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Radiobiology of metastases

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, α/β ratios in the range 13–23 Gy for pulmonary metastases and 16–28 Gy for hepatic metastases were estimated. For CRC metastases the estimated α/β ratio was 43.1 ± 4.7 Gy compared to 21.6 ± 7.8 Gy for non-CRC metastases. Typical isocenter dose prescriptions of 3×12 Gy, 3×14.5 Gy and 3×17 Gy applied within 5 days were predicted sufficient to control 90% of lung, liver and CRC metastases after 1 yr, respectively.

Conclusions: α/β 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.

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 be 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 α/β ratio for SBRT would be larger than the usually assumed 10 Gy, since only beyond this ratio the quadratic (β) 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 α component representing lethal DNA damage would gain importance over the sub-lethal damage β component as doses are increased, leading to a continuously increasing α/β ratio with dose [11]. Indeed, recent evidence supports α/β ratios of NSCLC treated with SBRT in the range $\geq$20 Gy [10,12,13]. Nevertheless, studies investigating the α/β ratio of metastases treated with SBRT are lacking.

The main aim of this project was to explore the α/β 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 DigitizeIt 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 Θ 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 Θ 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

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

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:

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

where $\mathrm{TCP}_i^{\mathrm{model}}(\Theta)$ is the TCP for a given model expressed as a function of the model parameters Θ and the standard error s_i is given by $s_i = \mathrm{TCP}_i^{\mathrm{data}} \sqrt{\frac{1-\mathrm{TCP}_i^{\mathrm{data}}}{M_i * \mathrm{TCP}_i^{\mathrm{data}}}}$ 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 (χ^2) method which assumes that the data measurement errors are Gaussian [77]. In practice, $\mathrm{TCP}_i^{\mathrm{model}}$ 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.