Long-term Follow-up and Patterns of Recurrence of Patients With Oligometastatic NSCLC Treated With Pulmonary SBRT

Juliane Hörner-Rieber,[1,2,3,4] Denise Bernhardt,[1,2,3] Oliver Blanck,[5] Marciana Duma,[6] Hans Th. Eich,[7] Sabine Gerum,[8] Eleni Gkika,[9] Peter Hass,[10] Christoph Henkenberens,[11] Hans-Ulrich Herold,[12] Guido Hildebrandt,[13] Detlef Imhoff,[14] Henning Kahl,[15] Stefan Janssen,[16,17] Katrin Jurianz,[18] Robert Krempien,[19] Stefan Friedrich Lautenschläger,[20] Fabian Lohaus,[21,22,23] Arndt-Christian Mueller,[24] Cordula Petersen,[25] Irina Sackerer,[26] Davide Scafa,[27] Elsge Schrade,[28] Lorenz Uhlmann,[29] Andrea Wittig,[30] Matthias Guckenberger[31]

Abstract

This multicenter analysis included 301 patients with oligometastatic non–small-cell lung cancer treated with pulmonary stereotactic body radiotherapy for 336 lung metastases. In routine clinical practice, stereotactic body radiotherapy for pulmonary oligometastatic non–small-cell lung cancer achieved favorable local control and promising overall survival. The dominant failure pattern was distant with a continuously high risk of disease progression for many years. Prospective studies should therefore combine local therapy with novel systemic treatments.

Introduction: This multicenter study aims to analyze outcome as well as early versus late patterns of recurrence following pulmonary stereotactic body radiotherapy (SBRT) for patients with oligometastatic non–small-cell lung cancer (NSCLC). **Materials and Methods:** This analysis included 301 patients with oligometastatic NSCLC treated with SBRT for 336 lung metastases. Although treatment of the primary tumor consisted of surgical resection,

[1]Department of Radiation Oncology, University Hospital Heidelberg, Heidelberg, Germany
[2]Heidelberg Institute of Radiation Oncology, Heidelberg, Germany
[3]National Center for Tumor Diseases (NCT), Heidelberg, Germany
[4]Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany
[5]Department of Radiation Oncology, UKSH Universitätsklinikum Schleswig-Holstein, Kiel, Germany
[6]Department of Radiation Oncology, Klinikum Rechts der Isar, Technical University of Munich, Munich, Germany
[7]Department of Radiation Oncology, University Muenster, Muenster, Germany
[8]Department of Radiation Oncology, LMU Ludwig Maximilians University Munich, Munich, Germany
[9]Department of Radiation Oncology, University Medical Center Freiburg, Freiburg, Germany
[10]Department of Radiation Oncology, University Hospital Magdeburg, Magdeburg, Germany
[11]Department of Radiotherapy and Special Oncology, Medical School Hannover, Hannover, Germany
[12]CyberKnife Center Erfurt, Erfurt, Germany
[13]Department of Radiation Oncology, University of Rostock, Rostock, Germany
[14]Department of Radiation Oncology, University Hospital Frankfurt, Frankfurt, Germany
[15]Department of Radiation Oncology, Hospital Augsburg, Augsburg, Germany
[16]Medical Practice for Radiotherapy and Radiation Oncology, Hannover, Germany
[17]Department of Radiation Oncology, University of Lübeck, Lübeck, Germany
[18]Gamma Knife Centre Krefeld, Krefeld, Germany
[19]Department of Radiation Oncology, Helios Klinikum Berlin Buch, Berlin, Germany
[20]Department of Radiotherapy and Radiation Oncology, Philipps-University Marburg, University Hospital Giessen and Marburg, Marburg, Germany
[21]Department of Radiation Oncology, Medical Faculty and University Hospital C.G. Carus, Technical University Dresden, Dresden, Germany
[22]German Cancer Research Center (DKFZ), Heidelberg and German Cancer Consortium (DKTK) Partner Site Dresden, Dresden, Germany
[23]OncoRay - National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany
[24]Department of Radiation Oncology, University Hospital and Medical Faculty, Eberhard Karls University Tuebingen, Tuebingen, Germany
[25]Department of Radiation Oncology, University Hospital Hamburg-Eppendorf, Hamburg, Germany
[26]Radiation Oncology, Freising, Germany
[27]Department of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany
[28]Department of Radiation Oncology, Hospital Heidenheim, Heidenheim, Germany
[29]Institute of Medical Biometry and Informatics, University of Heidelberg, Heidelberg, Germany
[30]Department of Radiotherapy and Radiation Oncology, University Hospital Jena, Jena, Germany
[31]Department of Radiation Oncology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

Submitted: Mar 7, 2019; Revised: Jun 18, 2019; Accepted: Jun 19, 2019; Epub: Jun 27, 2019

Address for correspondence: Juliane Hörner-Rieber, MD, Department of Radiation Oncology, University Hospital Heidelberg, INF 400, 69120 Heidelberg, Germany
E-mail contact: juliane.hoerner-rieber@med.uni-heidelberg.de

1525-7304/$ - see frontmatter
https://doi.org/10.1016/j.cllc.2019.06.024

radiochemotherapy, and/or systemic therapy, pulmonary oligometastases were treated with SBRT. **Results:** The median follow-up time was 16.1 months, resulting in 2-year overall survival (OS), local control (LC), and distant control (DC) of 62.2%, 82.0%, and 45.2%, respectively. Multivariate analysis identified age ($P = .019$) and histologic subtype ($P = .028$), as well as number of metastatic organs ($P < .001$) as independent prognostic factors for OS. LC was superior for patients with favorable histologic subtype ($P = .046$) and SBRT with a higher biological effective dose at isocenter ($P = .037$), whereas DC was inferior for patients with metastases in multiple organs ($P < .001$) and female gender ($P = .027$). Early (within 24 months) local or distant progression was observed in 15.3% and 36.5% of the patients. After 24 months, the risk of late local failure was low, with 3- and 4-year local failure rates of only 4.0%, and 7.6%. In contrast, patients remained at a high risk of distant progression with 3- and 4-year failure rates of 13.3% and 24.1%, respectively, with no plateau observed. **Conclusion:** SBRT for pulmonary oligometastatic NSCLC resulted in favorable LC and promising OS. The dominant failure pattern is distant with a continuously high risk of disease progression for many years.

Clinical Lung Cancer, Vol. 20, No. 6, e667-77
Keywords: Local therapy, Non–small-cell lung cancer (NSCLC), Oligometastases, Patterns of recurrence, Stereotactic body radiotherapy

Introduction

Non–small-cell lung cancer (NSCLC) is the leading cause of cancer-related death worldwide, with about 40% to 50% of patients initially diagnosed with stage IV disease and many others developing metastatic spread during the course of disease.[1-3] Patients with stage IV disease have been treated with systemic therapy in palliative intent, leading to a median survival of only 8 to 18 months.[4-7] In the past years, treatment for patients with metastatic NSCLC has become more personalized, as subgroups of patients with NSCLC with specific molecular aberrations are nowadays treated with tyrosine kinase inhibitors, exhibiting improved prognosis. However, less than 15% of patients with NSCLC show druggable driver mutations and therefore benefit from these targeted therapies.[8,9] Recently, immunotherapy with checkpoint inhibitors has become first-line treatment for patients with metastatic NSCLC without driver mutations combined with programmed death ligand 1 (PD-L1) expression > 50% on tumor tissue. However, this high expression is observed in only about 30% of patients with NSCLC.[7,10]

Another approach for a more personalized therapy is radical treatment of patients in the so-called oligometastatic state, representing an intermediate state between locoregional tumor spread and widely metastatic cancer.[11] Several studies have suggested that selected patients with NSCLC with oligometastatic disease have long-term survival, and local treatment of metastatic disease contributes to this favorable prognosis.[12-17] Indeed, a recent phase II study analyzing local consolidative therapy and maintenance systemic treatment versus maintenance treatment alone for patients with oligometastatic NSCLC without progression after first-line systemic therapy was prematurely stopped as it showed significantly improved progression-free survival (PFS) for the local treatment group.[18,19] Based on these and other experiences, the oligometastatic state in patients with NSCLC is currently recognized in the new eighth edition of the TNM classification of lung cancer as a separate tumor stage with an improved prognosis, leading to the M1a and new M1b category.[20] For definitive treatment for pulmonary oligometastases, surgical metastasectomy has been mostly performed, with 5-year survival rates of 36% to 46%.[15,21,22] However, stereotactic body radiotherapy (SBRT) offers a non-invasive and effective treatment option, which is safely possible in inoperable patients despite relevant comorbidities.[17,23-25]

Nevertheless, the current literature of SBRT for patients with oligometastatic NSCLC mainly consists of small heterogeneous and retrospective, single-center studies with mostly limited follow-up. Hence, further studies are needed for evaluating long-term outcome as well as long-term failure patterns to optimize follow-up. The working group Stereotactic Radiotherapy and Radiosurgery of the German Society of Radiation Oncology (DEGRO) therefore conducted a multi-institutional patterns-of-care and patterns-of-outcome analysis of patients with NSCLC with SBRT for pulmonary oligometastases in routine clinical practice.

Material and Methods

Patient and Treatment Characteristics

The current analysis is based on a retrospective multi-institutional database of the DEGRO Working Group Stereotactic Radiotherapy and Radiosurgery, which includes more than 800 patients treated with SBRT for more than 1000 pulmonary metastases. Detailed description of the database has been published before.[24,26,27] For the current study, an update of the database was performed in April 2018. In total, patients with NSCLC with pulmonary oligometastases treated at 24 different German (n = 23) and Swiss centers (n = 1) between 1997 and 2017 were analyzed. Corresponding to the most common definition of the oligometastatic state, only patients with NSCLC with 5 or fewer synchronous or metachronous metastases were included in this analysis.[3,13,28,29] All centers inserted relevant patient, tumor, and treatment characteristics and outcome data in an anonymized electronic file and sent this file to the coordinating center, which set up a pooled database. The analysis was approved by the Ethics committee of the University Hospital Heidelberg (S-280/2014).

Pulmonary SBRT was performed if patients were either classified medically inoperable, diagnosed with technically unresectable lung metastases, or refused surgical resection. All centers applied

risk-adapted fractionation schemes, meaning that the number of fractions and single-fraction doses were adjusted to tumor size and location (peripheral vs. central). Metastases were classified to be "peripheral" or "central" according to the Radiation Therapy Oncology Group (RTOG) definition.[30,31]

The biological effective dose (BED) was calculated for correlating irradiated doses with clinical results: an α/β ratio of 10 Gy was assumed for the pulmonary metastases. BED was determined using the linear-quadratic model:[32]

$$\text{BED (Gy)} = \text{fractional dose} \times \text{number of fractions} \left(1 + \frac{\text{fractional dose}}{\frac{\alpha}{\beta}}\right)$$

Endpoints and Toxicity Analysis

Overall survival (OS), local control (LC), and distant control (DC) were analyzed as endpoints. For survival analysis, the first course of SBRT was defined as the start of follow-up. Although LC was calculated on the basis of each individually treated metastasis, OS and DC were calculated on a patient-basis following SBRT for the first, index pulmonary lesion if several pulmonary metastases were treated. LC was defined as no progressive disease of the metastasis within the high-dose area. Local recurrences distant to the treated primary pulmonary metastasis but located in the same lobe were not classified as local but as distant failure. Data for DC was only available for 276 patients, whereas OS was analyzed for 301 patients.

Statistical Analysis

The statistical analysis aimed to evaluate OS, LC, and DC following SBRT for pulmonary metastases and to identify prognostic factors possibly predicting these outcomes. For patients who received SBRT for multiple metastases to the lung, only the first treated metastasis was included in the study. Univariate Cox proportional hazard models were used to assess the potential influence of all patient, tumor, and treatment characteristics on OS, LC, and DC. Multivariate analysis was performed using the Cox proportional hazard method with backward exclusion of nonsignificant variables; all variables that with $P \leq .1$ in univariate analysis were included (separately for OS, LC, and DC). Because we had to deal with missing values, we used a multiple imputation approach. A P-value $\leq .05$ was considered statistically significant. All statistical analyses were performed with SPSS software (version 20.0).

Results

Patient and Treatment Characteristics

Only patients with histologically diagnosed NSCLC were taken into analysis. In total, 301 patients with oligometastatic NSCLC met the inclusion criteria and were treated with SBRT for a total of 336 pulmonary oligometastases. Fluoro-deoxy-glucose positron emission tomography (PET) imaging was performed in 51.8% of the patients, and biopsy confirmation was only taken when the metastatic origin of the pulmonary lesion was questioned (15.6%). Mutation analyses as well as PD-L1 expression testing were not mandated at the time of diagnosis in most of the centers, and hence data was only available for 33.9% (n = 102) and 9.0% (n = 27) of patients, respectively. In 8.8% (n = 9) of patients, for whom mutation data was available, an epithelial growth factor receptor (EGFR) mutation and in 2.0% (n = 2), an EML4-ALK translocation was detected. PD-L1 expression > 1% was found in 22.2% (n = 6) of the patients for whom PD-L1 testing was performed.

The median follow-up was 16.1 months (range, 0.6-131.7 months) for all patients; long-term follow-up beyond 2 years, 3 years, and 5 years was available for 104, 59, and 17 patients, respectively. Eighty-five (43.1%) patients with less than 2 years of follow-up were still alive at analysis. Detailed patient and treatment characteristics are summarized in Tables 1 and 2. Two hundred two (67.1%) patients had a solitary pulmonary metastasis, 63 (20.9%) patients had 1 additional metastasis, 19 (6.3%) patients had 2 additional metastases, 11 (3.7%) patients had 3 additional metastases, 5 (1.7%) patients had 4 additional metastases, and data was missing for 1 (0.3%) patient. Two hundred thirty-six (78.4%) patients were only diagnosed with pulmonary metastases, whereas the remaining patients had metastases in several organs. Additional oligometastases were located in the lung (n = 58), the brain (n = 26), the bone (n = 15), the liver (n = 2), or at other locations (n = 25). At the time of pulmonary SBRT, 80.3% received complete consolidative therapy, meaning that both the primary tumor and potential further metastases were controlled, whereas the remaining 18.7% of the patients were diagnosed with, in median, 1 further metastasis (range, 1-4), which was classified as uncontrolled. The additional metastases were treated with stereotactic radiotherapy in 63 patients, with surgery in 22 patients, with conventional radiotherapy in 19 patients, with chemotherapy in 18 patients, and with targeted systemic therapy in 4 patients. SBRT treatment of the pulmonary metastasis was delivered in a median of 23.2 months (range, 0.7-63.3 months) after diagnosis of the primary tumor. The time interval between diagnosis of the pulmonary metastasis and SBRT treatment was 2.0 months (range, 0.0-43.4 months) in median. Only 5.6% of the patients received concurrent systemic treatment while pulmonary SBRT was performed (4 weeks before and after SBRT).

OS

One-, 2-, 3-, and 5-year OS were 80.8%, 62.2%, 48.1%, and 28.8%, respectively (Figure 1A). One hundred twenty-eight (42.5%) patients died during follow-up time. The results of univariate analysis of factors influencing OS, LC, and DC are displayed in Table 3. Age and histologic subtype, as well as number of metastatic organs, were identified as independent prognostic factors for

Table 1 Patient and Lung Metastases Characteristics

Patients	No. Patients	All Patients (A), n (%)	Patients Without Early Progression (B), n (%)	Patients With Early Progression (C), n (%)	*P* Value (Comparison Group A vs. B + C)	*P* Value (Comparison Group B vs. C)
Gender	301		57	47		
Male		200 (66.4)	43 (75.4)	31 (66.0)	.376	.288
Female		101 (33.6)	14 (24.6)	16 (34.0)		
Median age (range), y	301	68.5 (40.7-87.6)	68.2 (47.2-86.1)	66.5 (40.7-79.0)	.234	.531
Median Karnofsky performance score (range), %	281	80 (40-100)	80 (60-100)	80 (60-100)	.285	.734
T-stage at first diagnosis	293		55	43		
T1		74 (25.3)	15 (27.3)	10 (23.3)	.637	***.013***
T2		107 (36.5)	25 (45.5)	17 (39.5)		
T3		66 (22.5)	5 (9.1)	14 (32.6)		
T4		46 (15.7)	10 (18.1)	2 (4.6)		
N-stage at first diagnosis	296		57	44		
N0		155 (52.4)	34 (59.6)	24 (54.5)	.705	***.018***
N1		52 (17.6)	8 (14.0)	10 (22.7)		
N2		69 (23.3)	14 (24.6)	4 (9.1)		
N3		20 (6.8)	1 (1.8)	6 (13.6)		
No. Metastases	301		57	47		
Solitary		202 (67.1)	41 (71.9)	29 (61.7)	.970	.286
Multiple		99 (32.9)	16 (28.1)	18 (38.3)		
Time to metastasis	300		57	47		
Synchronous		75 (25.0)	15 (26.3)	11 (23.4)	.841	.733
Metachronous		225 (75.0)	42 (73.7)	36 (76.6)		
Histology	301		57	47		
Squamous cell carcinoma		144 (47.8)	27 (47.4)	19 (40.4)	.525	.478
Adenocarcinoma		157 (52.2)	30 (52.6)	28 (59.6)		
Mutation type	102		57	47	.807	.893
None		91 (89.2)	13 (86.7)	15 (88.2)		
EGFR		9 (8.8)	2 (13.3)	2 (11.8)		
EML4ALK		2 (2.0)	0 (0)	0 (0.0)		
Complete consolidative therapy	294		57	47		
Yes		236 (80.3)	50 (87.7)	42 (89.4)	.059	.794
No		58 (19.7)	7 (12.3)	5 (10.6)		

Pulmonary Metastases	No. Pulmonary Metastases	All Pulmonary Metastases (A), n (%)	Patients Without Early Progression (B), n (%)	Patients With Early Progression (C), n (%)	*P* Value (Comparison Group A vs. B + C)	*P* Value (Comparison Group B vs. C)
Maximum metastasis diameter, (range) cm	320	1.8 (0.2-8.0)	1.6 (0.9-7.0)	1.9 (0.6-4.9)	.445	.884
Metastasis location	312		56	48		
Central		52 (15.7)	4 (7.1)	8 (16.7)	.298	.130
Peripheral		263 (84.3)	52 (92.9)	40 (83.3)		

Significant *P* values are marked in bold.
Abbreviations: EGFR = epithelial growth factor receptor; SBRT = stereotactic body radiotherapy.

OS in multivariate analysis (hazard ratio [HR], 1.027; 95% confidence interval [CI], 1.004-1.050; $P = .019$; HR, 0.667; 95% CI, 0.466-0.956; $P = .028$; and HR, 2.360; 95% CI, 1.574-3.537; $P < .001$) (Table 4).

LC of Pulmonary Metastases

Forty-one (12.2%) local failures were diagnosed during follow-up time leading to 1-, 2-, 3-, and 5-year LC of 91.9%, 82.0%, 76.4%, and 70.3%, respectively (Figure 1B). When accounting for

Table 2 Treatment Characteristics

Patients	No. Patients	All Patients (A), n (%)	Patients Without Early Progression (B), n (%)	Patients With Early Progression (C), n (%)	*P* Value (Comparison Group A vs. B + C)	*P* Value (Comparison Group B vs. C)
Primary treatment of the NSCLC at first diagnosis	301		57	47		
Surgery	298		57	45	.715	.501
Yes		175 (58.7)	33 (57.9)	29 (64.4)		
No		123 (41.3)	24 (42.1)	16 (35.6)		
Adjuvant CHT	175				.611	.706
Yes		70 (40.0)	11 (33.3)	11 (37.9)		
No		105 (60.0)	22 (66.7)	18 (62.1)		
Adjuvant RT	175				.523	.569
Yes		37 (21.1)	5 (15.2)	6 (20.7)		
No		138 (78.9)	28 (84.8)	23 (79.3)		
Adjuvant targeted therapy	175				.752	.345
Yes		4 (2.3)	1 (3.0)	0 (0.0)		
No		171 (97.7)	32 (97.0)	29 (100.0)		
Definitive RT/RCHT	123				.341	.588
Yes		99 (80.5)	21 (87.5)	13 (81.25)		
No		24 (19.5)	3 (12.5)	3 (18.75)		
CHT	123				.397	.273
Yes		23 (18.7)	3 (100.0)	2 (67.7)		
No		100 (74.1)	0 (0.0)	1 (33.3)		
Targeted therapies	123				.452	.273
Yes		1 (0.8)	0 (0.0)	1 (33.3)		
No		122 (99.2)	3 (100.0)	2 (67.7)		

Metastases	No. Metastases	All Pulmonary Metastases (A)	Patients Without Early Progression (B)	Patients With Early Progression (C)	*P* Value (Comparison Group A vs. B + C)	*P* Value (Comparison Group B vs. C)
Single fraction dose (PTV encompassing), (range) Gy	336	12.0 (3.3-30.5)	12.5 (4.3-30.2)	15.0 (3.3-30.2)	.835	.116
BED at isocenter (range), Gy	336	128.2 (37.5-323.4)	118.2 (50.7-173.1)	117.0 (54.0-189.0)	.120	.833
BED at PTV periphery (range), Gy	336	87.5 (37.5-165.3)	84.4 (37.5-151.2)	85.4 (45.9-161.7)	.346	.939
Dose inhomogeneity (PTV periphery dose/maximum dose), (range) %	336	73.5 (50.0-100.0)	80 (60.0-100.0)	80 (50.0-100.0)	.336	.244
No. SBRT fractions (range)	336	3 (1-12)	3 (1-10)	3 (1-12)	.448	.092

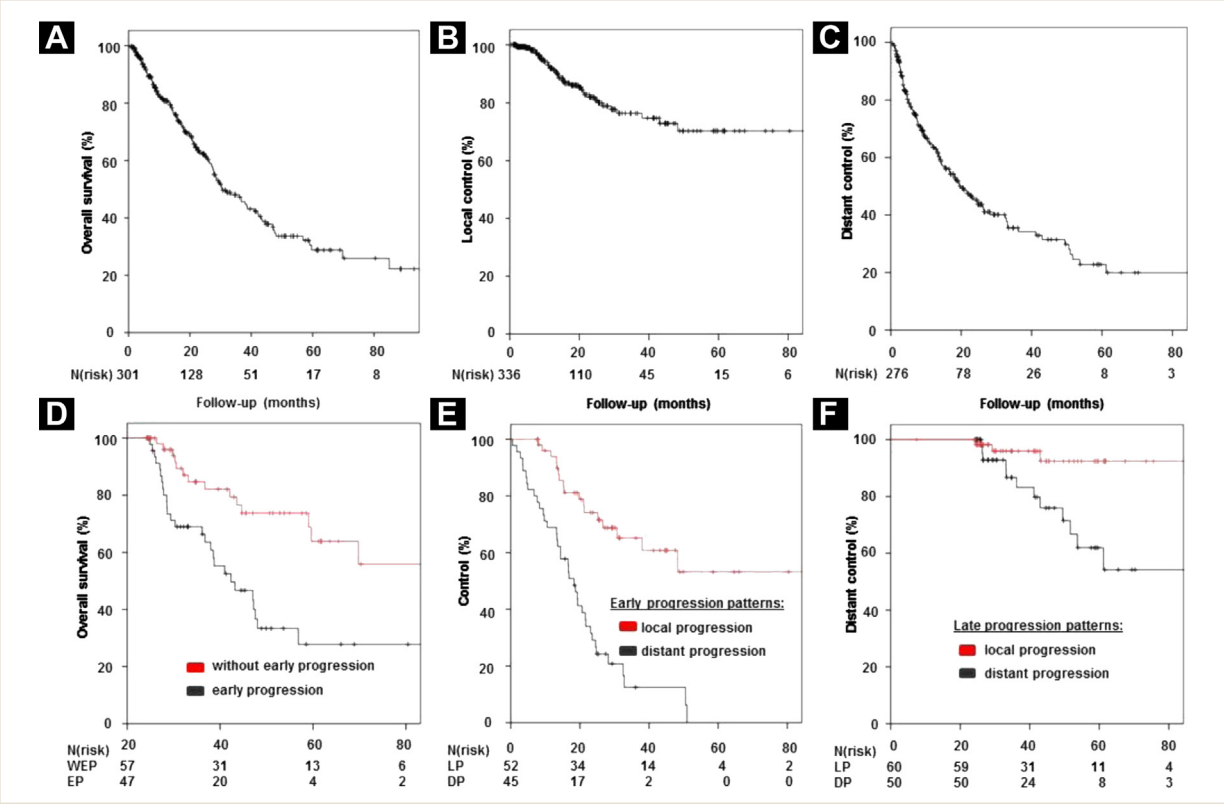
Abbreviations: BED = biological effective dose; CHT = chemotherapy; NSCLC = non–small-cell lung cancer; PTV = planning target volume; RCHT = radiochemotherapy; RT = radiotherapy; SBRT = stereotactic body radiotherapy.

potential confounding variables on multivariate analysis, BED at planning target volume isocenter (HR, 0.989; 95% CI, 0.979-0.999; $P = .037$) remained as independent prognostic factors. Furthermore, patients with adenocarcinoma histology showed superior LC (HR, 0.526; 95% CI, 0.280-0.988; $P = .046$) (Tables 3 and 4).

DC

During follow-up time, 136 (49.3%) distant failures occurred, with 1-, 2-, 3-, and 5-year DC of 64.0%, 45.2%, 35.5%, and 22.8%, respectively (Figure 1C). Patients with metastases in only 1 single organ (the lung) (HR, 2.690; 95% CI, 1.851-3.909; $P < .001$) and with male gender (HR, 1.487; 95% CI,

Figure 1 Overall Survival (A), Local Control (B), and Distant Control (C) Following Stereotactic Body Radiotherapy in 301 Patients With Non—small-cell Lung Cancer With 336 Pulmonary Oligometastases. Subgroup Analysis for Patients With a Follow-up Time of More Than 24 Months (D): Early (E) and Late Progression (F) Patterns



1.046-2.116; $P = .027$) were at significantly lower risk of developing distant progression in multivariate analysis (Tables 3 and 4).

Early Versus Late Patterns of Failure

Subgroup analysis was performed in patients with a follow-up of more than 24 months aiming to compare early (during the first 2 years) versus late (after 2 years) patterns of disease progression. In total, 104 patients were identified with follow-up information > 24 months treated with SBRT to 112 pulmonary metastases. The median follow-up for the subgroup was 39.2 months (range, 24.1-131.7 months). No statistically significant differences were observed in any patient, tumor, or treatment parameter between the whole study population and the subgroup with longer follow-up (Tables 1 and 2).

In this subgroup of 104 patients with minimum follow-up of 24 months, 47 (45.2%) patients were diagnosed with progression during the first 24 months, whereas 57 (54.8%) patients had neither local nor distant progression 24 months post-treatment. Three-year OS, LC, and DC were 76.8%, 82.6%, and 52.7%, respectively, for the whole subgroup. For patients with early progression, 3-year and 4-year LC and DC rates were constantly low (65.1% and 60.8% as well as 12.5% and 6.2%, respectively). Median OS, LC, and DC was 36.7 months, 26.2 months, and 18.3 months, respectively, for patients with early progression, whereas patients without early progression showed median OS, LC, and DC rates of 43.0 months, 41.1 months, and 36.2 months, respectively (Figure 1D-F). Only significantly higher T- and N- tumor stages at first diagnosis were found for patients with early versus late progression ($P = .013$ and $P = .018$, respectively) (Tables 1 and 2). Late first progression after 2 years occurred in 13 (22.8%) of 57 patients with 3 (4.9%) local and 12 (21.1%) distant failures. Although late local failure was rarely observed, resulting in 3-year and 4-year LC rates of 96.0% and 92.4%, respectively, the hazard for late distant progression remained high during follow-up, with 3-year and 4-year DC rates of 86.7% and 75.9%, respectively (Figure 1F). Hence, the yearly risk for local failure was 4.0%, 3.6%, and 0% in the third, fourth, and fifth year, whereas the yearly risk for distant failure was calculated to be 13.3%, 10.8%, and 14.0% after 3, 4, and 5 years, respectively. Late distant progression was mainly diagnosed in the lung (65%) followed by the bone (12%), the liver (6%), and other locations (17%).

Discussion

To our knowledge, this multicenter patterns-of-care study of SBRT for NSCLC pulmonary oligometastases is the largest study examining the long-term outcome of patients treated in routine clinical practice. Three hundred thirty-six pulmonary metastases treated with SBRT in 301 patients with oligometastatic NSCLC

Table 3 Univariate Analysis of Factors Influencing Overall Survival, Local Survival, and Distant Control

Factors	Overall Survival			Local Control			Distant Control		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age, y	1.023	1.001-1.044	**.036**	1.009	0.972-1.046	.648	0.978	0.959-0.998	**.030**
Gender (female ref.)	0.808	0.543-1.202	.292	0.777	0.384-1.574	.484	1.476	1.039-2.097	**.030**
Pretreatment performance scale (Karnofsky index), %	0.985	0.970-1.001	.063	0.986	0.955-1.017	.366	1.014	0.998-1.030	.094
BED at PTV isocenter (BEDISO), Gy	0.995	0.990-1.000	.062	0.989	0.980-0.999	**.032**	1.003	0.999-1.007	.189
Histologic subtype (adenocarcinoma ref.)	0.690	0.486-0.970	**.038**	0.540	0.288-1.012	.055	1.037	0.741-1.453	.831
Mutation type (EGFR/EML4ALK ref.)	0.200	0.028-1.459	.112	1.342	0.155-11.606	.789	0.716	0.258-1.991	.522
T-stage (T1 ref.)			.478			.718			.086
T2	0.913	0.569-1.464		0.403	0.164-0.987		0.774	0.448-1.227	
T3	1.271	0.752-2.148		0.968	0.418-2.241		1.383	0.854-2.238	
T4	1.461	0.828-2.578		0.700	0.246-1.991		1.377	0.814-2.331	
N-stage (N0 ref.)			.206			.365			**.029**
N1	1.236	0.769-1.987		1.120	0.478-2.624		1.317	0.833-2.082	
N2	1.479	0.967-2.261		0.703	0.285-1.738		0.971	0.618-1.525	
N3	0.737	0.318-1.710		0.387	0.052-2.871		2.757	1.626-4.675	
Metastasis location (peripheral ref.)	1.234	0.750-2.033	.408	0.582	0.178-1.905	.371	1.455	0.913-2.318	.115
No. metastases (solitary ref.)	0.845	0.587-1.216	.365	0.920	0.487-1.737	.797	0.513	0.366-0.721	**<.001**
Time to metastasis (metachronous ref.)	0.873	0.580-1.315	.516	0.393	0.154-1.002	.051	1.292	0.895-1.866	.171
Complete consolidative therapy (complete ref.)	0.783	0.504-1.216	.275	1.799	0.651-4.974	.257	0.588	0.398-0.868	**.008**
No. metastatic organs (multiple ref.)	1.943	1.303-2.896	**.001**	0.847	0.343-2.092	.719	2.515	1.706-3.707	**.005**

The variables histologic subtype, mutation type, T-stage, N-stage, metastasis location, number of metastases, time to metastasis, and complete consolidative therapy as well as number of metastatic organs were analyzed as categorical variables, whereas the other variables were taken as continuous variables for analysis.
Significant *P* values are marked in bold.
Abbreviations: BED = biological effective dose; CI = confidence interval; EGFR = epithelial growth factor receptor; HR = hazard ratio; PTV = planning target volume; ref = reference; SBRT = stereotactic body radiotherapy.

were analyzed. Two-year OS, LC, and DC were 62.2%, 82.0%, and 45.2%, respectively. Other studies reported comparable survival data for patients with oligometastatic NSCLC with 2-year OS rates of 38% to 75% and LC rates of 75% to 89%, although most studies did not primarily focus on pulmonary metastases.[14,28,33-38] The dominant failure pattern was distant in our study: although LC was promising with 3- and 5-year LC rates of 76.4% and 70.3%, respectively, patients failed predominantly distantly with the development of new metastatic lesions. Three- and 5-year control of distant metastases was therefore low at 35.5% and 22.8%, respectively.

Our study focused on the analysis of early versus late patterns-of-failure: within the first 24 months after SBRT for pulmonary oligometastases, patients were at relevant risk for both local and systemic disease progression. Two-year local and distant failure rates were 11.4% and 32.9% for the whole subgroup and 25.9% and 70.9% for patients with early progression. Patients diagnosed with early progression only showed significantly higher T- and N- tumor stages compared with those without local or distant recurrences. Interestingly, neither the metastatic tumor load nor the control of the primary tumor and/or further metastases significantly influenced the risk of early progression.

After 24 months, the patterns of disease progression changed. Late local progression was rarely observed, with excellent 3- and 5-year local failure rates of 4% and 7.6%, respectively. However, the risk for late distant progression remained high and further increased during follow-up, with 3- and 5-year distant failure rates of 13.3% and 38.1%, with constant annual risks for distant disease progression of about 11% to 14% (Figure 1E and F). The survival curve for distant control did not reach a plateau, underlining that the risk for distant progression is persistently high for many years. These results are confirmed by a recently updated prospective study with long-term follow-up about radical treatment to all metastatic sites of patients with oligometastatic NSCLC, which only reported local recurrence in 7.7% of the cases, whereas PFS was only 8% after 5 years also with no plateau reached.[39]

In the era before the implementation of local ablative therapies, failures mainly occurred at already involved tumor sites following systemic treatment in patients with oligometastatic NSCLC.[40] Precisely, a study of the University of Chicago analyzed further disease progression in patients with metastatic NSCLC treated only with systemic therapy: they reported that 65% of the patients with 4 or fewer lesions had stable or progressive disease only at sites that were initially involved at diagnosis without developing any new metastatic tumors.[40] Local ablative pulmonary SBRT shifted the patterns of failure from already known local to new distant sites in our analysis. Two recently published randomized phase II trials reported superior PFS and one also OS (Gomez et al) by the addition of radical local treatment to systemic therapy for patients with oligometastatic NSCLC.[18,19,41] Intriguingly, both studies illustrated the same change in patterns of relapse as detected in our study. The addition of local ablative treatment caused a shift in failure from treated sites of known disease to new sites of distant progression. Furthermore, in our study, DC was also superior for patients who received local consolidative therapy to all lesions (Table 3). This finding was also confirmed by the above-mentioned 2 phase II trials that also reported that the additional

Table 4 Multivariate Analysis of Factors Influencing Overall Survival, Local Control, and Distant Control

Factors	Overall Survival			Local Control			Distant Control		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age, y	1.027	1.004-1.050	**.019**						
Gender (female ref.)							1.487	1.046-2.116	**.027**
BED at PTV isocenter, Gy				0.989	0.979-0.999	**.037**			
Histologic subtype (adenocarcinoma ref.)	0.667	0.466-0.956	**.028**	0.526	0.280-0.988	**.046**			
Time to metastasis (metachronous ref.)				0.428	0.167-1.093	.076			
No. metastatic organs (multiple ref.)	2.360	1.574-3.537	**<.001**				2.690	1.851-3.909	**<.001**

The variables histologic subtype and time to metastatis, as well as number of metastatic organs, were analyzed as categorical variables, whereas the other variables were taken as continuous variables for analysis.
Significant *P* values are marked in bold.
Abbreviations: BED = biological effective dose; CI = confidence interval; HR = hazard ratio; PTV = planning target volume; ref = reference; SBRT = stereotactic body radiotherapy.

administration of local consolidative therapy significantly prolonged the time to the appearance of a new lesion,[18,41] suggesting that LC of all visible tumor lesions can result in less disease progression at new sites.[42]

Several independent prognostic factors for superior OS, LC, and DC were identified in the current analysis. Histologic subtype was significantly associated with both LC and OS in multivariate analysis. Although patients with adenocarcinoma of the lung showed an increased 2-year LC and OS of 86.3% and 71.5%, respectively, patients diagnosed with squamous cell carcinoma suffered from significantly reduced 2-year LC and OS of only 77.9% and 53.0% following SBRT to their pulmonary metastases (Table 4). Regarding SBRT for early stage NSCLC, histologic subtype has recently been described as an important factor, which significantly affects not only survival but also local recurrence.[43-46] We now confirmed in a large cohort of 301 patients that this correlation is also true for SBRT of pulmonary oligometastases from different histologic NSCLC subtypes. Further data are needed to determine if treatment algorithms for pulmonary SBRT have to be adapted depending on different histologic NSCLC subtypes.

Beyond histologic subtype, our data also indicate that the number of metastatic organs (single vs. multiple) significantly influenced survival as well as distant disease progression (Table 4). In a large retrospective series including 186 patients with oligometastatic NSCLC from the Dana-Faber Cancer Institute, the diagnosis of metastases to multiple organs was also associated with inferior survival.[47] A meta-analysis about the optimal therapy for patients with synchronous oligometastatic NSCLC also reported superior outcome for patients classified in the single-organ metastases group.[48] Currently, there is no consensus about the appropriate cutoff for the number of metastases to define the oligometastatic state. The most widely accepted number of metastatic lesions to be considered oligometastatic is ≤ 5.[29] Nearly all published clinical trials examining local treatment of patients with oligometastatic NSCLC limited inclusion to patients with ≤ 5 metastases. Furthermore, most of these trials only enrolled patients with ≤ 3 metastases.[49] Based on the above-mentioned results, the inclusion of patients with up to 5 metastases in different organs in the oligometastatic state might have to be reconsidered.

As patients with oligometastatic NSCLC who only receive local treatment are at high risk of failing distantly by the occurrence of new lesions, there is a profound need for the combination of local ablative therapies with systemic treatment. However, patients with metastasized NSCLC treated with standard systemic chemotherapy often only have a survival prognosis of less than 12 months.[7] Future trials should therefore focus on the combination of local ablative treatment with targeted therapies against molecular alterations (eg, *EGFR, ALK, ROS1, BRAF*) or with immunotherapy. Two studies have already reported about the favorable combination of local ablative therapy including SBRT and EGFR-tyrosine kinase inhibitor therapies.[50,51] The addition of immunotherapy to local ablative therapies, especially SBRT, seems even more promising. Radiation therapy can promote immunogenic cell death enhancing tumor-specific immune responses.[52,53] The recently fully published PACIFIC (Phase III, Randomised, Double-blind, Placebo-controlled, Multi-centre, International Study of MEDI4736 as Sequential Therapy in Patients With Locally Advanced, Unresectable Non–Small-Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy) trial illustrated that the admission of the anti-PD-L1 antibody durvalumab as consolidation therapy following chemoradiotherapy in stage III NSCLC significantly prolonged PFS as well as OS by reducing the frequency of new lesions by 33%.[54,55] Further support for the combination of SBRT with immunotherapy is provided by preliminary data of the Pembro-RT (Randomized phase II study of pembrolizumab after stereotactic body radiotherapy versus pembrolizumab alone in patients with advanced non–small-cell lung cancer) trial. This trial analyzed the admission of pembrolizumab alone versus pembrolizumab preceded by SBRT to a single metastasis in patients with advanced NSCLC ($\geq$ second-line systemic therapy). Intriguingly, overall response to pembrolizumab was doubled and PFS was more than tripled by the addition of SBRT to only 1 metastasis.[56] Currently, a number of ongoing trials further evaluate the potential of adding local ablative therapies (eg, SBRT) to systemic therapy for patients with metastasized NSCLC (eg, NCT03256981 [HALT; Targeted Therapy With or Without Dose Intensified Radiotherapy for Oligo-progressive Disease in Oncogene-addicted Lung Tumours], NCT02417662 [SARON; Stereotactic Ablative Radiotherapy for Oligometastatic Non–small-Cell Lung Cancer. A Randomised Phase III Trial], NCT03137771 [LU002; Maintenance Systemic Therapy Versus Local Consolidative Therapy plus Maintenance Systemic Therapy for Limited Metastatic Non–Small-Cell Lung Cancer: A Randomized Phase II/III Trial]).

We acknowledge that the retrospective multicenter nature of the study has some limitations. First, despite the quite long analysis time (1997-2017), the median follow-up time was rather short, at 16.1 months. Second, owing to the long analysis time, PET imaging was only applied in 51.8% of the patients, increasing the risk of also including patients with non-oligometastatic disease. We recently showed that improved patient selection with pre-SBRT PET is an independent prognostic factor for superior outcome of patients with oligometastatic lung disease.[27] Third, there was no central review for progression, follow-up examinations were performed by the individual center according to German guidelines, and outcome data was taken as reported by the specific institution.[2] Forth, histologic confirmation of the metastases was only taken when the metastatic origin of the pulmonary lesion was questioned (15.6%). Hence, also patients with second primary lung tumors might have been included in the analysis, although inclusion was restricted to the occurrence of the pulmonary metastasis within 5 years following diagnosis of the primary tumor.

Conclusion

This multi-institutional patterns-of-care analysis confirmed favorable LC and promising OS following SBRT for pulmonary metastases in patients with NSCLC with oligometastatic stage IV disease outside prospective trials. However, the risk for distant progression with the development of new metastatic sites remains high for a minimum of 5 years, indicating the need for clinical trials combining effective local with advanced systemic treatment modalities for oligometastatic NSCLC.

Clinical Practice Points

- The purpose of this multicenter study was to analyze outcome as well as early versus late patterns of recurrence following pulmonary SBRT for patients with oligometastatic NSCLC.
- A total of 301 patients with oligometastatic NSCLC treated with SBRT for 336 lung metastases at 24 German and Swiss departments between 1997 and 2017 were included in the analysis.
- Outside of prospective trials, SBRT for pulmonary oligometastatic NSCLC resulted in favorable LC and promising OS.
- The dominant failure pattern was distant with a continuously high risk of disease progression for many years.
- Although local recurrence rarely occurred after 2 years, with 3-year and 4-year local failure rates of only 4.0%, and 7.6%, the risk of distant progression remained high, with 3-and 4-year distant failure rates of 13.3% and 24.1% with no plateau observed.
- Future studies therefore need to focus on the combination of local ablative therapy with more effective systemic treatments (eg, immunotherapy).

Acknowledgments

This work was supported by the Medical Faculty of Heidelberg University, which provided a research grant for JHR.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Ettinger DS, Akerley W, Borghaei H, et al; NCCN (National Comprehensive Cancer Network). Non-small cell lung cancer. *J Natl Compr Canc Netw* 2012; 10: 1236-71.
2. Goeckenjan G, Sitter H, Thomas M, et al; German Respiratory Society; German Cancer Society. Prevention, diagnosis, therapy, and follow-up of lung cancer: interdisciplinary guideline of the German Respiratory Society and the German Cancer Society. *Pneumologie* 2011; 65:39-59.
3. Tumati V, Iyengar P. The current state of oligometastatic and oligoprogressive non-small cell lung cancer. *J Thorac Dis* 2018; 10:S2537-44.
4. Grossi F, Kubota K, Cappuzzo F, et al. Future scenarios for the treatment of advanced non-small cell lung cancer: focus on taxane-containing regimens. *Oncologist* 2010; 15:1102-12.
5. Ramalingam S, Belani C. Systemic chemotherapy for advanced non-small cell lung cancer: recent advances and future directions. *Oncologist* 2008; 13(Suppl 1):5-13.
6. Kulkarni S, Vella ET, Coakley N, et al. The use of systemic treatment in the maintenance of patients with non−small cell lung cancer: a systematic review. *J Thorac Oncol* 2016; 11:989-1002.
7. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft DK, AWMF):. Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms. *Langversion 10, 2018*. 2018. Available at http://leitlinienprogramm-onkologie.de/Lungenkarzinom.98.0.html. Accessed: March 5, 2019.
8. Ettinger DS, Wood DE, Aisner DL, et al. Non−small cell lung cancer, version 5. 2017, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2017; 15:504-35.
9. Ettinger DS, Wood DE, Akerley W, et al. Non−small cell lung cancer, version 6. 2015. *J Natl Compr Canc Netw* 2015; 13:515-24.
10. Reck M, Rodriguez-Abreu D, Robinson AG, et al; KEYNOTE-024 Investigators. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016; 375:1823-33.
11. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol* 1995; 13:8-10.
12. Altoos B, Amini A, Yacoub M, et al. Local control rates of metastatic renal cell carcinoma (RCC) to thoracic, abdominal, and soft tissue lesions using stereotactic body radiotherapy (SBRT). *Radiat Oncol* 2015; 10:218.
13. Ashworth A, Rodrigues G, Boldt G, Palma D. Is there an oligometastatic state in non-small cell lung cancer? A systematic review of the literature. *Lung Cancer* 2013; 82:197-203.
14. Griffioen GH, Toguri D, Dahele M, et al. Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (NSCLC): patient outcomes and prognostic factors. *Lung Cancer* 2013; 82:95-102.
15. Pastorino U, Buyse M, Friedel G, et al; International Registry of Lung Metastases. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. *J Thorac Cardiovasc Surg* 1997; 113:37-49.
16. Tree AC, Khoo VS, Eeles RA, et al. Stereotactic body radiotherapy for oligometastases. *Lancet Oncol* 2013; 14:e28-37.
17. Rusthoven CG, Yeh N, Gaspar LE. Radiation therapy for oligometastatic non-small cell lung cancer: theory and practice. *Cancer J* 2015; 21:404-12.
18. Gomez DR, Blumenschein GR Jr, Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol* 2016; 17:1672-82.
19. Gomez DR, Tang C, Zhang J, et al. Local consolidative therapy (LCT) improves overall survival (OS) compared to maintenance therapy/observation in oligometastatic non-small cell lung cancer (NSCLC): final results of a multicenter, randomized, controlled phase 2 trial. *Int J Radiat Oncol Biol Phys* 2018; 102:1604.
20. Eberhardt WE, Mitchell A, Crowley J, et al; International Association for Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Board Members, and Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for the revision of the M descriptors in the forthcoming eighth edition of the TNM Classification of Lung Cancer. *J Thorac Oncol* 2015; 10:1515-22.
21. Adam R, Chiche L, Aloia T, et al; Association Francaise de Chirurgie. Hepatic resection for noncolorectal nonendocrine liver metastases: analysis of 1,452 patients and development of a prognostic model. *Ann Surg* 2006; 244:524-35.
22. Casiraghi M, De Pas T, Maisonneuve P, et al. A 10-year single-center experience on 708 lung metastasectomies: the evidence of the "International Registry of Lung Metastases." *J Thorac Oncol* 2011; 6:1373-8.
23. Borm KJ, Oechsner M, Schiller K, et al. Prognostic factors in stereotactic body radiotherapy of lung metastases. *Strahlenther Onkol* 2018; 194:886-93.
24. Rieber J, Streblow J, Uhlmann L, et al. Stereotactic body radiotherapy (SBRT) for medically inoperable lung metastases-a pooled analysis of the German working group "stereotactic radiotherapy." *Lung Cancer* 2016; 97:51-8.
25. Stera S, Balermpas P, Chan MKH, et al. Breathing-motion-compensated robotic guided stereotactic body radiation therapy: patterns of failure analysis. *Strahlenther Onkol* 2018; 194:143-55.
26. Guckenberger M, Klement RJ, Allgauer M, et al. Local tumor control probability modeling of primary and secondary lung tumors in stereotactic body radiotherapy. *Radiother Oncol* 2016; 118:485-91.
27. Rieber J, Abbassi-Senger N, Adebahr S, et al. Influence of institutional experience and technological advances on outcome of stereotactic body radiation therapy for oligometastatic lung disease. *Int J Radiat Oncol Biol Phys* 2017; 98:511-20.
28. Ashworth AB, Senan S, Palma DA, et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. *Clin Lung Cancer* 2014; 15:346-55.
29. Juan O, Popat S. Ablative therapy for oligometastatic non-small cell lung cancer. *Clin Lung Cancer* 2017; 18:595-606.
30. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006; 24:4833-9.
31. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010; 303:1070-6.
32. Park C, Papiez L, Zhang S, Story M, Timmerman RD. Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy. *Int J Radiat Oncol Biol Phys* 2008; 70:847-52.
33. De Rose F, Cozzi L, Navarria P, et al. Clinical outcome of stereotactic ablative body radiotherapy for lung metastatic lesions in non-small cell lung cancer oligometastatic patients. *Clin Oncol* 2016; 28:13-20.
34. Kwint M, Walraven I, Burgers S, et al. Outcome of radical local treatment of non-small cell lung cancer patients with synchronous oligometastases. *Lung Cancer* 2017; 112:134-9.
35. Merino Lara T, Helou J, Poon I, et al. Multisite stereotactic body radiotherapy for metastatic non-small-cell lung cancer: delaying the need to start or change systemic therapy? *Lung Cancer* 2018; 124:219-26.
36. Mazzola R, Fersino S, Ferrera G, et al. Stereotactic body radiotherapy for lung oligometastases impacts on systemic treatment-free survival: a cohort study. *Med Oncol* 2018; 35:121.
37. Lopez Guerra JL, Gomez D, Zhuang Y, et al. Prognostic impact of radiation therapy to the primary tumor in patients with non-small cell lung cancer and oligometastasis at diagnosis. *Int J Radiat Oncol Biol Phys* 2012; 84:e61-7.
38. Fleckenstein J, Petroff A, Schafers HJ, Wehler T, Schope J, Rube C. Long-term outcomes in radically treated synchronous vs. metachronous oligometastatic non-small-cell lung cancer. *BMC Cancer* 2016; 16:348.
39. De Ruysscher D, Wanders R, Hendriks LE, et al. Progression-free survival and overall survival beyond 5 years of NSCLC patients with synchronous oligometastases treated in a prospective phase II trial (NCT 01282450). *J Thorac Oncol* 2018; 13:1958-61.
40. Mehta N, Mauer AM, Hellman S, et al. Analysis of further disease progression in metastatic non-small cell lung cancer: implications for locoregional treatment. *Int J Oncol* 2004; 25:1677-83.
41. Iyengar P, Wardak Z, Gerber DE, et al. Consolidative radiotherapy for limited metastatic non−small-cell lung cancer: a phase 2 randomized clinical trial. *JAMA Oncol* 2018; 4:e173501.
42. Senan S, Rusthoven CG, Slotman BJ, Siva S. Progress in radiotherapy for regional and oligometastatic disease in 2017. *J Thorac Oncol* 2018; 13:488-96.

43. Baine MJ, Verma V, Schonewolf CA, Lin C, Simone CB 2nd. Histology significantly affects recurrence and survival following SBRT for early stage non-small cell lung cancer. *Lung Cancer* 2018; 118:20-6.
44. Horner-Rieber J, Bernhardt D, Dern J, et al. Histology of non-small cell lung cancer predicts the response to stereotactic body radiotherapy. *Radiother Oncol* 2017; 125:317-24.
45. Leeman JE, Rimner A, Montecalvo J, et al. Histologic subtype in core lung biopsies of early-stage lung adenocarcinoma is a prognostic factor for treatment response and failure patterns after stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2017; 97:138-45.
46. Woody NM, Stephans KL, Andrews M, et al. A histologic basis for the efficacy of SBRT to the lung. *J Thorac Oncol* 2017; 12:510-9.
47. Parikh RB, Cronin AM, Kozono DE, et al. Definitive primary therapy in patients presenting with oligometastatic non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2014; 89:880-7.
48. Li D, Zhu X, Wang H, Qiu M, Li N. Should aggressive thoracic therapy be performed in patients with synchronous oligometastatic non-small cell lung cancer? A meta-analysis. *J Thorac Dis* 2017; 9:310-7.
49. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2019; 30:863-70.
50. Iyengar P, Kavanagh BD, Wardak Z, et al. Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. *J Clin Oncol* 2014; 32: 3824-30.
51. Xu Q, Zhou F, Liu H, et al. Consolidative local ablative therapy improves the survival of patients with synchronous oligometastatic NSCLC harboring EGFR activating mutation treated with first-line EGFR-TKIs. *J Thorac Oncol* 2018; 13: 1383-92.
52. Ko EC, Raben D, Formenti SC. The integration of radiotherapy with immunotherapy for the treatment of non−small cell lung cancer. *Clin Cancer Res* 2018; 24: 5792-806.
53. Bhalla N, Brooker R, Brada M. Combining immunotherapy and radiotherapy in lung cancer. *J Thorac Dis* 2018; 10:S1447-60.
54. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non−small-cell lung cancer. *N Engl J Med* 2017; 377:1919-29.
55. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med* 2018; 379:2342-50.
56. Theelen W, Peulen H, Lalezari F, et al. Randomized phase II study of pembrolizumab after stereotactic body radiotherapy (SBRT) versus pembrolizumab alone in patients with advanced non-small cell lung cancer: the PEMBRO-RT study. *J Clin Oncol* 2018; 36:9023.