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

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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% ($n = 82$)

Table 1
Patient and treatment characteristics in this study. Two-sided *p*-values have been estimated through Wilcoxon rank sum test and χ^2-test for continuous and discrete variables, respectively.

	Primary NSCLC ($N = 399$)		Pulmonary metastases ($N = 397$ with 525 lesions)		*p*-Value
	Number	Median (range)	Number	Median (range)	
Age [years]	399	72 (31–92)	397	67 (15–99)	<0.0001
Baseline Karnofsky Index	373	80 (40–100)	294	90 (40–100)	<0.0001
Gender					
Male	282		266		0.30
Female	117		131		
Maximum tumor diameter [cm]	210	2.60 (0.80–4.80)	461	1.90 (0.4–9.0)	<0.0001
Tumor location	374		452		0.45
Peripheral	316		372		
Central	58		80		
Local control	399		525		
Yes	350		455		0.71
No	49		70		
Number of fractions	399	3 (1–17)	525	3 (1–12)	0.005
Prescribed (PTV encompassing) dose [Gy]	399	12.5 (2.9–33.0)	525	12.5 (3.0–32.3)	0.06
Maximum (isocenter) dose [Gy]	399	20.8 (3.1–41.2)	525	20.0 (3.3–38.4)	0.45
BED at PTV periphery (BEDPTV) [Gy]	399	84.4 (38.3–180)	525	84.4 (22.5-180)	0.19
BED at isocenter (BEDISO) [Gy]	399	168.2 (48.0–262.5)	525	138.1 (24.3-288.3)	<0.0001
Dose inhomogeneity (PTV periphery dose/maximum dose) [%]	399	65 (60–100)	525	78 (55-105)	<0.0001

patients $\geqslant 2$ additional metastases. In the majority of patients (144/194 patients for which this information was available) the additional metastases were also located in the lung. Local control was achieved in 350 (87.7%) and 455 (86.7%) of the primary and secondary lung tumors, respectively.

In order to determine the model, which describes tumor control of the metastases data best, it was assumed that TCP is mainly influenced by the irradiation dose BED and the maximum tumor diameter *d*. Accordingly, four different models model_1–model_4 were evaluated (Table 2): (model_1) constant β_0 (constant effect independent of dose); (model_2) BED_{ISO}; (model_3) BED_{ISO} and *d*; (model_4) BED_{ISO}, *d* and an interaction $BED_{ISO} \times d$ between BED_{ISO} and *d*. There was a strong dose–response relationship when using BED_{ISO} as an input variable. Furthermore, the evidence for model_2 is slightly higher than for models model_3 and model_4, indicating that inclusion of tumor size into the model does not improve the fit. We repeated the model comparison using exclusively the 461 lesions with known tumor diameter and obtained results consistent with Table 2.

Datasets of the primary NSCLC and the metastatic patients were combined into one and tumor entity (primary NSCLC versus metastases), BED_{ISO} and an interaction term were included in the Bayesian logistic regression model. The regression coefficients for tumor entity and $BED_{ISO} \times$ tumor entity interaction were -0.14 ± 0.22 (SE) and 0.12 ± 0.45, respectively, indicating no significant differences of the dose–response between primary NSCLC and lung metastases.

Additionally, two separate models were fitted to the primary NSCLC and metastases data (Table 3 and Fig. 2). The BED_{ISO} TCD90 (the dose to achieve 90% TCP) median point estimates and 95% credible intervals were 160 Gy (123–237) for the metastatic cohort and 176 Gy (151–223 for the primary NSCLC cohort, respectively. Thus, primary NSCLC may require slightly higher irradiation doses compared to metastases, although the estimates overlap within their standard errors and differences were not statistically significant. For the metastases of NSCLC origin the estimate for BED_{ISO} TCD90 was 167 Gy (100–249), again not significantly different to primary NSCLC.

In the multilevel model, dose–response relationships were fitted separately for each of the eight most frequent primary cancer sites using BED_{ISO} as both the within-group and between-group predictor [12]. This simultaneously generated a dose–response relationship for an average metastasis as well as the deviation from this relation for each primary cancer site (Fig. 3; Table 3). Although all TCP curves were very similar above a $BED_{ISO} \gtrsim 150$ Gy, results do not exclude variations by primary cancer site in the lower dose range: metastases of breast cancer, RCC, esophagus carcinoma and sarcoma appeared to follow a shallower dose–response relationship than NSCLC or other metastases.

Finally, Bayesian logistic regression was used to compare dose–response curves of the three metastatic subgroups with the largest sample sizes (NSCLC $n = 148$; CRC $n = 133$; RCC $n = 56$). No statistically significant differences between the dose–response curves were detected; there was only a trend for RCC metastases having a more shallow dose–response curve compared to NSCLC metastases ($p = 0.10$).

Discussion

The current study has two main findings. (1) There were no significant differences in tumor control probability models between primary NSCLC and secondary NSCLC, between primary NSCLC and secondary lung tumors in general and between pulmonary metastases of various solid cancers. (2) TCD90 values were below maximum tolerated doses, which may form the rational for dose de-escalation trials especially in metastatic stage of disease.

From a radiobiological perspective, this large multi-institutional study based on >1500 SBRT treatments offered the unique opportunity to perform tumor control probability modeling of cancers independently from their original host (micro-) environment and mostly independently from tumor volume. Despite some variability in the TCP curves was observed in the lower-dose region, TCD90 values for primary NSCLC, secondary NSCLC and pulmonary metastases in general differed by <10% and differences did not reach statistical significance. Consequently, our analysis does not support the hypothesis that SBRT irradiation doses need to be adapted to primary tumor site.

A number of mostly small, retrospective and single-institution studies about SBRT in the metastatic setting has been published. The majority of authors, however, report on heterogeneous patient collectives regarding primary tumor, number and location of metastases e.g. liver, bone, adrenal and other metastases. Several studies described a dose–response relationship for local tumor

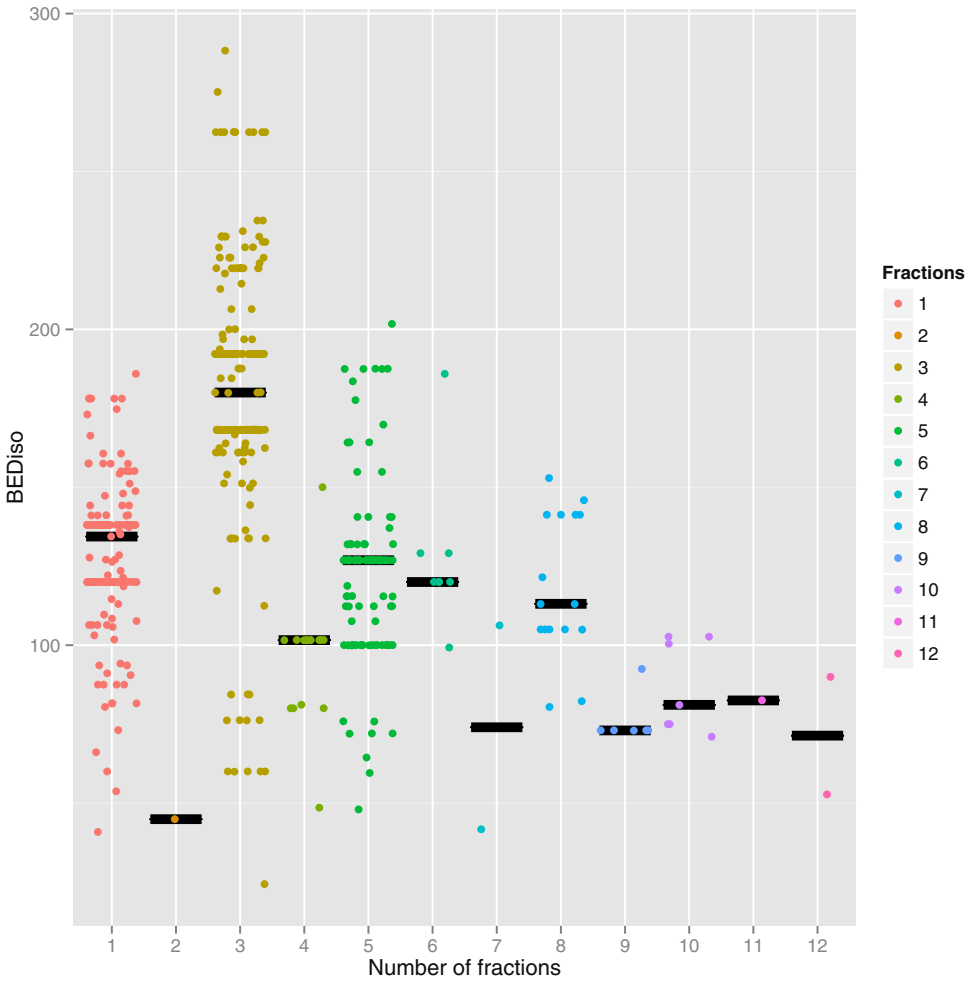

Fig. 1. Distribution of number of SBRT fractions and BED doses.

Table 2
Each cell gives the ratio of the likelihood of the model on top of the column to the likelihood of the model on the left of the corresponding row, also termed the evidence ratio. Evidence ratios can be interpreted such that values above 3 start to indicate positive strength of evidence in favor of one model over the other: (−) Insignificant differences (ratio <3); (+) Strong evidence in favor of one model compared to the other (ratio >20); (++) Very strong evidence in favor of one model compared to the other (ratio>100).

	M_1	$M_2(BED_{ISO})$	$M_3(BED_{ISO}, d)$	$M_4(BED_{ISO}, d)$
M_1	1	$514^{(++)}$	$273^{(++)}$	$161^{(++)}$
$M_2(BED_{ISO})$	1.9×10^{-3}	1	0.53	0.31
$M_3(BED_{ISO}, d)$	3.7×10^{-3}	$1.9^{(-)}$	1	0.59
$M_4(BED_{ISO}, d)$	6.2×10^{-3}	3.2	$1.7^{(-)}$	1

control [13–16]. However, patient numbers and statistical methods were insufficient for comprehensive TCP modeling. Most importantly, all existing studies were too small for a modeling of primary cancer specific dose–response relationships. While some studies reported decreased local tumor control for CRC metastases [17–20], this was not confirmed by others [13,21,22]. The current analysis includes the largest number of CRC lung metastases treated with SBRT ($n = 133$) but did not find a difference in the dose–response relationship as compared to lung metastases of other primaries.

The finding of very similar TCP dose–response relationships between lung metastases originating from various primary cancer sites and between primary and metastatic cancer is surprising considering the genetic variability, which is expected in our patient cohort. This genetic variability, however, does not appear to influence radio-sensitivity in the context of hypo-fractionated SBRT. It is important to note that we only had information about the classical histo-pathological diagnosis. More in-depth data about molecular tumor characteristics are lacking. This may be important based on a recent study by De La Rosa et al., where EGFR mutation and ALK translocation were independent prognostic factors for local control after radiosurgery for brain metastases in NSCLC patients [23].

Until today, the practice of SBRT for lung metastases has frequently been adapted from experiences of SBRT for primary stage I NSCLC. There, the maximum tolerated dose is based on a phase I dose escalation study, which established an accepted international standard: three fractions of 18 Gy as PTV encompassing dose with PTV maximum doses of 20–30 Gy [24]. Three dose escalation studies have been performed in the oligo-metastatic setting [25–27] and maximum tolerated SBRT doses appear similar compared to primary NSCLC. However, it is questionable whether the maximum tolerated dose is truly the best practice in the metastatic setting. The average number of metastases was 1–2 in all three phase I trials. However, many oligo-metastatic patients present with >1–2 pulmonary lesions and safety of SBRT in this setting remains unknown. Additionally, many patients will develop distant progression and the lung is the most frequent organ for recurrence [28]: if still oligo-metastatic, safety of another SBRT course might be compromised if the maximum tolerated dose

Table 3
Sample sizes and regression coefficients corresponding to the multilevel model fitted to the pulmonary metastases cohort as well as for the primary NSCLC cohort. Note that the regression coefficients have been estimated with BED_{ISO} standardized to have mean 0 and standard deviation 0.5.

Sample	Primary cancer site	Sample size	Number with local control	BED_{ISO} [Gy]	β_0	β_1 [Gy^{-1}]	BED_{ISO} TCD90 [Gy]
MET	Breast	33	32	138.1 (41.7–219.4)	2.15 ± 0.14	0.52 ± 0.46	151
	NSCLC	148	123	137.8 (60.0–288.3)	1.84 ± 0.09	1.51 ± 0.29	167
	CRC	133	115	141.1 (44.9–262.5)	1.97 ± 0.11	1.09 ± 0.33	162
	RCC	56	51	120.7 (40.8–262.5)	2.14 ± 0.12	0.57 ± 0.39	151
	Sarcoma	20	14	144.3 (24.3–206.4)	1.92 ± 0.13	1.24 ± 0.42	165
	Esophagus	15	14	138.1 (76.2–219.4)	2.13 ± 0.15	0.59 ± 0.49	151
	Melanoma	15	13	154.9 (112.3–262.5)	2.02 ± 0.16	0.95 ± 0.51	161
	Others	105	93	138.1 (52.7–262.5)	2.07 ± 0.11	0.78 ± 0.36	159
	Average	525	455	138.1 (24.3–288.3)	2.04 ± 0.17	0.89 ± 0.39	160
NSCLC		399	350	168.2 (48.0–262.5)	2.11 ± 0.17	1.28 ± 0.33	176

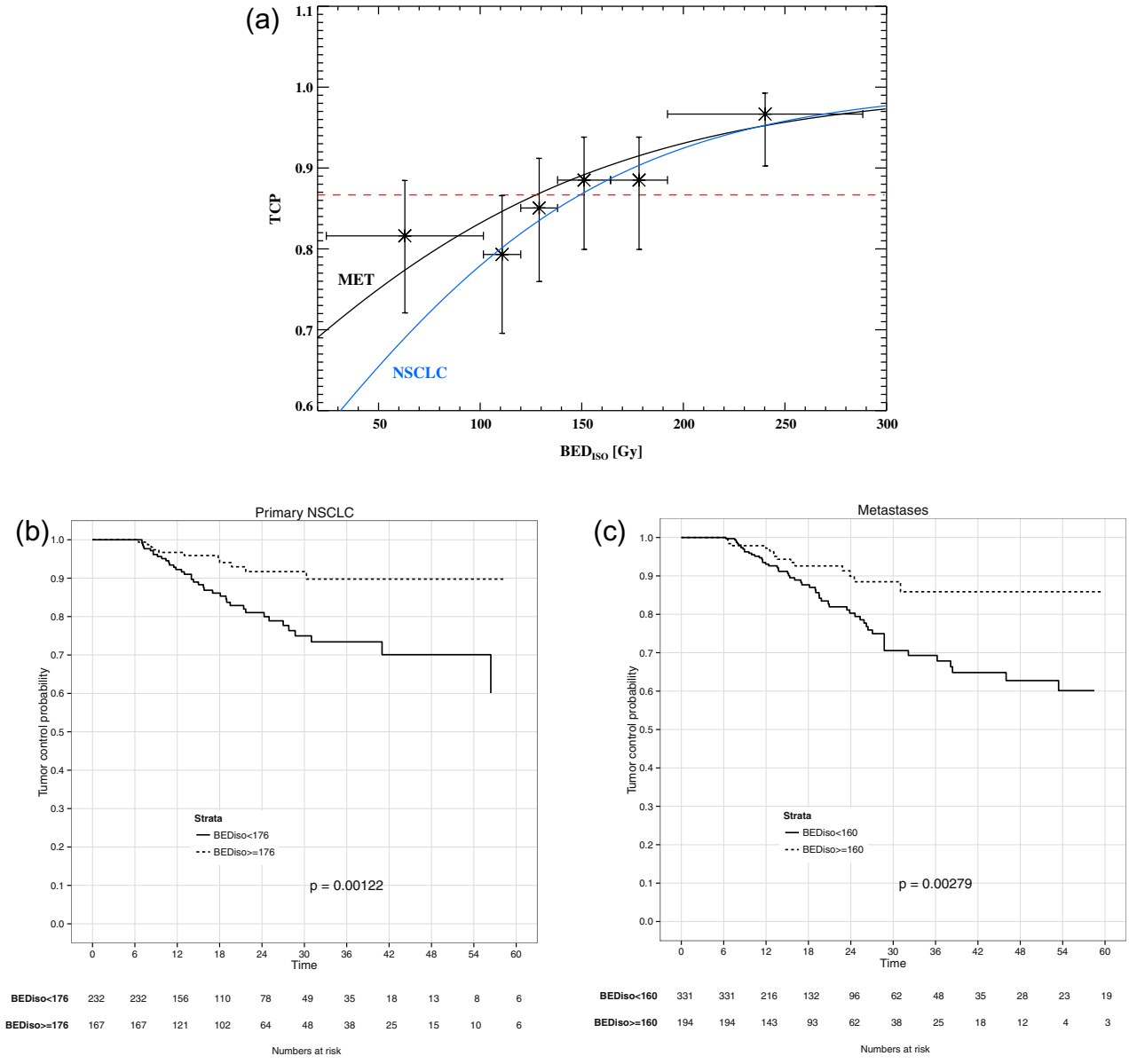

Fig. 2. (a) Dose–response relationship of the metastatic (black) and primary NSCLC (blue) cohort. The crosses show the proportion of metastatic lesions for which local control was achieved in six equally sized bins. The bin width is indicated by the horizontal bars, while the vertical bars show the adjusted 95% Wald confidence interval. (b) Kaplan–Meier curve showing local tumor control for primary NSCLC with irradiation doses <TCD90 and ⩾TCD90. (c) Kaplan–Meier curve showing local tumor control for lung metastases with irradiation doses <TCD90 and ⩾TCD90. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

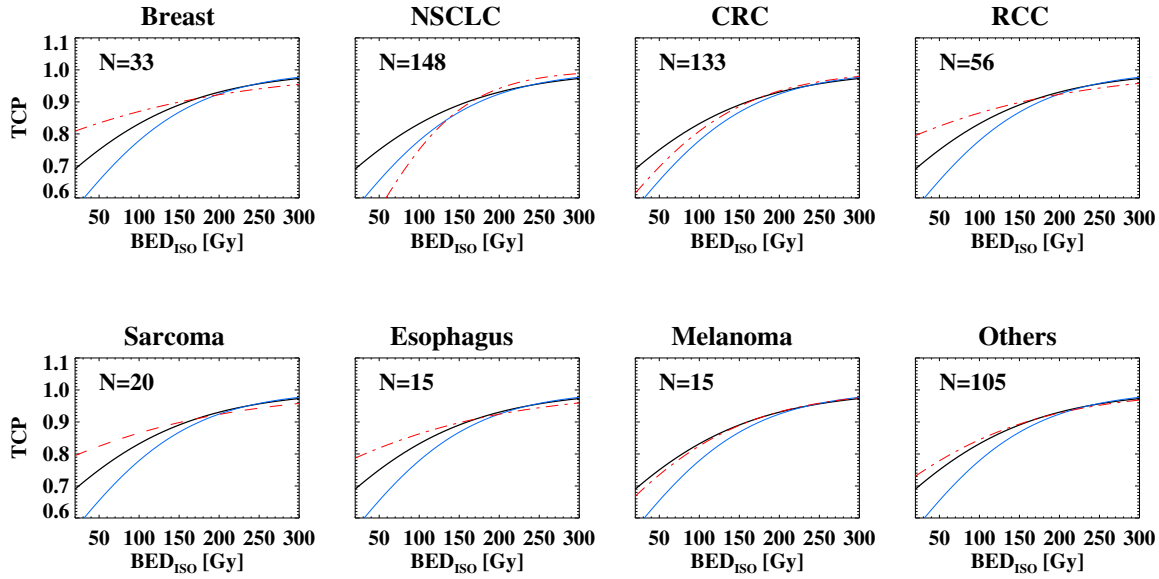

Fig. 3. Each panel shows the dose–response relationship with the best-fit regression line separately for the most frequent primary cancer sites of the metastatic cohort (dash-dotted red line) as well as the dose–response of an average metastasis (solid black), both obtained from the multilevel model with varying slope and intercept. The best-fit regression line for the primary NSCLC sample is plotted for comparison (solid blue). CRC: Colorectal cancer; RCC: Renal cell carcinoma. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

has already been delivered because there is limited recovery of lung tissue from previous irradiation. Finally, maximization of local tumor control beyond 90% is questionable in a clinical situation with high competing risk of distant progression.

In our metastatic cohort, the plateau of the dose–response curve with 90% TCP was reached at 160 Gy BED (PTV maximum dose). This dose was delivered in a median of 3 fractions. For a three-fraction protocol, our dose recommendation is equivalent to 3×18.7 Gy as maximum PTV dose. Using the RTOG planning constraints, this results in PTV encompassing doses of 11.2–16.8 Gy (60% – 90% of maximum dose). Consequently, 90% TCP is achieved at irradiation doses 7–38% and 10–53% below the current standard (3×18 Gy PTV encompassing) based on physical and biologically effective doses, respectively. Our study may therefore form the basis for dose de-escalation trials in the future, especially in the metastatic setting because of the high competing risk of distant progression.

Limitations of our study include the neglect of factors besides dose and tumor size that might influence local control, and the assumption of an α/β ratio of 10 Gy for all metastases independent of their origin when computing BEDs. The applicability of the LQ model is discussed controversially for calculation of BED in high dose per fraction SBRT. However, we have previously demonstrated that local tumor control in fractionated SBRT for primary NSCLC is well modeled using the classical LQ formula [29]. Furthermore, sample sizes of the metastases subgroups might have been too small to detect small differences in dose–response relationships. The retrospective nature is an obvious limitation but it simultaneously generated a cohort with large variability of irradiation doses, which is a pre-requisite for dose–response modeling as performed in our study. Finally, patients treated for secondary lung tumors are at increased risk for systemic progression compared to patients treated for stage I NSCLC. Local and systemic progression was captured as separate variables in our database. In the primary NSCLC and metastatic patient cohorts, follow-up for evaluation of local control was further assessed after detection of systemic progression in 60% and 55% of the cases, respectively, indicating no systematic difference in the follow-up practice.

Concluding, in this largest study of SBRT for primary and secondary lung tumors, a clear dose–response relationship for local tumor control was observed. No significant differences in TCP dose–response relationships according to primary and secondary lung cancer and according to different primary cancer sites in the metastatic cohort were observed. We therefore suggest not adapting the irradiation dose to the primary cancer site in SBRT for oligometastatic lung disease. TCD90 for both primary and secondary lung tumors were lower than currently used maximum tolerated doses, which could form the rational for dose de-escalation trials in the future, especially for secondary lung tumors with a high competing risk of systemic progression.

Funding

None.

Conflicts of interest

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

Appendix A

The multilevel logistic regression model may be written as,

$$\mathrm{TCP}_i \equiv \Pr(y_i = 1) = \mathit{logit}^{-1}(\alpha_{j[i]} + \beta_{j[i]}\mathrm{BED}_{\mathrm{ISO},i})$$

where $j = 1, \ldots, 8$ is the group index denoting the primary metastasis site, $i = 1, \ldots, n$ the index for the treated metastasis, and $j[i]$ codes the group membership. For example, it is $j[20] = 3$, meaning that metastasis number 20 stems from primary site "3" (colorectal cancer). Both the intercept α and the slope β are allowed to vary across the different groups and are estimated for each group separately using $\mathrm{BED}_{\mathrm{ISO}}$ as the individual-level predictor, but not by using least squares as would be the case if a separate regression model would be fitted for each group individually. Instead, the α_j's and β_j's are assigned a probability distribution

$$\begin{pmatrix} \alpha_j \\ \beta_j \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_\alpha \\ \mu_\beta \end{pmatrix}, \begin{pmatrix} \sigma_\alpha^2 & \rho\sigma_\alpha\sigma_\beta \\ \rho\sigma_\alpha\sigma_\beta & \sigma_\beta^2 \end{pmatrix} \right), \qquad \textit{for} \quad j = 1, \ldots, 8$$

with the means, variances and between-group correlation parameter ρ estimated from the data. In this way, the estimates for α_j and β_j are pulled toward their mean estimates, but to different extents, basically depending on how many observations there are in each group [12].

Compared to using different groups directly as predictors in the logistic regression model (and thus performing regression in each group separately), the multilevel model thus has the advantage that it automatically takes care of the uncertainty associated with small group sample sizes by pulling the regression coefficients more toward the estimates that would be obtained by performing regression on all groups pooled together. For groups with large sample size, on the other hand, the regression coefficients are close to those that would be obtained when regression would be performed on these groups separately.

There is basically no lower limit for the number of observations in each group required to fit a multilevel model – even two data points can provide partial information that allows estimation of the coefficients and variance parameters of the individual- and group-level regressions [12].

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