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## Radiobiological parameters of liver and lung metastases derived from tumor control data of 3719 metastases

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## ABSTRACT

**Background and purpose:** The radiobiological parameters for liver and lung metastases treated with stereotactic body radiation therapy (SBRT) are poorly defined. This project aimed at estimating these parameters from published tumor control probability (TCP) data, and separately for metastases with colorectal cancer (CRC) and non-CRC histology.

**Materials and methods:** A total of 62 studies with 89 different treatment prescriptions for a total of 3719 metastases were analyzed in a Bayesian framework using four different radiobiological models: The LQ, mLQ, LQ-L and the regrowth model which accounts for tumor regrowth after SBRT.

**Results:** Depending on the particular model,  $\alpha/\beta$  ratios in the range 13–23 Gy for pulmonary metastases and 16–28 Gy for hepatic metastases were estimated. For CRC metastases the estimated  $\alpha/\beta$  ratio was  $43.1 \pm 4.7$  Gy compared to  $21.6 \pm 7.8$  Gy for non-CRC metastases. Typical isocenter dose prescriptions of  $3 \times 12$  Gy,  $3 \times 14.5$  Gy and  $3 \times 17$  Gy applied within 5 days were predicted sufficient to control 90% of lung, liver and CRC metastases after 1 yr, respectively.

**Conclusions:**  $\alpha/\beta$  ratios for liver and lung metastases are higher than the usually assumed 10 Gy. Differences between CRC and non-CRC histology were found. Future studies confirming these findings in individual patient data are needed.

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In 1995, Hellman and Weichselbaum [1] proposed the idea of oligometastases as an intermediate state in the natural development of many cancers which manifests as the presence of one up to a few metastases confined to one or only a few organs. The implication of this theory, that local ablative treatments could lead to a halt or delay of the natural course of the disease, has meanwhile gained substantial support [2]. Liver and lung are two major sites of oligometastatic disease. While surgery is a standard practice of treatment, stereotactic body radiotherapy (SBRT) has emerged as a second, non-invasive treatment option [3]. So far, however, dose prescriptions have mostly been based on the schedules used for early stage non-small cell lung cancer (NSCLC) in case of pulmonary metastases or on maximally tolerable doses for organs at risk in case of liver irradiation. This is problematic at least for two reasons: First, the possibility exists that pulmonary and hepatic metastases respond differently to ionizing radiation than NSCLC or hepatocellular carcinoma, respectively, particularly in light of the histological variety among metastases. Second, the radiobiological principles of SBRT are in general still debated in

the first place [4,5]. While prospective studies investigating optimal dosing schedules are lacking for SBRT of extra-cranial metastases, radiobiological modeling can be a useful tool for comparing different dose prescriptions and finding those that predict a favorable outcome.

As with SBRT of NSCLC, the validity of the linear-quadratic (LQ) model can be questioned on theoretical grounds [5]. The reason is that *in vitro*, cell survival curves deviate from the linear-quadratic behavior at large doses similar to those used in SBRT, becoming more linear again and thus showing less cell killing than predicted by a continuously bending survival curve [6]. However, using a large database of SBRT treatments for early stage NSCLC, we have shown that the LQ model fits the tumor control probability (TCP) data at least as good as one of its linear extensions, the so-called linear-quadratic-linear model [7]. Meanwhile, three other studies have independently confirmed this result, implying that in clinical data the LQ model works at least as well as many of its proposed extensions for predicting TCP [8–10]. It has been argued that the discrepancy between the laboratory and clinical data could be solved if the  $\alpha/\beta$  ratio for SBRT would be larger than the usually assumed 10 Gy, since only beyond this ratio the quadratic ( $\beta$ ) component dominates, from which cell survival curves have been shown to deviate [4,5]. Tomé pointed out the possibility that for

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SBRT, the  $\alpha$  component representing lethal DNA damage would gain importance over the sub-lethal damage  $\beta$  component as doses are increased, leading to a continuously increasing  $\alpha/\beta$  ratio with dose [11]. Indeed, recent evidence supports  $\alpha/\beta$  ratios of NSCLC treated with SBRT in the range  $\geq 20$  Gy [10,12,13]. Nevertheless, studies investigating the  $\alpha/\beta$  ratio of metastases treated with SBRT are lacking.

The main aim of this project was to explore the  $\alpha/\beta$  ratio of pulmonary and hepatic metastases treated with SBRT using published TCP data. This study was motivated by a recent paper from Liu et al. [10] in which they fitted a total of six radiobiological models to pooled TCP data of NSCLC treated with SBRT, showing that  $\alpha/\beta \approx 20$  Gy. Since there have been hints in the literature that metastases originating from colorectal cancer (CRC) might be particularly radioresistant, a second goal of this analysis was to determine radiobiological parameters for CRC and non-CRC metastases separately.

## Materials and methods

### Data collection

Using the search terms “stereotactic radiotherapy lung metastases NOT brain” and “stereotactic radiotherapy liver metastases NOT brain”, PubMed was searched for original studies reporting outcomes after SBRT for pulmonary or liver metastases that were published between January 2000 and October 2016. Also, the reference lists of relevant papers and review articles were searched for additional studies on this topic. Only studies fulfilling all of the following criteria were selected for data extraction:

- (i) SBRT treatment of pulmonary or hepatic metastases with at least 4 Gy per fraction.
- (ii) At least one estimate of the actuarial TCP at 1, 2 or 3 years after completion of SBRT reported or extractable from a data table or Kaplan–Meier graph (using the software Digitizelt 2.3.2).
- (iii) TCP estimates being based on pulmonary and hepatic lesions only, with no more than 30% primary tumors contributing to any extracted TCP estimate.
- (iv) TCP estimates being representative of a particular fractionation scheme, with either a maximum contamination of 30% from lesions treated with a different number of fractions or a clear indication in the paper that TCP was not influenced by different fractionation schemes.

Whenever possible, TCP estimates were extracted separately for lung and liver metastases, for metastasis of CRC and non-CRC origin, and for different fractionation schemes. For any particular fractionation associated with a TCP estimate, mean or median doses and dose heterogeneity values were extracted to obtain a typical dose prescription. Furthermore, the number of treated lesions, median patient age, metastases proportion, median lesion diameter/volume and duration of the complete SBRT treatment in days were extracted from each study.

A total of 62 individual studies fulfilling the inclusion criteria were identified (Supplementary Table 1). Of these, 31 studies contained information specific to lung tumors [14–44], 23 contained information specific to liver tumors [45–67], 4 studies reported outcomes specific for both sites separately [68–71], and 4 studies reported outcomes pooled from both sites [72–75]. The studies of McCammon et al. [73] and Van den Begin et al. [75] thereby contained 67.1% and 60.9% lung tumors, respectively, and were assigned to the lung studies, while the studies of Hoyer et al. [72] and Fumagalli et al. [74] contained 70% and 81.3% liver tumors and were assigned to the liver studies. The total number of treated

metastases was 3719. Details are provided in Table 1. A total of 89 fractionation schemes were extracted from the studies. Because the influence of different dose calculation algorithms on the isocenter dose is substantially smaller compared to the PTV encompassing dose [76], all dose prescriptions were converted to doses at the isocenter by dividing the single fraction doses by the prescribed heterogeneity. For 11 dose prescriptions (12.4%) for which no heterogeneity was given in the paper, a prescription to 80% of the isocenter dose was assumed. The total prescribed dose, isocenter dose, number of fractions, number of treated metastases and actuarial local control rates were not significantly different between both organ sites (Table 1). All missing treatment duration variables were imputed with the median treatment duration that was typical for the given number of fractions.

### Model fitting technique

I used a Bayesian approach to fit different TCP models to the clinical TCP data, which naturally accounts for uncertainties associated with parameter heterogeneity. Let  $\Theta$  denote the set of model parameters. According to Bayes' theorem, the joint posterior distribution of the model parameters is then obtained from their joint prior distribution and the data likelihood:

$$P(\Theta|D, M) = P(D|\Theta, M)P(\Theta|M)/P(D|M) \quad (1)$$

Here  $P(\Theta|M)$  is the joint prior distribution of the parameters under the specific model,  $P(D|\Theta, M)$  is the likelihood of parameter values  $\Theta$  in the model  $M$  for data  $D$ , and  $P(D|M)$  denotes the “marginal likelihood” or “evidence” for model  $M$ . The marginal likelihood is given as

$$P(D|M) = \int d\Theta P(D|\Theta, M)P(\Theta|M) \quad (2)$$

and for the models considered here cannot be computed analytically. I therefore used Markov chain Monte Carlo (MCMC) approximation to estimate the posterior distribution of the model parameters. Briefly, the Markov chain collects samples from the parameter space such that their distribution approaches  $P(\Theta|D, M)$ , the actual joint posterior parameter distribution. The collected samples can thus be used to make inferences about statistical properties of  $P(\Theta|D, M)$  of which I chose the sample means and standard deviations as point estimates for the parameter values and their uncertainties.

The likelihood function is given as

$$P(D|\Theta, M) = \prod_{i=1}^N \text{TCP}_i^{\text{data}} \quad (3)$$

where  $N$  is the number of data points. A normal likelihood was assumed for the individual study observations restricted to the range between 0 and 1:

$$\text{TCP}_i^{\text{data}} \sim N(\text{TCP}_i^{\text{model}}(\Theta), s_i^2)I(0, 1) \quad (4)$$

where  $\text{TCP}_i^{\text{model}}(\Theta)$  is the TCP for a given model expressed as a function of the model parameters  $\Theta$  and the standard error  $s_i$  is given by

$$s_i = \text{TCP}_i^{\text{data}} \sqrt{\frac{1 - \text{TCP}_i^{\text{data}}}{M_i \cdot \text{TCP}_i^{\text{data}}}}$$

with  $M_i$  the number of treated lesions in study  $i$ . This is similar to the approach of Liu et al. [10] who used the least chi-squared ( $\chi^2$ ) method which assumes that the data measurement errors are Gaussian [77]. In practice,  $\text{TCP}_i^{\text{model}}$  depends on the model parameters both directly and indirectly through the biologically effective dose (BED). Since this is an exploratory analysis, I applied uniform priors for the model parameters restricted to a realistic range. More details are provided in the Appendix A.

**Table 1**  
Treatment characteristics of the selected studies.

Parameter	Lung metastases (N = 52)		Liver metastases (N = 37)		p-Value
	Number	Median (range)	Number	Median (range)	
Number of treated lesions	52	29 (8–125)	37	30 (10–150)	0.5684
Median age [years]	39	66 (52–73)	33	64 (52–79)	0.0180
Median maximum lesion diameter [mm]	16	19 (14–25)	14	26 (14–35)	0.0042
Percentage CRC [%]	46	21.3 (0–100)	37	50.0 (0–100)	0.0004
Prescribed dose [Gy]	52	46.5 (20–60)	37	45 (22–75)	0.4085
Dose per fraction [Gy]	52	12.5 (4.5–30)	37	13.5 (5–37.5)	0.7927
Number of fractions	52	3 (1–10)	37	3 (1–10)	0.8725
Dose heterogeneity [%]	44	86 (60–100)	34	80 (60–100)	0.9437
Isocenter dose per fraction [Gy]	44	17.4 (4.5–37.5)	34	18.8 (5–50)	0.1987
Overall treatment duration [days]	40	4 (1–15)	27	5.5 (1–14)	0.0550
1 year TCP [%]	50	93 (40.5–100)	36	92.9 (53–100)	0.8978
2 year TCP [%]	43	84 (12–100)	34	77 (38–100)	0.3493
3 year TCP [%]	30	77.5 (0–100)	12	65.5 (28–92)	0.5038

Two-sided p-values were calculated by the Wilcoxon rank sum test.

**Radiobiological models**

The models used for fitting the TCP data can broadly be divided into two classes. The first class does not depend on the follow-up time and thus can be used to fit the TCP data at specific time points only. The second class contains a dependence on the follow-up time and thus can be used to fit the 1-, 2-, and 3-year TCP data simultaneously. Models of the first class considered in this analysis are:

1. The LQ model:

$$BED^{LQ} = nd \left( 1 + \frac{d}{\alpha/\beta} \right) \tag{5}$$

with  $\alpha$  and  $\beta$  the intrinsic radiosensitivity parameters of the tumor cells, and  $n$  and  $d$  are the number of fractions and fraction dose, respectively.

2. The mLQ model [78]:

$$BED^{mLQ} = nd \left( 1 + \frac{d}{\frac{\alpha}{\beta} \left( 1 + \frac{\beta}{\gamma} d \right)} \right) \tag{6}$$

where  $\gamma$  is a parameter to account for high fractionation dose effects.

3. The LQ-L model [7,79]:

$$BED^{LQ-L} = \begin{cases} nd \left( 1 + \frac{d}{\alpha/\beta} \right), & d < d_T \\ nd_T \left( 1 + \frac{d_T}{\alpha/\beta} \right) + n \left( 1 + \frac{2d_T}{\alpha/\beta} \right) \cdot (d - d_T), & d \geq d_T \end{cases} \tag{7}$$

where  $d_T$  is the dose beyond which the surviving fraction of radiated cells declines exponentially, leading to a transition of the quadratic bending survival curve toward linear behavior in a logarithmic plot. For these three models the TCP is given as

$$TCP = \exp(-K_0 * e^{-\alpha * BED}) \tag{8}$$

where  $K_0$  is the number of clonogenic cells at the beginning of radiotherapy. The three LQ-like models were compared using the deviance information criterion (DIC), a Bayesian analog to the Akaike information criterion [80].

As a model of the second class I considered

4. The Regrowth model [10]:

$$BED^{Regrowth} = nd \left( 1 + \frac{d}{\alpha/\beta} \right) - \frac{\ln 2}{T_P} \frac{\Gamma}{\alpha} \tag{9}$$

$$TCP = 1 - \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-\frac{x^2}{2}} dx \tag{10}$$

with

$$t = \frac{e^{-\left[ \alpha * BED - \left( \frac{\ln 2}{T_P} \right) \delta \right]} - K_{cr}/K_0}{\sigma_K/K_0} \tag{11}$$

Here,  $\Gamma$  denotes the treatment duration,  $T_P$  the effective potential tumor doubling time and  $\tau$  the follow-up time. The exponent  $\delta$  characterizes the speed of tumor cell regrowth after treatment: as  $\delta \rightarrow 1$ ,  $T_P$  approaches the conventional doubling time.  $K_{cr}$  is the critical number of tumor clonogens above which the patient will experience local failure, and  $\sigma_K$  is the Gaussian width for the distribution of  $K_{cr}$ . The regrowth model thus has the six independent parameters:  $\Theta^{Regrowth} = \left\{ \alpha, \frac{\alpha}{\beta}, T_P, \delta, \frac{K_{cr}}{K_0}, \frac{\sigma_K}{K_0} \right\}$ .

**Data analysis**

The radiobiological models described above were fitted to the lung and liver metastases separately in order to determine eventual differences in radiation response according to tumor site. The same approach for analyzing differences between CRC and non-CRC metastases was hampered by the fact that most studies did not report outcomes separately for both histologies, but at best the fraction of CRC metastases. I first tried to take this into account by repeatedly building random samples of both CRC and non-CRC metastases, whereby a data point was allocated to the CRC sample if its fraction of CRC metastases was greater than or equal to a uniformly distributed random number between 0 and 1; otherwise it was assigned to the non-CRC data sample. The LQ and the regrowth model were then fitted to each of a large number ( $\cong 100$ ) of such random samples, each time storing the posterior MCMC samples of the model parameters and finally pooling them together for parameter estimation. However, I found that this approach led to large uncertainties and poor fits for both models, so I decided to combine lung and liver metastases and build pure samples of data points for which the fraction of CRC metastasis was exactly 0 ( $N=32$ ) or 1 ( $N=48$ ). These data were then fitted with the regrowth model in order to utilize the full information of sequential TCPs.

**Results**

The posterior parameter estimates for the LQ model are given in **Supplementary Table 2**. All  $\alpha/\beta$  estimates were significantly larger than 10 Gy. The fits with the mLQ model resulted in essentially the same estimates for  $\alpha$ ,  $\alpha/\beta$  and  $K_0$  and yielded large  $\gamma$  values

(>2400 Gy<sup>-1</sup>), indicating that the second-order correction term  $\beta/\gamma$  is negligible. Similarly, there was no indication for a linear extension of the LQ-model as the LQ-L model yielded essentially the same goodness of fit judged by its DIC and basically was reduced to the LQ model due to very large threshold dose  $d_T$  estimates exceeding the largest fractional isocenter doses applied (Supplementary Table 2). Panels A–C of Fig. 1 show the fits of the LQ model to the clinical lung data, and panels A–B of Fig. 2 show the fits of the LQ model to the clinical liver data. Due to a very small number of data points for 3 yr TCP of hepatic metastases ( $N = 12$ ), no fit to these data with the LQ-like models was attempted. For lung and liver metastases, the LQ model predicts that effective doses of  $BED_{13.5Gy} = 68$  Gy and  $BED_{28.0Gy} = 65$  Gy would be sufficient to control 90% of the tumors after 1 year.

The result of fitting the regrowth model to the lung and liver data is tabulated in the two left columns of Supplementary Table 3 and plotted in Figs. 1D and 2C. Contrary to the LQ-like models, the regrowth model did not converge toward TCP = 1 at large BED values, but reached an asymptotic plateau between 0.95 and 1 for BED larger than about 100 Gy. The regrowth model predicts that effective doses of  $BED_{15.0Gy} = 65$  Gy and  $BED_{16.3Gy} = 82$  Gy would be needed to control 90% of the lung and liver metastases after 1 year.

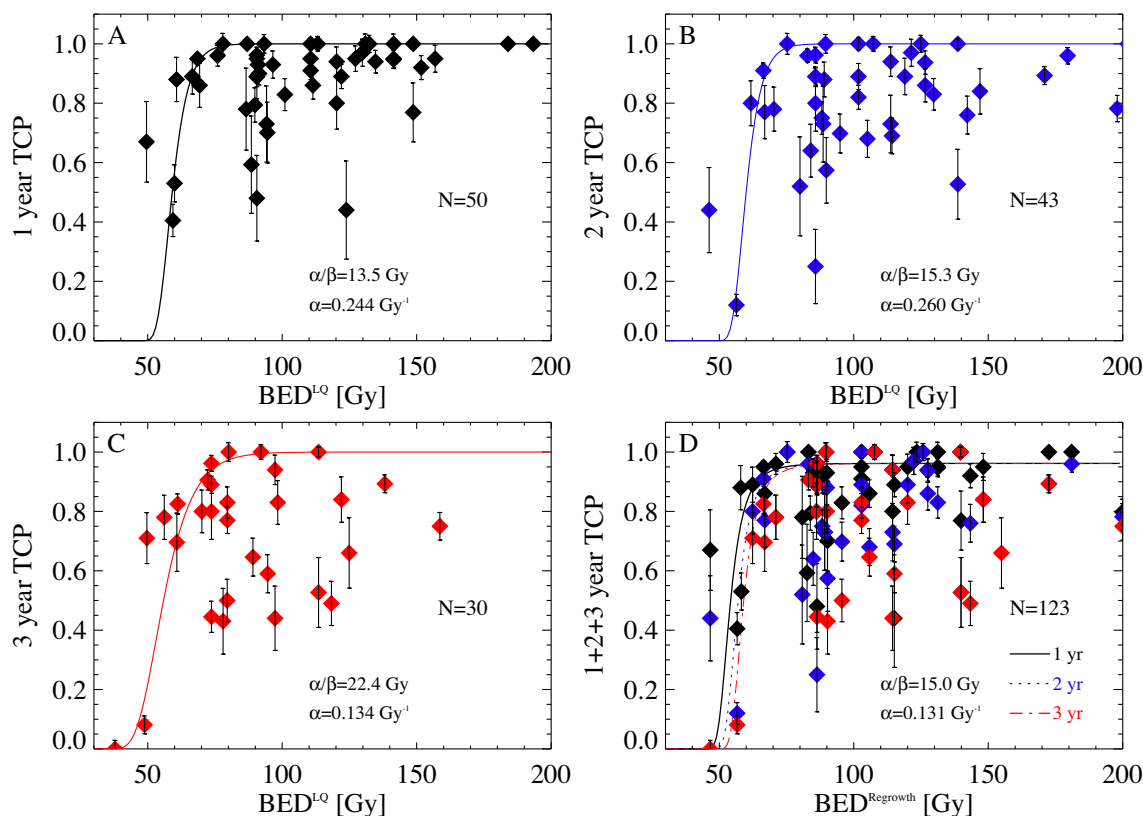
Finally, Fig. 3 shows the fit of the regrowth model to the CRC and non-CRC metastases data for lung and liver metastases combined. The posterior parameter estimates are provided in the two right columns of Supplementary Table 3. The dose–response relationship of CRC metastases appears much shallower than that derived for non-CRC metastases or that shown in Figs. 1 and 2. A large  $\alpha/\beta$  ratio of 43.1 Gy was estimated for CRC metastases, albeit with large uncertainty (95% highest posterior density interval = [33.3, 49.7]). With 80% probability, however, the  $\alpha/\beta$  ratio of CRC

metastases was estimated higher than that of other histologies (the 80% highest posterior density intervals did not overlap). The regrowth model predicts that a  $BED_{43Gy}$  of 71 Gy would have to be delivered to the isocenter in order to control 90% of CRC metastases after 1 yr, which translates into  $3 \times 17$  Gy given over a course of 5 days. For non-CRC metastases, the corresponding result is  $BED_{22Gy} = 59$  Gy, translating into  $3 \times 12.5$  Gy to the isocenter.

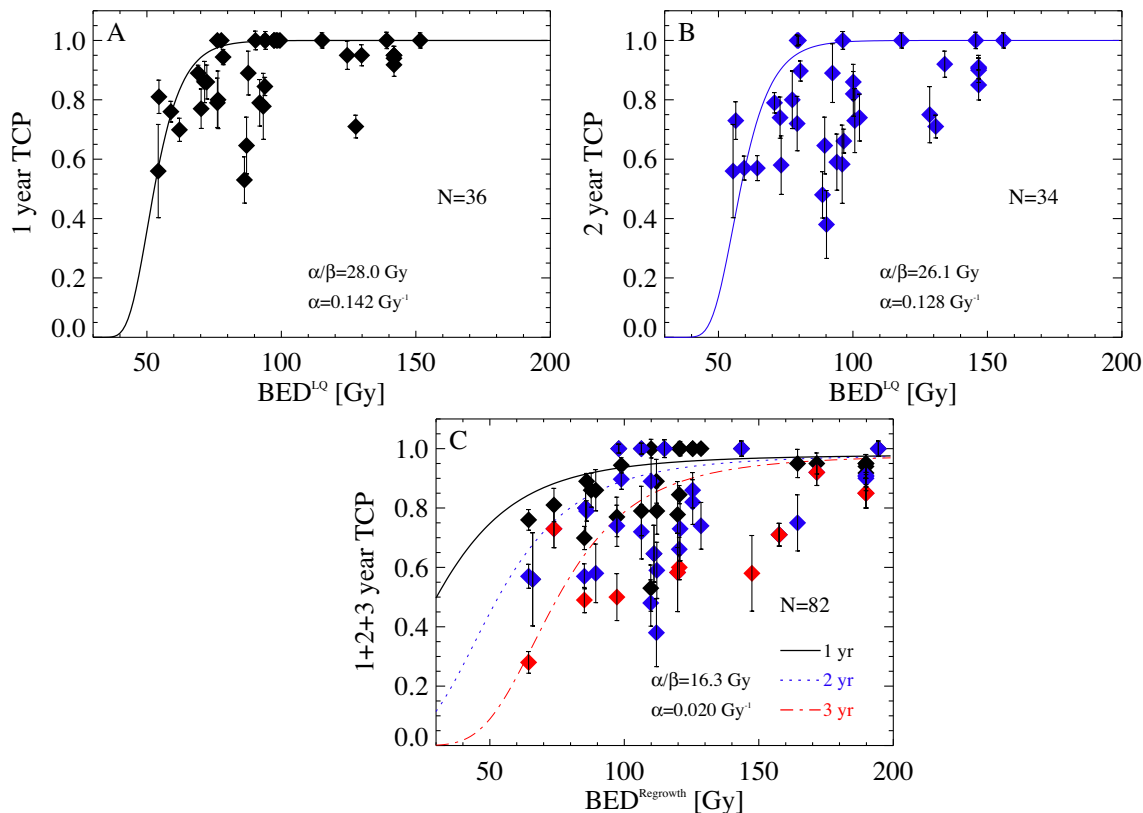
## Discussion

A main result of this analysis is that the data support an  $\alpha/\beta$  ratio in the range 13–23 Gy for pulmonary metastases and 16–28 Gy for hepatic metastases, depending on the specific model applied. The lower  $\alpha/\beta$  values of lung metastases could illustrate differences in the parenchyma and vasculature of lung and liver tissue and/or oxygenation status of the respective tumors, although the difference was only significant for the LQ-type models, but not the regrowth model. Nevertheless, the parameters estimated in this study could have important implications for designing optimal dose prescriptions for the stereotactic treatment of oligometastatic disease.

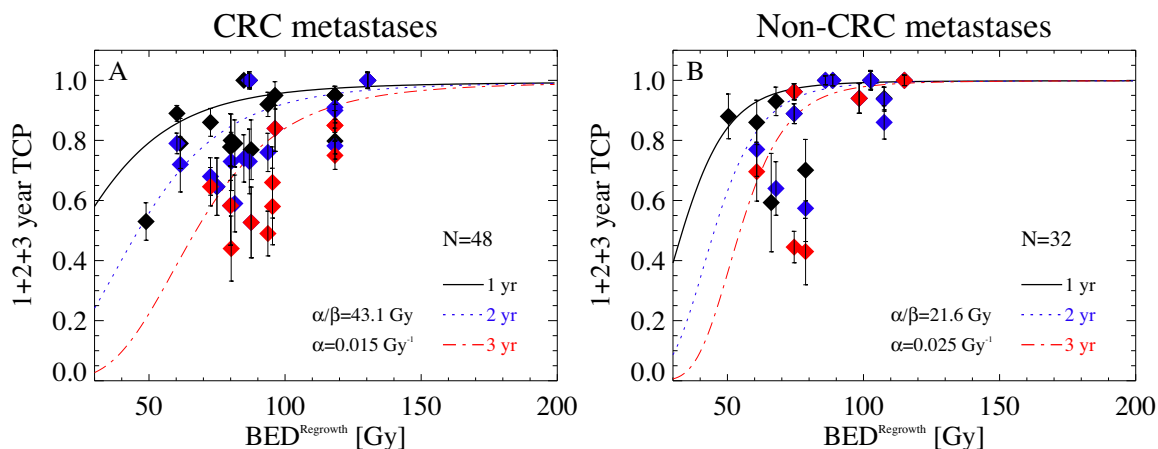
Previous studies found no superiority of the LQ-L model over the simpler LQ model for SBRT treatment of early stage NSCLC [7–9]. This study extends this finding also for hepatic and pulmonary metastases. I found that some radiobiological parameter estimates were strongly dependent on their prior specification. For example, when the uniform prior for  $\log_{10}(K_0)$  was allowed to reach smaller, yet biologically implausible values, the optimal fit of the LQ model for liver metastases was attained at  $K_0 = 10^{1.7 \pm 0.3}$  and  $K_0 = 10^{1.8 \pm 0.3}$  for the 1 yr and 2 yr TCP data, respectively,



**Fig. 1.** Dose–response relationships from the LQ and the regrowth model fitted to the lung metastases data. Panels A–C show fits of the LQ model to the 1 yr (black), 2 yr (blue) and 3 yr (red) TCP data. The individual data points and their uncertainties are also plotted. Panel D shows predictions of the regrowth model for TCP at 1 yr (black), 2 yr (blue) and 3 yr (red) as a function of biologically effective dose. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



**Fig. 2.** Dose–response relationships from the LQ and the regrowth model fitted to the liver metastases data. Panels A and B show fits of the LQ model to the 1 yr (black) and 2 yr (blue) TCP data. The individual data points and their uncertainties are also plotted. Panel C shows predictions of the regrowth model for TCP at 1 yr (black), 2 yr (blue) and 3 yr (red) as a function of biologically effective dose. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



**Fig. 3.** Dose–response relationship for metastases with CRC (panel A) and non-CRC (B) histology. The fits were obtained with the regrowth model and are plotted for 1 yr (black), 2 yr (blue) and 3 yr (red) TCP predictions as a function of biologically effective dose. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

resulting in  $\alpha/\beta$  ratios of  $26.4 \pm 3.5$  Gy and  $21.7 \pm 2.7$  Gy. The prior range of (3,7) for  $\log_{10}(K_0)$  was chosen because  $10^5$  is a biologically plausible initial clonogen number [8] and  $10^3$  a plausible lower limit, and Liu et al. [10] reported estimates between  $10^4$  and  $10^6$ . It is important to point out that the prior specification is part of a Bayesian model; it requires one to think carefully as to what really to expect *a posteriori*. The need to pre-specify a prior for the initial clonogen number is avoided in the regrowth model.

Contrary to Liu et al. [10] no attempt was made to compare the LQ-like models with the regrowth model, since the latter is

designed to fit a different type of data by including temporal information and is *a priori* expected to yield a better fit for sufficient data due to the larger number of free parameters. Liu et al. claimed that the regrowth model would provide a better fit to the data based on the reduced  $\chi^2$  measure which is the  $\chi^2$  value of the model divided by its number of degrees of freedom, conventionally defined as the number of data points minus the number of free model parameters. However, this approach is problematic because for non-linear TCP models, this definition of degrees of freedom is incorrect and the number of degrees of freedom unknown [77].



Following the philosophical reasoning of Gelman and Shalizi [81], I consider the regrowth model preferable over the LQ-like models whenever temporal information is available simply based on the fact that it expands the latter by incorporating the biological principle of tumor cell regrowth after SBRT. In the future, model expansion should further continue by also incorporating reoxygenation, a radiobiological phenomenon that is expected to have a dominating influence on cell kill in very hypofractionated or single-fraction SBRT [5].

It is interesting to compare the results for the pulmonary metastases to results for early stage NSCLC from Liu et al. [10] and Tai et al. [13] who used the same regrowth model as this study. While the  $\alpha/\beta$  ratio for metastases ( $\alpha/\beta = 15.0 \pm 1.1$  Gy) agrees well with the result of Tai et al. derived from multi-institution NSCLC data ( $\alpha/\beta = 15.9 \pm 1.0$  Gy), it is somewhat lower than the result obtained by Liu et al. [10] ( $\alpha/\beta = 20.7 \pm 1.0$  Gy), consistent with a longer effective doubling time of the secondary compared to primary tumors ( $T_p = 235 \pm 130$  days versus  $T_p = 63.8 \pm 5.8$  days). It is important to point out that contrary to Tai et al. [13], the BED used by Liu et al. [10] and this study contains a correction term accounting for tumor cell repopulation already during treatment (Eq. (9)) which if not accounted for reduces the  $\alpha/\beta$  estimates. Smaller  $\alpha/\beta$  values for secondary compared to primary lung tumors would translate into a higher biological effect for a given dose prescription. Using a pooled database of 399 stage I NSCLC tumors and 525 lung metastases, we recently estimated that the BED<sub>10Gy</sub> ( $\alpha/\beta$  was fixed at 10 Gy) required to control 90% of lesions would be 160 Gy (95% CI: 123–237 Gy) for pulmonary metastases compared to 176 Gy (151–223 Gy) for early stage NSCLC. While these differences were not statistically significant, they would be consistent with a putatively larger  $\alpha/\beta$  value of NSCLC compared to pulmonary metastases. On the other hand, Hamamoto et al. [28] found that lung metastases, the majority of which were of CRC origin, had significantly worse local control rates than Stage I NSCLC for a prescription of 48 Gy in 4 fractions. With a sample size of only 12 metastases and 56 NSCLC tumors this result should be interpreted with more caution, but could also hint toward an effect of CRC histology.

Confounding by different histological subtypes such as CRC could be a general problem for studying putative differences between primary and secondary tumors. While in individual data from pulmonary metastases no TCP differences between histological subtypes became apparent [82], the separate analysis of CRC and non-CRC metastases provided here indicates that CRC histology predicts for worse TCP at a given dose prescription, with  $\alpha/\beta$  values around 43 Gy. That CRC metastases respond worse to SBRT treatment than those of other origin has been noticed in several previous studies [29,40,47,53,66,83,35]. It must be kept in mind that patients with CRC metastases are conventionally pre-treated with chemotherapy which could confound the dose–effect relationship as we showed previously for pulmonary and hepatic metastases [84,85]. In a pooled analysis of colorectal liver metastases from three large institutions, 73% of the patients had received at least one chemotherapy regime prior to SBRT [86]. That study estimated that a total dose of 46–52 Gy in 3 fractions would have to be prescribed in order to achieve 90% TCP at 1 yr follow-up, corresponding to  $\approx 19$  Gy minimum isocenter dose per fraction if the typical prescription to the 80% isodose line is applied. This is consistent with the result of my analysis (17 Gy) which was, however, derived from both liver and lung metastases combined.

The non-consideration of prior chemotherapy is one of the limitations of this study. Also, tumor sizes were not accounted for in model building, but could influence the TCP, although we previously found that the influence of maximum tumor diameter on the BED–TCP relationship of 525 pulmonary metastases was negligible [82]. The most obvious limitation of this study is its inherent

meta-analytical character, with a probably large amount of heterogeneity between the studies such as different definitions of tumor control and progression, patient characteristics, primary histologies of the metastases, motion management and imaging techniques, SBRT experience of the treating institution, etc. The relation between characteristic study prescriptions and TCPs does also not necessarily reflect the relation between individual lesion treatment parameters and individual outcomes. TCP model parameters found in this study may therefore be biased because models were fit to study effects, not individual lesion outcomes. The same would apply to similar analyses such as those for NSCLC [8–10].

To investigate this further, an attempt was made to collect individual lesion data from the studies and aggregating them into a single file, either by requesting them from the authors or extracting them from data tables or – in the majority of cases but only if at least the number of events or a numbers at risk table was available – from the Kaplan–Meier plots using the method of Guyot et al. [87]. In this way, a total of 2127 individual lesion data were extracted from 38 studies (1086 lung and 1041 liver metastases). Based on these data, actuarial 1- and 2-year local control rates were computed as 84.7% (95% CI 82.3–87.1%) and 74.1% (70.8–77.5%) for lung and 87.9% (85.7–90.2%) and 78.9 (75.9–82.1%) for liver metastases which was significantly different in the log-rank test ( $p = 0.0121$ ). While the actuarial TCP estimates for liver metastases agree very well with those derived from applying the same methodology to a total of 13 papers as reported by Ohri et al. [88], they are not consistent with the study-level results given in Table 1. The higher TCPs for liver metastases thus point toward a selection effect due to missing information in some studies that did not allow extraction of reliable individual lesion data. The regrowth model which allows incorporation of the follow-up times was fit to all individual lesion data for lung and liver separately. Thereby, the normal likelihood function from Eq. 3 was replaced by a Bernoulli likelihood

$$P(D|\Theta, M) = \prod_{i=1}^N [\text{TCP}_i^{\text{Regrowth}}(\Theta, M)]^{y_i} [1 - \text{TCP}_i^{\text{Regrowth}}(\Theta, M)]^{(1-y_i)} \quad (12)$$

where  $i = 1, \dots, N$  now denotes the lesion number and  $y_i \in \{0, 1\}$  is defined such that  $y_i = 1$  means local control and  $y_i = 0$  local failure at the time of last assessment. The results are tabulated in Supplementary Table 4. The  $\alpha/\beta$  ratios resulting from the individual-level TCP data were  $26.0 \pm 8.5$  Gy for lung and  $27.8 \pm 14.3$  Gy for liver metastases. This exercise illustrates two points: First, it is clear that the individual data simulated from the Kaplan–Meier plots are themselves biased because in most cases of censored observations at best a time interval is known, yet specific follow-up times are used in the model fit and thus influence the parameters. Therefore one could not expect the same results from fitting these individual lesion data and fitting the study-level data. Second, parameter uncertainties derived from individual lesion data are greater than those obtained from the study-level data. This is also expected because the Bernoulli likelihood function of each individual lesion data point  $i$  has standard deviation  $\text{TCP}_i(1 - \text{TCP}_i)$  which is usually larger than the standard deviation of the normal likelihood function of each study data point (Eq. 4). Two other analyses of hypofractionated treatment for liver tumors and brain metastases, respectively, also extracted individual lesion data from Kaplan–Meier plots provided in the literature using the same methodology as employed here [88,89]. However, these studies applied a fixed  $\alpha/\beta$  ratio of 10 Gy to compute BEDs and subsequently grouped the data together according to a few BED values in order to perform TCP modeling. Thus their modeling technique, while being useful for demonstration of a dose–response relationship, is not applicable to the problem of radiobiological parameter estimation. The exam-

ple provided in this work was the first attempt to fit the regrowth model directly to individual lesion data. Despite the many approximations made in the derivation of these data [87], the resulting  $\alpha/\beta$  ratios are consistent with evidence from this and other studies that the usually assumed  $\alpha/\beta = 10$  Gy is too small for SBRT.

## Conclusions

This study implicates that  $\alpha/\beta$  ratios for pulmonary and hepatic metastases are larger than the usually adopted 10 Gy. The regrowth model, which accounts for tumor cell repopulation and thus allows fitting TCP data at various time points simultaneously, predicts that biologically effective doses of  $BED_{15Gy} = 65$  Gy and  $BED_{16.3Gy} = 82$  Gy are sufficient to control 90% of the lung and liver metastases after 1 year, respectively. Such BEDs would be achieved with  $3 \times 12$  Gy or  $3 \times 14.5$  Gy to the isocenter, respectively, delivered over 5 days. Larger doses of  $3 \times 17$  Gy would be needed to achieve the same effects for metastases from CRC whose radiobiology, however, might have been influenced by the frequent application of pre-SBRT chemotherapy which I was not able to account for in the models. Future studies utilizing individual lesion data should be conducted in order to confirm the radiobiological parameters derived in this and similar studies.

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## Conflict of interest statement

I have no conflicts of interest.

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## Appendix A

### A.1 Parameter priors

For this exploratory analysis, uniform priors were used, assuming minimal prior information besides a realistic range for the parameters of interest. For the LQ, mLQ and LQ-L models, the priors are

$$\alpha \sim U(0.01, 0.4) \text{ Gy}^{-1} \quad (\text{A1})$$

$$\alpha/\beta \sim U(1, 50) \text{ Gy} \quad (\text{A2})$$

$$\log_{10}(K_0) \sim U(3, 7) \quad (\text{A3})$$

For the regrowth model the same priors for  $\alpha$  (Eq. A1) and  $\alpha/\beta$  (Eq. A2) were applied; the other priors are:

$$T_p \sim U(1, 1000) \text{ days} \quad (\text{A4})$$

$$\delta \sim \text{Beta}(1, 1) \quad (\text{A5})$$

$$K_{cr}/K_0 \sim \text{Beta}(1, 1) \quad (\text{A6})$$

$$\sigma_K/K_0 \sim \text{Beta}(1, 1) \quad (\text{A7})$$

where Beta(1,1) is the beta distribution which is uniform over the range (0,1).

## A.2 Technical details

Models were fitted using the Gibbs sampler Markov chain implemented in OpenBUGS. For each model, two chains were randomly initialized and run for 50,000 iterations as the burn-in period. From the next 100,000 iterations of each chain, only every 4th posterior sample was kept in order to decrease the correlation between successive samples. For inference, all posterior samples from both chains were pooled together.

## Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.radonc.2017.03.014>.

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