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Lung SBRT

Local tumor control probability modeling of primary and secondary lung tumors in stereotactic body radiotherapy

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ABSTRACT

Background and purpose: To evaluate whether local tumor control probability (TCP) in stereotactic body radiotherapy (SBRT) varies between lung metastases of different primary cancer sites and between primary non-small cell lung cancer (NSCLC) and secondary lung tumors.
Materials and methods: A retrospective multi-institutional ($n = 22$) database of 399 patients with stage I NSCLC and 397 patients with 525 lung metastases was analyzed. Irradiation doses were converted to biologically effective doses (BED). Logistic regression was used for local tumor control probability (TCP) modeling and the second-order bias corrected Akaike Information Criterion was used for model comparison.
Results: After median follow-up of 19 months and 16 months (n.s.), local tumor control was observed in 87.7% and 86.7% of the primary and secondary lung tumors (n.s.), respectively. A strong dose–response relationship was observed in the primary NSCLC and metastatic cohort but dose–response relationships were not significantly different: the TCD90 (dose to achieve 90% TCP; BED of maximum planning target volume dose) estimates were 176 Gy (151–223) and 160 Gy (123–237) (n.s.), respectively. The dose–response relationship was not influenced by the primary cancer site within the metastatic cohort.
Conclusions: Dose–response relationships for local tumor control in SBRT were not different between lung metastases of various primary cancer sites and between primary NSCLC and lung metastases.
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The lung is the first site of distant metastases in many cancers making resection of pulmonary metastases a frequent intervention. Already in 1965, Thomford et al. [1] postulated patient selection criteria for resection of lung metastases, namely: (1) controlled primary tumor; (2) R0 resection feasible; (3) no extra-pulmonary lesions (except resectable liver lesions) and (4) sufficient functional status. These criteria remained mostly unchanged until today and validated biomarkers for selection of truly oligo-metastatic patients are still not available. Nevertheless,

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long-term overall survival is reported in about 20% of the patients after resection of lung metastases [2], similar to the experiences in oligo-metastatic liver disease [3].

Based on the promising results of stereotactic body radiotherapy (SBRT) for early stage non-small cell lung cancer (NSCLC), the value of SBRT is currently explored in the treatment of pulmonary metastases. The practice of SBRT for pulmonary metastases has been mostly adapted from experiences of SBRT for primary stage I NSCLC [4–6]. Few phase I dose escalation studies specifically addressed lung metastases and they reported the safety of irradiation doses similar to primary NSCLC. However, there is a lack of evidence for which irradiation dose is actually needed or sufficient to achieve local tumor control in SBRT for pulmonary metastases. Additionally, it is unknown whether to adjust the irradiation dose according to the primary cancer. To address these issues, the working group "Stereotactic Radiotherapy" of the German Society of Radiation Oncology (DEGRO) established a retrospective multi-national and multi-institutional database of SBRT for pulmonary metastases and stage I NSCLC, in which >1500 SBRT treatments are recorded.

Materials and methods

This analysis is based on a retrospective multi-institutional and multi-national database of SBRT for primary stage I NSCLC and lung metastases. Patients were treated at German, Austrian and Swiss institutions, mostly academic centers, between 1998 and 2011. The NSCLC cohort consists of 582 NSCLC patients with clinical stage IA or IB treated at 13 institutions [7]. The lung metastasis cohort comprises of 715 patients treated for 964 lesions at 22 institutions. The analysis was approved by the Ethics committee of the University Hospital Heidelberg (S-280/2014).

In the current analysis we included only patients with follow-up periods $\geqslant$6 months and complete information on physical treatment planning parameters, resulting in 399 NSCLC patients with one lesion each and 397 metastatic patients with a total of 525 lesions.

The dose calculation algorithm varied between institutions and over time (unknown 13%; Pencil beam (PB) 36%; Collapsed Cone (CC) 31%; Anisotropic Analytical Algorithm (AAA) 15%; Monte Carlo (MC) 5%). The influence of the dose calculation algorithm on the isocenter dose is substantially smaller compared to the PTV encompassing dose and we therefore used the isocenter dose for modeling in this study [8]. The isocenter was located in the center of the gross tumor volume (GTV) and is approximately the maximum planning target volume (PTV) dose. Biologically effective doses (BEDs) were calculated using the linear-quadratic model with an α/β ratio of 10 Gy. Missing values of the maximum tumor diameter for 64 (12%) metastatic lesions were estimated with maximum-likelihood-values from a linear regression model using the number of fractions, prescribed dose, dose heterogeneity, type of primary tumor and institution as predictors.

Follow-up for evaluation of local control was performed using CT imaging in all institutions. Local tumor recurrence was defined as tumor progression or regrowth in the treated area observed in CT follow-up. In cases of uncertainties to differentiate between local tumor recurrence and pulmonary fibrosis, FDG-PET imaging was performed with local failure defined as increased FDG uptake Local progression was captured separately to distant progression in the database.

Statistical analysis

Tumor control probability (TCP) was defined as the probability that no clonogenic cell survives the treatment. For generic lesion i, a binomial response variable y_i was specified such that $y_i = 1$ if local control was achieved at last follow-up and $y_i = 0$ if not. TCP for lesion i was then modeled using Bayesian logistic regression in which the regression parameters are assumed to follow a weakly informative prior t-distribution with one degree of freedom and scale 2.5 [9]:

$$\mathrm{TCP}_i \equiv \Pr(y_i = 1) = logit^{-1}\left(\alpha + \sum_{k=1}^{K} \beta_k x_k\right)$$

K is the number of predictors. All input variables used for the regression were standardized to have mean 0 and standard deviation 0.5 in order to make the magnitude of the regression coefficients β_k comparable and more easily interpretable [10].

To find the dose–response model that best fits the metastases data we compared different logistic regression models using the second-order bias corrected Akaike Information Criterion (AICc) from which evidence ratios giving the relative probability of one model versus the other can be estimated [11]. To compare dose–response curves between primary NSCLC and metastatic tumors, both datasets were combined and the tumor entity (NSCLC or metastasis) and its interaction with $\mathrm{BED}_{\mathrm{ISO}}$ as predictors were included into the dose–response model. This methodology is equivalent to fitting two different regression lines with different intercepts and slopes to the NSCLC and metastatic data, respectively.

For a more thorough analysis including the influence of the primary tumor site on the dose–effect relationship in the metastatic group, a multilevel/hierarchical logistic regression model was used, in which the slope and intercept are allowed to vary by primary cancer site of the metastases [12]. This generated an average dose–response relationship for metastases as well as a dose–response relation separately for each primary tumor site. The multilevel model considers the uncertainty associated with small group sample sizes by pulling the regression coefficients more toward the average estimates that would be obtained by performing regression on all groups pooled together (see Appendix for more details).

Model fitting was done using R version 3.0.2 together with the arm package.

Results

Both patient cohorts are compared in Table 1. Median tumor diameter was 2.6 cm (0.8–4.8) and 1.9 cm (0.4–9.0) for patients with primary NSCLC and pulmonary metastases, respectively ($p < 0.0001$). Tumor diameter was missing for 47% (primary NSCLC) and 12% (metastases) of the lesions. Median follow-up was 19 months (6–139; primary NSCLC) and 16 months (6–125; metastases) ($p = 0.15$). A large range of irradiation doses and fractionations was used for primary NSCLC and pulmonary metastases. Most treatments were planned with inhomogeneous dose distributions: PTV encompassing doses were most frequently 80% (31% of all SBRT treatments), 65% (28%) and 60% (24%) of the maximum dose. BED doses at the isocenter were significantly lower in the metastases cohort compared to the primary NSCLC cohort, whereas PTV encompassing BED doses were not different between the cohorts. The distribution of SBRT doses is illustrated in Fig. 1.

Biopsy confirmation of the treated lung lesion was performed in 86% and 21% of patients in the NSCLC and pulmonary metastases cohort, respectively. Most frequent primaries of lung metastases were NSCLC (28%), colorectal cancer (CRC) (25%) and renal cell cancer (RCC) (11%). Information on chemotherapy prior to SBRT was available in 89% ($n = 352$) of the metastatic patients, of whom 49% ($n = 173$) had received chemotherapy. Information on the number of additional metastases was available in 76% ($n = 302$) of the patients. Of these, 52% ($n = 157$) had a solitary metastasis, 21% ($n = 63$) had one additional metastasis and 27% ($n = 82$)