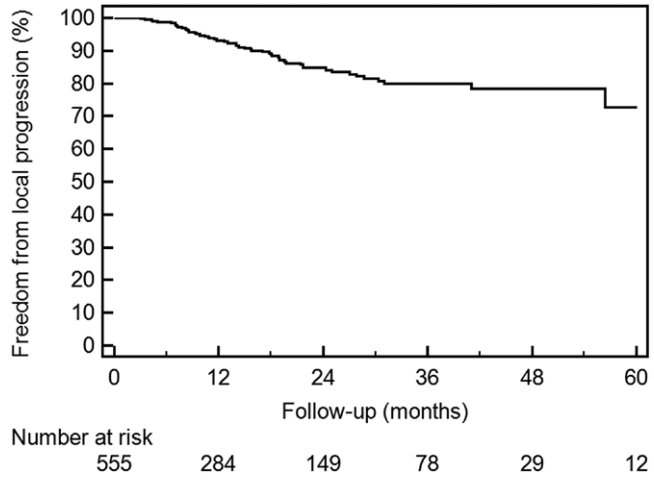

FIGURE 3. Freedom from local progression for the total patient population.

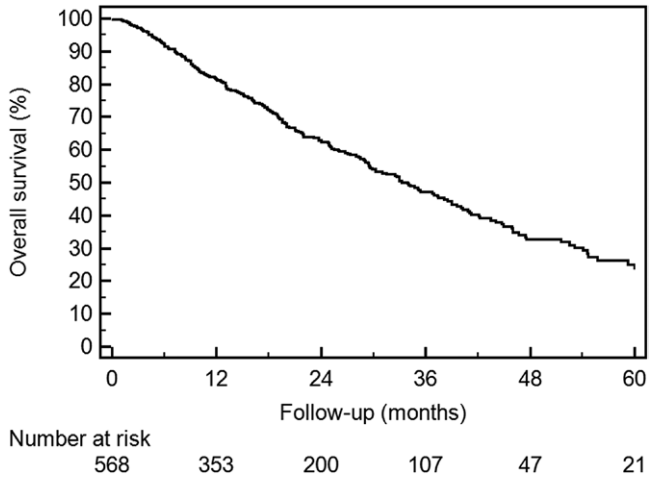

FIGURE 4. Overall survival for the total patient population.

TABLE 2. Univariate Analysis of Factors Influencing OS and FFLP

		OS		FFLP	
Cutoff	**No. of Patients**	***p***	**3a OS**	***p***	**3a FFLP**
Age (yrs)		0.33		0.53	
<75 yr	358				
≥75 yr	224				
Sex		0.69		0.65	
Male	405				
Female	177				
Performance status		0.0002		0.79	
<80	184		35.4		
≥80	358		53.0		
Pre-SBRT FEV_1 (%)		0.03		0.29	
<58	222		43.2		
≥58	224		55.7		
Stage		0.003		0.048	
IA	327		53.1		84.0
IB	236		40.0		74.3
Histopathology		0.05		0.02	
No biopsy	99		27.4		64.4
SCC	195		44		75.3
Adeno Ca	231		56.3		86.5
Other	55		50.3		92.5
Staging FDG-PET		0.09		0.056	
Yes	415				
No	142				
PTV-encompassing dose (Gy BED)		0.0001		0.001	
<106	418		42.4		74.1
≥106	164		62.1		92.1
Dose inhomogeneity (PTV-encompassing dose/ maximum dose) (%)		0.87		0.005	
<80	377				86.8
≥80	205				69.1
Dose calculation algorithm		0.002		0.19	
Type A			46.0		
Type B			51.3		
Patient setup		0.20		0.006	
Stereotactic	70				66.7
IGRT outside	165				77
IGRT inside	347				83.1
SBRT procedures / institution		0.13		0.056	
<22	247				
≥22	335				
SBRT procedures / year and institution		0.03		0.01	
<9	341		44.1		73.9
≥9	241		51.2		87.7

Three-year (3a) OS and FFLP is only shown for significant differences.

OS, overall survival; FFLP, freedom from local progression; SBRT, stereotactic body radiotherapy; BED, biological effective dose; PTV, planning target volume; FDG, ; PET, positron emission tomography; IGRT, image-guided radiotherapy; SCC, squamous cell carcinoma; Adeno.Ca, adenocarcinoma.

meta-analysis suggested the best therapeutic ratio for SBRT at intermediate doses between 83.2 and 146 Gy BED: OS was significantly decreased after SBRT with doses more than 146 Gy BED, indicating occult toxicity. Doses more than 146 Gy BED were used in only 2.7% of our patients ($n = 16$) and the low 3-year OS of 47% confirms the hypothesis by Zhang et al.[22]

TABLE 3. Multivariate Analysis of Factors Influencing OS and FFLP

		OS			FFLP		
Parameter		***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**
Performance status	<80	0.02	1.44	1.05 to 1.97			
Clinical stage	IB	0.007	1.52	1.12 to 2.07	0.08	1.66	0.95 to 2.92
Baseline FEV_1 (%)	Continuous variable	0.07	0.99	0.99 to 1.00			
Biopsy status	No biopsy	0.09	1.49	0.94 to 2.35	0.02	2.53	1.17 to 5.48
Staging FDG-PET	Yes				>0.1		
Histology	SCC				0.03	2.03	1.06 to 3.89
PTV-encompassing dose (Gy BED)	≥106	0.01	0.62	0.43 to 0.90	0.04	0.39	0.16 to 0.93
Dose inhomogeneity (PTV-encompassing dose / maximum dose) (%)	≥ 80				0.06	1.74	0.98 to 3.08
IGRT technology	In-room IGRT				>0.1		
SBRT procedures/institution and year	<9	>0.1			>0.1		

OS, overall survival; CI, confidence interval; FFLP, freedom from local progression; HR, hazard ratio; FEV_1, forced expiratory volume in 1 second; SCC, spindle cell carcinoma; SBRT, stereotactic body radiotherapy; BED, biological effective dose; FDG-PET, fluoro-deoxy-glucose positron emission tomography; IGRT, image-guided radiotherapy; PTV, planning target volume.

The strong dose–effect relationship observed in our study maybe surprising considering the large range of single-fraction doses up to 33 Gy, where applicability of the linear-quadratic model is uncertain. In addition, the analyzed PTV-encompassing doses may or may not be representative of the true tumor dose, considering the variability in the target volume and safety margin concepts, dose calculation algorithms, and differences in IGRT practice. However, another interpretation could be that all these uncertainties are of smaller clinical relevance than previously estimated. The irradiation dose was significantly correlated with all outcome parameters in the MVA, where all available confounding factors like tumor stage, use of advanced technologies, and experience in SBRT were included. This conclusion is supported by the close agreement of our results with a recent multicenter analysis, where the plateau of the dose–effect relationship for local tumor control was found at 105 Gy BED,[24] which is identical to our results.

A recent national patterns-of-care analysis in the United States described large interinstitutional variability in the practice of lung SBRT.[25] In our study, we observed a similar interinstitutional variability and, furthermore, substantial time trends of SBRT planning and delivery, which occurred in parallel to introduction of SBRT. Centers in our study were among the pioneers evaluating advanced technologies like FDG-PET staging,[26] advanced dose calculation algorithms,[27] and volumetric in-room IGRT[28] for lung SBRT. As a consequence of their rapid adoption, these technologies became the standard of care from 2003 to 2008, with application in more than 50% of the patients and centers. In 2010 and 2011, these three technologies were routine practice in 11 of 13 centers.

It was interesting that the introduction of these modern technologies did not significantly improve any outcome parameter: staging using FDG-PET, image guidance instead of stereotactic patient setup, and more accurate type B dose calculation algorithms did not influence OS or recurrence patterns (local, regional, and distant failures; detailed data not shown). However, the introduction of these more accurate radiotherapy technologies was accompanied by a parallel escalation of the irradiation dose. This intensification of SBRT was not associated with increased rates of radiation-induced pneumonitis: the rates of pneumonitis grade 2 or more were 6.8% and 7.6% in the time periods 1998–2005 (low-dose period) and 2006–2011 (high-dose period), respectively. This indicates that more precise SBRT planning and delivery compensated the potentially more toxic effect of substantially increased irradiation doses. A detailed analysis of toxicity remains to be performed. Furthermore, advanced technologies have streamlined the SBRT work-flow and increased the confidence into the treatment accuracy and might therefore have contributed to the rapid adoption of SBRT in the radiotherapy community.

The institution where SBRT was performed and institutional-specific experience in SBRT with total number of SBRT procedures and number of SBRT procedures per year were not significantly correlated with OS or recurrence rates. In addition, no learning curve based on the number of patients treated after the introduction of SBRT in each institution was observed. These results indicate that SBRT outside of homogeneous study protocols is safe and effective despite details in SBRT practice, which varied substantially between the institutions.

However, this needs to be interpreted in the specific context of our analysis. The working group Extracranial Stereotactic Radiotherapy of the German Society for Radiation Oncology was established in 2004, and this group has organized annual teaching courses about SBRT. National guidelines with detailed recommendations about all major clinical, technical, and quality-assurance aspects of SBRT have been published in 2006. Consequently, results of this analysis were achieved in an academic environment, and implementation of SBRT was guided by multiprofessional support of a dedicated working group. Similar guidelines have been published recently on a national and international level.[13,29–32] Although

not all technical details are defined in these guidelines, adherence to such recommendations, participation in structured teaching events, and strict quality-assurance protocols are considered as essential for safe implementation of modern and complex technologies.

In contrast to the time trends in SBRT practice and interinstitutional variability in the methods of SBRT, there was no significant interinstitutional variability in patient age and pulmonary function, which is the dominant reason for being medically inoperable and being treated with SBRT. This indicates that the indication for SBRT was rather uniform in Germany and Austria. Our data further suggest that the indication for SBRT in Germany and Austria has not changed systematically over time: no time trend in the patient characteristics to younger age, better pretreatment performance status, and better pulmonary function was observed.

Some limitations of our analysis need to be discussed, most are inherent to retrospective multicenter analyses. The number of variables was limited such that not all aspects of SBRT and all potential factors influencing outcome were available. Definition of local tumor progression is challenging in SBRT, with many patients developing fibrosis in the treated volume.[33] We did not have a central review of all local recurrences but FFLP was taken as reported by the specific institution. In addition, it is highly likely that definition of local progression changed in the 14-year period of this analysis: FDG-PET for staging became available in 2000 and was practiced in more than 50% of the patients from 2003: a similar time trend for FDG-PET–based differentiation of fibrosis and local progression is expected.

Strengths of our analysis are the comprehensive coverage of the patterns of SBRT practice and outcome in Germany and Austria from the very beginning of SBRT introduction in 1998; potential SBRT practice in private practice outside of academic centers was not analyzed. The large number of patients, sufficiently long follow-up, and especially, the variability in important aspects of SBRT practice allowed modeling and analysis of factors influencing outcome of SBRT, which is not possible in standardized prospective trials.

CONCLUSIONS

SBRT for stage I NSCLC was safe and effective in this multi-institutional environment and treatment outside of prospective clinical trials. Despite variability in the details of SBRT practice, consistent results were observed without evidence of a learning curve or improvement of results with larger SBRT experience and implementation of new radiotherapy technologies. However, strict quality assurance and structured implementation within an academic environment and assistance of a dedicated working group of the national radiotherapy society were the basis for our results. In addition, radiotherapy dose was identified as a major treatment factor influencing local tumor control and OS.

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