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Original article

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

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ABSTRACT

Background: Stereotactic body radiotherapy (SBRT) for oligometastatic disease is characterized by an excellent safety profile; however, experiences are mostly based on treatment of one single metastasis. It was the aim of this study to evaluate safety and efficacy of SBRT for multiple pulmonary metastases.
Patients and methods: This study is based on a retrospective database of the DEGRO stereotactic working group, consisting of 637 patients with 858 treatments. Cox regression and logistic regression were used to analyze the association between the number of SBRT treatments or the number and the timing of repeat SBRT courses with overall survival (OS) and the risk of early death.
Results: Out of 637 patients, 145 patients were treated for multiple pulmonary metastases; 88 patients received all SBRT treatments within one month whereas 57 patients were treated with repeat SBRT separated by at least one month. Median OS for the total patient population was 23.5 months and OS was not significantly influenced by the overall number of SBRT treatments or the number and timing of repeat SBRT courses. The risk of early death within 3 and 6 months was not increased in patients treated with multiple SBRT treatments, and no grade 4 or grade 5 toxicity was observed in these patients.
Conclusions: In appropriately selected patients, synchronous SBRT for multiple pulmonary oligometastases and repeat SBRT may have a comparable safety and efficacy profile compared to SBRT for one single oligometastasis.
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Oligometastases have first been defined as an intermediate stage between local and systemic disease, where radical local treatment of the primary cancer and all metastatic lesions might have a curative potential [1]. Oligometastatic disease is recognized in the 8th TNM system for non-small cell lung cancer (NSCLC) as stage M1b (a single extrathoracic metastasis) and radical local treatment is recommended, for example in the latest NCCN guidelines. As a consequence, a recent survey among >1000 radiation oncologists revealed that >60% of all survey participants were practicing stereotactic body radiotherapy (SBRT) for oligometastatic disease [2].

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

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

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

Materials and methods

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

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

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

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

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

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

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

Results

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

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