Stereotactic Body Radiotherapy (SBRT) for lung metastases - a pooled analysis of the German working group ”stereotactic radiotherapy“

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Abstract

Objectives:

The current literature on stereotactic body radiotherapy (SBRT) for oligometastatic disease is characterized by small patient cohorts with heterogeneous primary tumors, metastases location and dose regimes. Hence, this study established a multi-institutional database of 700 patients treated with SBRT for pulmonary metastases to identify prognostic factors influencing survival and local control.

Materials and Methods:

All German radiotherapy departments were contacted and invited to participate in this analysis. A total number of 700 patients with lung metastases treated with SBRT in 20 centers between 1997 and 2014 were included in a database. Primary and metastatic tumor characteristics, treatment characteristics and follow-up data including survival, local control, distant metastases, and toxicity were evaluated.

Results:

After a median follow-up time of 14.3 months, 2-year local control (LC) and overall survival (OS) were 81.2% and 54.4%, respectively. In multivariate analysis, OS was most significantly influenced by pretreatment performance status, maximum metastasis diameter, primary tumor histology, time interval between primary tumor diagnosis and SBRT treatment and number of metastases. For LC, independent prognostic factors were pretreatment performance status, biological effective dose (BED) at PTV isocenter (BEDISO) and single fraction (PTV-encompassing) dose in multivariate analysis. Radiation-induced pneumonitis grade 2 or higher was observed in 6.5% of patients. The only factor significantly influencing toxicity was BEDISO (p=0.006).

Conclusion:

SBRT for medically inoperable patients with pulmonary metastases achieved excellent local control and promising overall survival. Important prognostic factors were identified for selecting patients who might benefit most from this therapy approach.

key words: stereotactic body radiotherapy (SBRT), extracranial stereotactic radiotherapy, pulmonary SBRT, radiosurgery, lung metastases, oligometastases

Introduction

Until some years ago, the standard therapy for patients with stage IV tumor disease focused on systemic treatment given with palliative intent. In 1995, Hellman and Weichselbaum established the term “oligometastases” for an intermediate stage between locoregional tumor spread and disseminated metastases[1]. In line with this concept, some patients with oligometastatic disease have long term overall survival and it is believed that local treatment of metastatic disease contributes to this favorable outcome[2-5]. Indeed, retrospective studies of pulmonary and hepatic metastasectomy from different primary tumors reported 5-year survival of 20-47%[6-11].

Stereotactic body radiotherapy (SBRT) has a history of more than 15 years and today is well established in the treatment of early-stage non-small cell lung cancer (NSCLC)[12, 13]. SBRT is the treatment of choice for elderly patients diagnosed with early-stage NSCLC who are inoperable due to comorbidities or insufficient pulmonary function. For medically inoperable stage I NSCLC patients, consistently high local tumor control rates of 84-98% are achieved in prospective and retrospective studies[14-19]. Recently, pooled analyses have been conducted and resulted in a better understanding of factors influencing local control, survival and toxicity for SBRT in early stage NSCLC[13, 20].

Based on these experiences in primary NSCLC, SBRT has also been introduced in the treatment of oligometastatic disease from various primary tumors and at various metastases locations. However, current scientific data on the outcome of SBRT for pulmonary oligometastases is characterized by small patient cohorts and heterogeneous SBRT practice. Up to now, there is a lack of comparability and standardization in literature.

Hence, the working group Stereotactic Radiotherapy of the German Society of Radiation Oncology (DEGRO) established a retrospective multi-national and multi-institutional database including 700 patients treated with SBRT for pulmonary metastases. This study

allows the analysis of sufficiently large subgroups aiming to describe patient and treatment factors influencing outcome and toxicity.

Material and Methods

In 2012 the working group Stereotactic Radiotherapy of the DEGRO invited all German radiotherapy centers to contribute to a pooled database of patients treated with SBRT for lung metastases. Participating centers were required to have experience in SBRT beyond the implementation phase: a minimum of 20 patients had to be treated with SBRT until 2012. We analyzed SBRT treatment of pulmonary metastases between 1997 and 2014. The analysis was approved by the Ethics committee of the University Hospital Heidelberg (S-280/2014).

Inclusion criteria were patients with lung metastases from different primary tumors. Clinical diagnosis was based on CT +/- FDG-PET imaging. SBRT was applied when the following criteria were met: patients with medically inoperable, unresectable pulmonary metastases or if patients refused operation. SBRT definition was not based on the number of treatment fractions (e.g. ≤ 5) but on combination of the target volume concept, conformal treatment planning (3-dimensional conformal, intensity-modulated radiation therapy, volumetric modulated arc therapy), stereotactic or image-guided patient setup and hypo-fractionated delivery of radical irradiation doses. All centers used risk-adapted fractionation schemes which meant that the number of fractions and single-fraction doses were adjusted to tumor size and location (peripheral vs. central). Intrafractional uncertainties were minimized using patient-immobilization devices like the stereotactic body frame, DIBH (Deep Inspiratory Breath Hold) with Active Breathing Coordinator or customized vacuum cushions by all institutions.

All 20 centers included the relevant patient data in an anonymized electronic file and sent this file to the coordinating center which set-up a pooled database. The database

consisted of more than 50 items including patient characteristics and underlying primary tumor characteristics with the date of primary diagnosis and further therapies. In addition, details about the pulmonary metastasis with modality of diagnosis (CT, PET-CT, histological confirmation) and lesion position and size were recorded. Treatment details and dose prescription (prescribed planning target volume (PTV) encompassing dose, biological effective dose (BED) at PTV periphery (BEDPTV), BED at isocenter (BEDISO), dose homogeneity, number of fractions) were evaluated.

Local control (LC) was defined as no progressive disease of the tumor within the treated area. Recurrences distant to the primary pulmonary lesion in the same lobe were not classified as local failure but as distant metastases. No central definition for local failure was available in terms of computed tomography (CT) morphological criteria, fluoro-deoxy-glucose positron emission tomography (FDG-PET) imaging, or biopsy confirmation. Local control, overall and distant metastases free survival were analyzed from the beginning of radiotherapy. Data for local control was only available for 600 patients, while overall survival was analyzed for 700 patients.

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

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

The aim of the statistical analysis was to evaluate OS and LC after SBRT for pulmonary metastases and to identify factors influencing outcome. Univariate cox models were used for analyzing all patient, tumor and treatment characteristics for OS and LC as outcome variables and then multivariable cox models were performed for OS and LC including all possible predictors in a single model (separately for OS and LC). We also implemented a step-wise variable selection procedure where we combined a backward and a forward selection procedure alternating in each step. In the backward step, the variable with the

highest p-value was excluded if the p-value was > 0.2. In the forward step, the variable with the lowest p-value was included if the p-value was <0.199.

Since we had to deal with missing values, we followed the RR approach proposed by Wood et al. as we imputed 50 datasets using chained equations[21]. Rubin's Rules were used to compute regression coefficients and the according confidence intervals and p-values[22]. The p-values were calculated using Wald tests.

The statistical analyses were realized using the software package R (version 3.2)[23] in combination with the packages "survival" (version 2.38-3) "xtable" (version 1.7-4) "mice" (version 2.22) "Rcpp" (version 0.12.2), "lattice" (0.22-33), and "mitools" (version 2.3).

Results

Patient and treatment characteristics

We analyzed data from 20 centers, which were located in Germany (n=19) and Switzerland (n=1) and except for three were academic hospitals. In total, data were collected from 700 patients treated with SBRT for pulmonary metastases. All patients were diagnosed with metastatic cancer and suffered in median from one metastasis (range 0-15) in addition to the treated pulmonary lesion. Further metastases were located in 73.6% in the lung and were treated in 44.4% with a second SBRT. 51.4% of the patients had received chemotherapy before SBRT treatment, while 5.3% were treated with chemotherapy during SBRT treatment. Chemotherapy was administered in 26.4% of the patients after SBRT. The most frequent primary tumor was non-small cell lung cancer (n=210), followed by colorectal cancer (n=153), sarcoma (n=51), renal cell carcinoma (n=48) and breast cancer (n=43). SBRT treatment of the pulmonary metastasis was applied in median 35.8 months (range 0 months-28.8 years) after diagnosis of the primary tumor. Time interval between diagnosis of the pulmonary metastasis and SBRT treatment was 2.7 months (0.1-111.7 months) in median. PET-CT staging was used in

45.4% of the analyzed patients. Detailed patient and treatment characteristics are summarized in table1 and 2.

Overall survival, local control and systemic progression

With a median follow-up time of 14.3 months (range 0-131.9 months), 1-year and 2-year overall survival rates were 75.1% and 54.4%, respectively (figure 1). In detail, 2-year survival was best for patients with colorectal (2-year-OS 67%) and breast cancer (2-year-OS 63%), while patients diagnosed with NSCLC or sarcoma suffered from worse 2-year survival with 54% and 39%, respectively.

73 local relapses (10.4%) were detected during follow-up time, hence local control was 90.9% after 1 year and 81.2% after 2 years, respectively (figure 2). The median time to local failure was 10.5 months. 1-year and 2-year distant metastases free survival was found to be 38.0%, and 21.1%. Therefore, the dominant failure pattern was distant with 55.1% of patients (n=386) developing distant progression. Distant metastases were diagnosed in the lung (n=209), the bone (n=66), the liver (n=65), the brain (n=39), and other locations (n=88).

Univariate Analysis

Results of univariate analysis are shown in table 3. Overall survival was most significantly influenced by pretreatment performance status and maximum metastasis diameter ($p \leq 0.001$). Additionally, number of metastases (solitary versus multiple), primary tumor histology, BEDPTV and time interval between primary tumor diagnosis and SBRT treatment significantly influenced overall survival ($p<0.05$).

Local control was significantly influenced by pretreatment performance status and prescribed single fraction (PTV-encompassing) dose ($p<0.05$). The variables “primary tumor histology” and “time interval between tumor diagnosis and SBRT treatment” were

excluded from univariate analysis as fitting a model including this variable was not possible due to small subgroups with few events. Further in-detail analysis and modeling of local tumor control for this cohort have already been conducted and have been published separately [24].

Multivariate Analysis

The most significant prognostic factors for overall survival were pretreatment performance status, maximum metastasis diameter and primary tumor histology ($p \leq 0.01$). Additionally, overall survival was significantly affected by number of metastases (solitary vs. multiple) and time interval between primary tumor diagnosis and SBRT treatment ($p \leq 0.05$) (table 4).

Local control was significantly influenced by single fraction (PTV-encompassing) dose, BEDISO and pretreatment performance status ($p \leq 0.03$). As the variable “BEDPTV” is highly correlated with “BEDISO”, we analyzed BEDPTV in a second model. BEDPTV also significantly affected local control ($p=0.011$). Furthermore, number of SBRT fractions and dose inhomogeneity also showed a strong trend for influencing local control ($p=0.052$; $p=0.056$). Additionally, patients with central metastasis showed a strong tendency towards reduced local control ($p=0.096$).

Toxicity Analysis

Toxicity data were only available for 648 patients. Radiation-induced pneumonitis grade 2 or higher was detected in 42 patients (6.5%) and grade 5 pneumonitis was reported for only one patient (0.2%). This patient was treated with SBRT for a large (6.7 cm in diameter) central metastasis. Besides radiation-induced pneumonitis, 21 patients developed toxicity grade 2 or higher (3.2%). In detail, the following side-effects grade 2 or higher were reported: dyspnea (8 patients, 38.1%), pulmonary fibrosis (3 patients,

14.3%), atelectasis (2 patients, 9.4%), chest wall pain (2 patients, 9.4%), bronchial stricture (1 patient, 4.8%), pleural effusion (1 patient, 4.8%), pneumothorax (1 patient, 4.8%), rib fracture (1 patient, 4.8%), fatigue (1 patient, 4.8%), nausea (1 patient, 4.8%). No further death due to toxicity was documented. The only factor significantly influencing toxicity was BEDISO (p=0.006).

Discussion

The presented cohort of patients with lung metastases treated with SBRT is to our knowledge the largest reported in literature. It is a retrospective analysis with all inherent limitations. This evaluation has, however, due to the large patient number, the potential to analyze relevant subgroups in this heterogeneous patient collective and identify prognostic factors influencing outcome and toxicity.

The existing literature of SBRT for lung metastases reports highly variable rates of local control and overall survival for patients with oligometastatic cancer. Retrospective analyses describe 2-year-local control rates of 77.9-89.0% and 2-year-overall survival rates of 53.7%-73.0% for patients suffering from pulmonary oligometastases[25-28]. Analyzing SBRT for pulmonary metastases in 700 patients, we observed 2-year local control of 81.2% and 2-year overall survival of 54.4%. For early- stage lung cancer, a BEDPTV > 100 Gy is known to be needed for optimized local control [29, 30]. We now confirmed in a large cohort of 700 patients that this correlation is also true for SBRT for pulmonary metastases from different primary tumors. BED at both isocenter and periphery was identified as one of the strongest predictors for local control. Hence, after treatment with radiation doses of more than 100 Gy BEDPTV, 2-year local control was 87.6%, which is in good agreement with the best results in the literature. If radiation doses were < 100 Gy BEDPTV, 2-year local tumor control was only 77.9%. This is further

supported by a recent prospective phase II trial, which also detected 2-year local control rates of 74-100% depending on total radiation dose and fractionation schemes[31].

In 1997, the “International Registry on Lung Metastases” published the results of 5206 lung metastasectomies including 4572 (88%) with complete resections[6]. Based on these data, long-term overall survival is expected in about 20% of the patients undergoing surgical resection of lung metastases. For selecting this subset of patients, internationally accepted criteria were defined: a good performance status, absence of extra-pulmonary metastases, control of the primary tumor, possibility of complete resection, and adequate respiratory function[32, 33].On the contrary, regarding SBRT for pulmonary metastases, only few consistent prognostic factors have been reported in various studies to support appropriate patient selection for the treatment of oligometastatic pulmonary tumors[34]. Analyzing 700 patients treated with SBRT for pulmonary metastases, we were able to identify prognostic factors for selecting patients who might benefit most from SBRT treatment. Similar to the above mentioned surgical criteria, one main prognostic factor was the pretreatment performance status in this analysis. Patients with a reduced performance status suffered from significantly worse survival and local control. Furthermore, overall survival was significantly influenced by primary tumor histology. While patients with breast cancer showed median survival of 34.2 months, median survival was only 14.3 months in sarcoma patients. In a large surgical series of 708 lung metastasectomies, Casighari et al. also reported primary tumor histology to be an independent prognostic factor for outcome[8]. Milano et al. analyzed oligometastastic patients with less than five lesions in various organs including the lung in their study and showed superior outcome of breast cancer patients compared to other tumor entities[35]. However, several others studies failed to show an influence of primary tumor histology on survival due to limited patient numbers.

Another important prognostic factor identified in this analysis was the number of metastases. Patients with multiple metastases showed significantly worse survival compared to patients diagnosed with only one solitary metastasis. In a review based on several analyses about surgical resection of pulmonary metastases from colorectal cancer, Pfannschmidt et al. also reported the number of metastases to be a prognostic factor for survival[10].

Analyzing 61 patients with oligometastic lung tumors treated with SBRT, Ricardi et al. described that a smaller tumor volume was associated with improved survival[26]. This result corresponds well to our analysis as we identified maximum metastatis diameter as an important prognostic variable for survival. Patients suffering from pulmonary metastases with larger maximum tumor diameter showed reduced overall survival in this analysis. Pfannschmidt et al. and Milano et al. also described a higher tumor volume to be significantly adverse associated with overall survival[10, 36].

Regarding surgical series, a disease-free interval of ≥ 36 months is known to be significantly associated with better prognosis[6, 8]. Ashworth et al. also reported that the timing of metastatic disease (synchronous vs. metachronous) was a key determinant of long-term survival by investigating a large cohort of oligometastic patients treated with local ablative therapies[37]. Other studies did not detect any significant difference between synchronous and metachronous metastatic spread[10, 38]. In our cohort, patients with a longer time interval between primary tumor diagnosis and SBRT treatment showed significantly better survival. As the timing of metastatic disease is supposed to decide upon prognosis, two trials were recently started both in the Unites States and the United Kingdom. The UPCI 10-028 trial and the CORE trial both focus on the metachronous setting, while the UPCI 10-027 trail and the SARON trial examine the synchronous setting[4, 39].

SBRT treatment for pulmonary metastases is decided upon when patients are classified medically inoperable or refuse surgery. Therefore, patients chosen for SBRT treatment usually present with lower performance status and multiple comorbidities compared to their surgical counterparts. For pulmonary metastasectomy, 5-year survival rates of 36%-61% have been reported[8, 10, 40]. However, studies directly comparing pulmonary metastasectomy and SBRT are still rare. In contrast, for early stage NSCLC, a recent study of two pooled randomized trials suggested that SBRT treatment might even be an option for medically operable patients diagnosed with stage I NSCLC[41]. For pulmonary oligometastases, only one study directly compared metastasectomy with pulmonary SBRT. Although only less suitable surgical candidates were offered SBRT in this study, local control and survival rates were comparable for surgery and SBRT[42]. Hence, prospective studies are truly needed to evaluate the role of both, metastasectomy and pulmonary SBRT in oligometastatic patients.

In summary, analyzing SBRT to pulmonary metastases in 700 patients, we showed that similar to early-stage NSCLC patients, radiotherapy doses in BED of more than 100 Gy are needed for optimizing local control. Furthermore, we identified pretreatment performance status, primary tumor histology, number of metastases, maximum metastasis diameter and time interval between primary tumor diagnosis and SBRT as potential factors for selecting patients who might benefit most from SBRT treatment. Interestingly, a recent study analyzed 321 patients treated with SBRT for 587 different metastases from primarily colorectal tumors and identified similar predictive factors. Hence, these prognostic factors might not only important for selecting patients for pulmonary SBRT but also for various other locations.

Limitations to this study were mainly caused by the fact of a multicenter retrospective analysis. Data was not available for each single patient for each variable. To account for this limitation which is inherent to a retrospective analysis, a multiple imputation approach

was conducted. Furthermore, treatment changed over time in respect to radiation doses and fractionation schemes. Additionally, definition of local tumor progression is known to be challenging in SBRT, as many patients develop fibrosis in the irradiated area. There was no central review for all local recurrence, but local control was taken as documented by the specific institution.

Conclusions

This multi-institutional analysis confirmed promising results of SBRT for lung metastases outside prospective trials. In analogy to the results of SBRT in early stage non-small lung cancer, local tumor control was mainly influenced by BED at both isocenter and periphery. Regarding outcome, several selection criteria for predicting survival were identified: survival was significantly better for patients in good performance status, with small and solitary pulmonary metastases and a preferably long time interval between primary tumor diagnosis and SBRT treatment as well as favorable primary tumor histology.

Conflict of interest

None of the authors has any conflict of interest relevant to this analysis.

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Figure 1: Overall survival after SBRT treatment

Figure 2: Local control after SBRT treatment