Radiotherapy and Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Estimation of the α/β ratio of non-small cell lung cancer treated with stereotactic body radiotherapy

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ARTICLE INFO

Article history:
Received 3 April 2019
Received in revised form 11 June 2019
Accepted 4 July 2019
Available online xxxx

Keywords:
Radiobiology
SBRT
NSCLC
Tumor control probability
Linear-quadratic model

ABSTRACT

Background: High-dose hypofractionated radiotherapy should theoretically result in a deviation from the typical linear-quadratic shape of the cell survival curve beyond a certain threshold dose, yet no evidence for this hypothesis has so far been found in clinical data of stereotactic body radiotherapy treatment (SBRT) for early-stage non-small cell lung cancer (NSCLC). A pragmatic explanation is a larger α/β ratio than the conventionally assumed 10 Gy. We here attempted an estimation of the α/β ratio for NSCLC treated with SBRT using individual patient data.

Materials and methods: We combined two large retrospective datasets, yielding 1294 SBRTs ($\leq$10 fractions) of early stage NSCLC. Cox proportional hazards regression, a logistic tumor control probability model and a biologically motivated Bayesian cure rate model were used to estimate the α/β ratio based on the observed number of local recurrences and accounting for tumor size.

Results: A total of 109 local progressions were observed after a median of 17.7 months (range 0.6–76.3 months). Cox regression, logistic regression of 3 year tumor control probability and the cure rate model yielded best-fit estimates of α/β = 12.8 Gy, 14.9 Gy and 12–16 Gy (depending on the prior for α/β), respectively, although with large uncertainties that did not rule out the conventional α/β = 10 Gy.

Conclusions: Clinicians can continue to use the simple LQ formalism to compare different SBRT treatment schedules for NSCLC. While α/β = 10 Gy is not ruled out by our data, larger values in the range 12–16 Gy are more probable, consistent with recent meta-regression analyses.

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The radiobiological principles of stereotactic body radiation therapy (SBRT) are currently vividly discussed [1–3]. Compared to conventional fractionation, SBRT may exhibit some unique biological features including beneficial effects such as enhancement of systemic anti-tumor immunity [4] and a better ability to kill cancer stem cells [5], but also a difficulty to overcome tumor hypoxia with one or only a few fractions due to limited reoxygenation [2,3]. More specifically, when cells *in vitro* are irradiated with doses comparably high to those used in SBRT, a deviation from the typical linear-quadratic shape of the cell survival curve beyond a certain threshold dose is observed, with a transition of the continuously bending quadratic curve into a linear decline [3]. Several phenomenological and mechanistic models have been developed with the aim to describe this shape of the survival curve, among them the universal survival curve (USC) model [6], generalized linear-

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https://doi.org/10.1016/j.radonc.2019.07.008
0167-8140/

quadratic model [7] and the linear-quadratic-linear (LQ-L) model [8].

Because the LQ model is expected to overestimate the effects of high SBRT doses [3], evidence for an alternative such as the LQ-L model has been sought in clinical data. Using a retrospective database of almost 400 patients with early stage non-small cell lung cancer (NSCLC) treated with SBRT, we previously investigated whether the LQ-L model would yield a better description of the dose–response relationship between the biologically effective dose (BED) and local tumor control probability (TCP) [9]. We found that the traditional LQ model was as good as, if not better, than the LQ-L model in describing the clinical data. Subsequently, two modelling studies confirmed our result by comparing the relationships between BED based on either the LQ or LQ-L model and TCP from published clinical data [10,11]. So why is the expected deviation from the LQ behavior at high doses applied in SBRT not obvious in the clinical data [12]?

A pragmatic explanation is that the α/β ratio of early stage NSCLC treated with SBRT could be higher than the 10 Gy that are usually assumed for NSCLC tumors, a point first articulated by Fowler in 2008 [13]. Larger α/β ratios are expected for rapidly repopulating tumors [13] as well as hypoxic cells [14], so may be theoretically justified for SBRT treatment of NSCLC. Along these lines, Brown et al. [2] have argued that by simply increasing the α/β ratio of the tumor, the LQ model curve would be nearly undistinguishable from the USC or LQ-L model curves based on a lower α/β ratio. Finally, Tomé pointed out the possibility that for 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 [15].

While these hypotheses imply a higher α/β ratio of NSCLC treated with SBRT than conventionally assumed, no study has provided confirmation of α/β ratios >10 Gy by analyzing individual patient data. It was therefore the aim of this study to estimate the α/β ratio from individual patient data.

Materials and methods

Data used for modeling

The data used for modeling were extracted from two large retrospective databases of non-metastasized NSCLC patients treated with SBRT, defined here as $\leq$10 fractions as proposed by Guckenberger et al. [16]. One is the database of the Elekta Collaborative Lung Research Group, comprising 1230 patients with 1337 individually treated tumors; the other is the database of the working group "Stereotactic Radiotherapy and Radiosurgery" of the German Society for Radiation Oncology (DEGRO) comprising 637 patients treated for 638 tumors [17]. In both databases, contour definitions were identical and tumor diameters were measured according to the diagnostic standards. A total of 74 patients from the University Hospital of Würzburg (Germany) treated between 23-02-1998 and 18-11-2011 were included in both databases and only considered once. Patients having received >10 fractions, lost to follow-up within one month after start of SBRT or with missing information on treatment dose, fractionation, maximum tumor diameter or outcome were excluded, leaving 938 patients with 1003 SBRT treatments from the Elekta consortium database and 290 patients with 291 SBRT treatments from the DEGRO database for analysis. The data were combined to yield 1294 treated tumors from 1228 patients (Fig. 1). Follow-up time was defined as the interval between the start of SBRT and local progression or censoring, respectively. In both databases, local progression had been defined as regrowth of the tumor within the treated area following institutional guidelines, but there was no central guideline in terms of computed tomography morphological criteria, 2-(^{18}F)fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) imaging, or biopsy confirmation. Competing risks such as death were not specifically accounted for and treated as censoring events.

It was previously shown that the maximum dose or dose at the isocenter predicts TCP significantly better than the prescribed near minimum PTV dose, possibly due to maximum doses being a better surrogate for the energy actually absorbed by the tumor [9,18]. Nevertheless, due to the large dose heterogeneity typical for SBRT, using maximum doses might be a suboptimal choice when the goal is to estimate the α/β ratio as it might significantly overestimate the dose delivered to the tumor and hence the biological effect, which would result in a correspondingly larger α/β ratio. In this analysis, therefore, we used an average between the near maximum dose, defined as D1% PTV from the dose-volume histogram (DVH), and the prescribed dose to the PTV periphery as a representative dose for modelling [19]. DVH parameters are only available in the Elekta database and a single institution subset of the DEGRO database; the rest of the DEGRO database does not include comprehensive DVH parameters. Near maximum doses were therefore estimated from the SBRT prescription dose divided by the prescribed dose heterogeneity and then transformed to a D1% PTV estimate based on a linear regression formula derived from 88 patients with known D1% and heterogeneity parameters (Supplementary Fig. B1):

$$\mathrm{D1\%\,PTV} = 1.865 + 0.967 \times 100/\mathrm{heterogeneity}[\%] \times \mathrm{D_{prescribed}} \quad (1)$$

The prediction standard errors of D1% PTV based on Eq. (1) ranged between 0.25 and 1.05 Gy (median 0.36 Gy) and were negligible for our results (Supplementary Fig. B1).

Cox regression modelling

For relating BED and maximal tumor diameter l with the time to local progression, we built several Cox regression models that differed only in the assumed value for the α/β ratio which was varied from 1 Gy to 50 Gy in steps of 0.1 Gy. The profile likelihood was derived from the maximum likelihood of each Cox model with respect to BED and l and used for estimating the optimal α/β ratio and a 95% confidence interval (CI).

Logistic TCP model

Logistic regression is a conventional TCP modelling technique that treats local control as a binomial variable taking on the value of either 0 or 1. We used a local control cutoff at three years, removing any patients that experienced local progression thereafter or who were censored prior to this cutoff. The three-year cutoff was chosen as a compromise between maximizing overall sample size and number of events for modelling. Indeed, 92 out of 109 (84.4%) events had occurred within three years. We then optimized a Bayesian logistic regression model in which the α/β ratio was assumed to be distributed according to a uniform $U(-10, 30)$ prior which has mean at 10 Gy, the value conventionally assumed for α/β:

$$TCP_i = \frac{\exp(b_0 + b_{BED} \cdot BED_i(\alpha/\beta) + b_l \cdot l_i)}{1 + \exp(b_0 + b_{BED} \cdot BED_i(\alpha/\beta) + b_l \cdot l_i)} \quad (2)$$

Here BED_i is the biologically effective dose derived from the average between SBRT prescription dose and near maximum physical dose received by tumor i, l_i denotes the maximal tumor diameter of tumor i, and b_0, b_{BED} and b_l are the regression coefficients for the intercept, BED and maximum tumor diameter, respectively. As in previous work, we also tested whether the LQ-L extension of the

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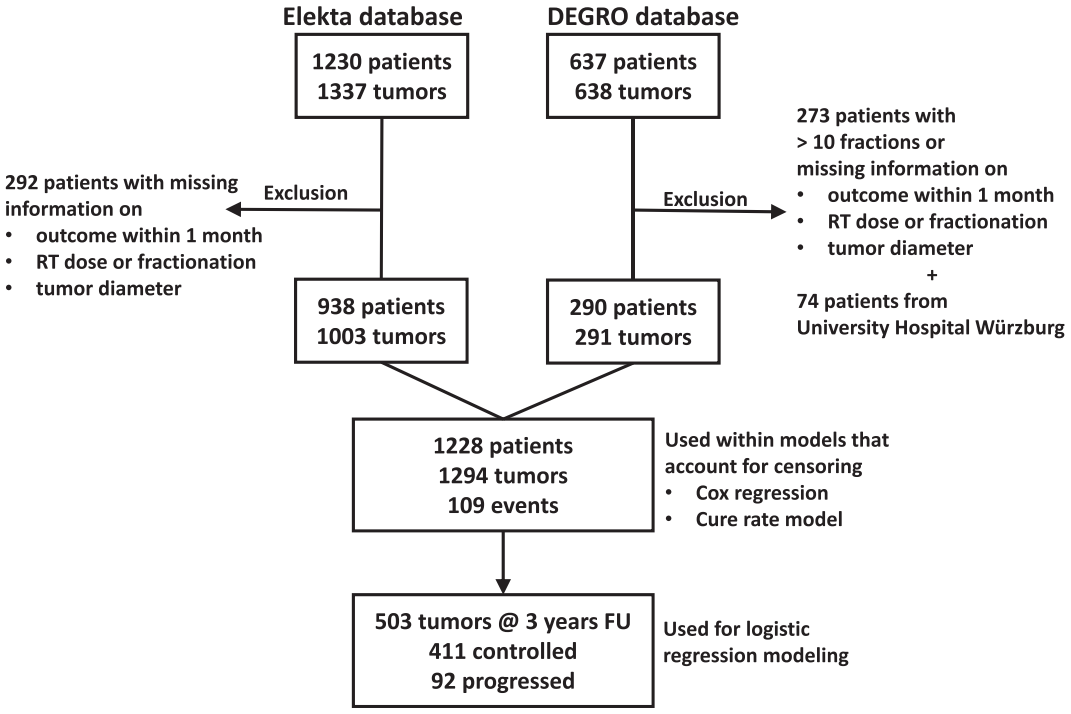

Fig. 1. Flow chart of patient selection and database merging.

LQ formalism would yield a better model fit. In its simplest form, the LQ-L model predicts that biological effects start to deviate from LQ behavior when single-fraction doses d_i exceed a certain threshold dose d_T [8,9] (n_i denotes the number of fractions used to treat tumor i):

$$\mathrm{BED}_i^{\mathrm{LQ-L}} = \begin{cases} n_i d_i\left(1+\frac{d_i}{\alpha/\beta}\right), & d_i < d_T \\ n_i d_T\left(1+\frac{d_T}{\alpha/\beta}\right) + n_i\left(1+\frac{2d_T}{\alpha/\beta}\right)\cdot(d_i - d_T), & d_i \geqslant d_T \end{cases} \tag{3}$$

Bayesian cure rate model formulation

The cure rate model is based on the model proposed by Chen et al. [20] that we have previously shown to predict local control of pulmonary metastases better than a mixture model and to be more flexible than the traditional Cox proportional hazards model [21]. In the cure rate model, the probability of local control TCP* depends both on the number of clonogens left intact after SBRT, K_i (which itself depends on the SBRT schedule and tumor size), as well as the time that it takes for any remaining clonogen to grow into a clinically detectable tumor (Appendix A.1):

$$\mathrm{TCP}_i^*(t_i, \mathrm{BED}_i, l_i) = \exp(-\theta_i(1 - S(t))) \tag{4}$$

Here, t_i denotes the progression time for tumor i which may be right censored, θ_i is the so-called cure parameter and $S(t)$ the latent survival function that determines the regrowth of the K_i clonogens into a newly detectable tumor. $S(t)$ is modelled as a Weibull distribution with parameters κ and η, so that $S(t) = \exp(-t^\kappa e^\eta)$. The number K_i is assumed to be sampled from a Poisson distribution with mean θ_i (the cure parameter) that we let depend on the biologically effective dose and maximal tumor diameter through

$$\theta_i = \exp\left(b_0 + b_l \cdot l_i - \alpha \cdot \mathrm{BED}_i\right) \tag{5}$$

Let Ω denote the set of model parameters; the likelihood of the observed data is then given as [22]:

$$P(D|\Omega) = \prod_{i=1}^{N}\left[-\frac{d}{dt_i}\log S(t_i)\right]^{v_i}\mathrm{TCP}_i^*(t_i) \tag{6}$$

Here, v_i is a censoring indicator taking the value 1 if t_i is a progression time and 0 if it is right censored. From $P(D|\Omega)$ the posterior probability density of the model parameters can be obtained via Bayes' theorem (Appendix A2).

Prior distributions

The main radiobiological parameter of interest, α/β, was modelled such that its mean was close to the conservative value of 10 Gy, but allowing for larger uncertainty in light of the results from recent studies by specifying a large standard deviation. The first prior was a uniform prior having mean at 10 Gy and standard deviation 11.5 Gy (although negative values of α/β are unphysical, they nevertheless are valid mathematically):

$$\alpha/\beta \sim \mathrm{U}(-10, 30) \tag{7.1}$$

Alternatively we place a lognormal prior on α/β with mean at 13 Gy, median at 10.3 Gy and standard deviation 10 Gy:

$$\alpha/\beta \sim \mathrm{LN}\left(\mathrm{m}_{\alpha/\beta}, \mathrm{s}^2_{\alpha/\beta}\right)$$

with

$$m_{\alpha/\beta} = \ln\left[\frac{\mu^2_{\alpha/\beta}}{\sqrt{\mu^2_{\alpha/\beta} + \sigma^2_{\alpha/\beta}}}\right]$$

$$s_{\alpha/\beta} = \sqrt{\ln\left[\left(\frac{\sigma^2_{\alpha/\beta}}{\mu^2_{\alpha/\beta}}\right) + 1\right]}$$

and

$$\mu_{\alpha/\beta} = 13\ \mathrm{Gy}, \sigma_{\alpha/\beta} = 10\ \mathrm{Gy} \tag{7.2}$$

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As a third alternative, we created four different models, only differing in the prior specification for α/β which was taken to be normal with small standard deviation:

$$\alpha/\beta \sim \mathrm{N}\left(\mu_{\alpha/\beta}, \sigma^2_{\alpha/\beta}\right) \text{ with } \mu_{\alpha/\beta} \in \{5, 10, 15, 20\}\,\mathrm{Gy},\ \sigma_{\alpha/\beta} = 2.5\,\mathrm{Gy} \tag{7.3}$$

The best of these models was selected using trans-dimensional Markov chain Monte Carlo (MCMC) [23 pp. 244–246]. Each model was given a 25% prior probability for selection, and the posterior probability for a particular model being selected within the sampled iterations was taken as an indicator which α/β value would fit the data best.

Prior distributions for all other model parameters are given in Appendix A3.

Results

Actuarial local control rates at 12, 24 and 36 months were 97.0% (95% CI 96.0–98.0%), 91.7% (89.9–93.6%) and 88.8% (86.6–91.1%), respectively (Fig. 2). A total of 109 patients experienced local progression after a median of 17.7 months (range 0.6–76.3 months). Maximum tumor diameter ranged from 0.5 cm to 9.6 cm with median, mean and standard deviation at 2.3 cm, 2.5 cm and 1.14 cm, respectively. The median prescription dose was 48 Gy (range 12–64 Gy) and median number of fractions were 3 (1–10); median near-maximum total dose was 64.9 Gy (19–95.6 Gy). The most frequent dose prescriptions were 3×18 Gy ($n = 354$), 4×12 Gy ($n = 318$) and 3×12.5 Gy ($n = 105$).

Cox proportional hazards regression with varying values for α/β resulted in a best fit at $\alpha/\beta = 12.9$ Gy with a 95% CI of [2.0, 34.8] Gy.

Within a three-year follow-up period, a total of 92 local progressions had occurred, while 411 lesions remained locally controlled. The Bayesian logistic regression model resulted in a posterior point estimate (median) for α/β of 14.9 Gy (95% HPDI 5.3–28.0 Gy) (Table 1). The model prediction for $\alpha/\beta = 14.9$ Gy is plotted in Fig. 3 together with the binomial proportions within 10 equal-sized bins. Bayesian binomial 95% CIs were estimated via the beta distribution quantile technique [24]. We also fitted a logistic dose–response model using either the near-maximum or SBRT prescription dose. The first case resulted in a slightly higher, the second in a slightly lower estimate for α/β; both model fits were worse than when using the average of near-maximum and SBRT prescription dose as judged by the deviance information criterion (DIC, Table 1). Finally, BEDs based on the LQ-L formalism (Eq. (3)) resulted in a model fit that was somewhat, but not substantially, better as judged by the DIC difference of 2.7 (Supplementary Table C1). The median point estimate (20.6 Gy) of the threshold dose d_T was thereby larger than the individual fraction doses received by 60.6% of the tumors, showing that the LQ model would remain valid for most of the SBRT treatments in our sample.

To model the full time course of local progressions including the plateau evident in Fig. 2, the Bayesian cure rate model was applied to the complete dataset of 1294 SBRTs. The parameter estimates derived from the Bayesian cure rate model are shown in Table 2. Several model fits (depending on BED and tumor size) are compared to the actual Kaplan-Meier curve in Fig. 4. Note the good agreement between the Kaplan-Meier curve and the model prediction when the $\mathrm{BED}_{16\mathrm{Gy}}$ and tumor size take on their average values. For a lesion with average size of 2.5 cm, the model predicts that a $\mathrm{BED}_{16\mathrm{Gy}}$ of 89, 129, 148 and 167 Gy would be required to achieve 95% TCP at one, two, three or five years, respectively. Note that the largest difference in $\mathrm{BED}_{16\mathrm{Gy}}$ needed to achieve stable 95% TCP occurs between 1 and 2 years, consistent with the steepest absolute decline of the actuarial local control curve in this time interval compared to later intervals of one year length (Figs. 2 and 4).

Using trans-dimensional MCMC with the narrow Gaussian priors (Eq. (7.3)) resulted in posterior probabilities of 25.0%, 31.5%, 26.2% and 17.3% for the models assuming α/β values of 10, 15, 20 and 25 Gy, showing that the prior probabilities of the first three models were raised at the expense of the last and that the model specifying $\alpha/\beta = 15$ Gy was favored by the data. The median, mean and standard deviation of α/β derived from jumping across the different models were 16.4, 16.7 and 5.3 Gy.

Discussion

We have conducted the first analysis which uses individual patient data to estimate the radiobiological LQ model parameters for SBRT of early stage NSCLC. Using three independent methods – Cox proportional hazards regression modelling, a logistic TCP model and a biologically motivated Bayesian cure rate model – we derived consistent results of most probable α/β estimates between 12–16 Gy.

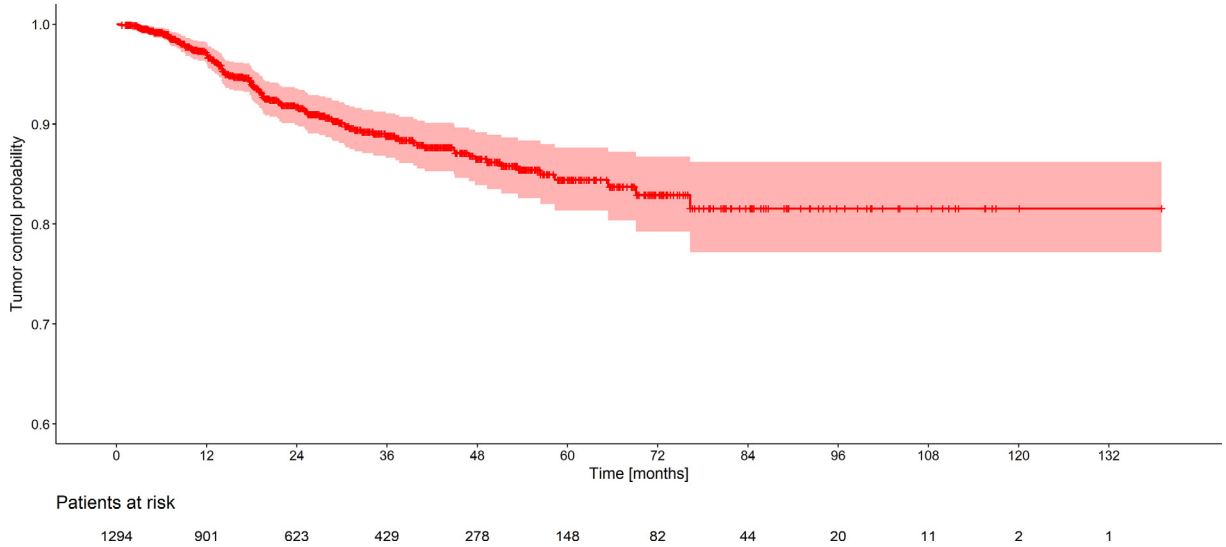

Fig. 2. Kaplan–Meier plot of tumor control probability with 95% confidence interval (shaded band).

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Table 1
Parameter estimates of the Bayesian logistic regression model for three different choices of the physical dose. The models can be compared according to the DIC (Deviance information criterion); smaller DIC values indicate a better fit, and differences ≥5 are considered to provide substantial evidence for one model over the other. HPDI: Highest posterior density interval.

Dose used for modelling	0.5 × (Near maximum dose + Prescription dose)			Near maximum dose (D1% PTV)			Prescription dose		
Parameter	Mean	Median	95% HPDI	Mean	Median	95% HPDI	Mean	Median	95% HPDI
α/β [Gy]	15.5	14.9	[5.3, 28.0]	16.7	16.3	[5.3, 28.6]	14.5	13.8	[4.3, 27.6]
b_0	−2.474	−2.466	[−3.673, −1.317]	−2.136	−2.128	[−3.272, −1.046]	−2.072	−2.065	[−3.21, −0.972]
b_{BED} [Gy^{-1}]	0.0348	0.0348	[0.0149, 0.0544]	0.0272	0.0274	[0.0107, 0.0429]	0.0377	0.0378	[0.0145, 0.06]
b_l [cm^{-1}]	−0.451	−0.450	[−0.688,−0.216]	−0.459	−0.458	[−0.693, −0.226]	−0.440	−0.440	[−0.673, −0.209]
DIC	410.7			413.6			418.6		

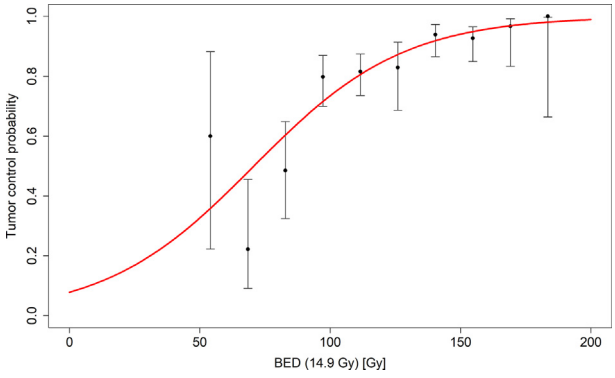

Fig. 3. Tumor control probability as a function of $BED_{14.9Gy}$ for a lesion with tumor size 2.5 cm (the mean value) as predicted by the logistic TCP model. The points show the TCP within 10 equal-sized $BED_{14.9Gy}$ bins together with Bayesian 95% Cis [24].

Even with 1294 treatments and 109 events going into our analysis, the range of α/β values supported by the data was large (Table 2). Apparently, the information contained within the data was not dominant enough to transform the weak prior information used into precise posterior estimates. It is possible that the large uncertainty of α/β reflects an actual large heterogeneity between tumors that could depend on factors not accounted for in this analysis such as histology, cell cycle distribution, hypoxia, the mutational landscape etc. Indeed, NSCLC cell lines can exhibit very different α/β ratios *in vitro* [5], and α/β estimates from modelling studies using clinical outcome data range from 2.8 Gy [19] over 8.2 Gy [25] to 20 Gy and beyond [26,27].

It is thereby noteworthy that studies exclusively focusing on data from SBRT of early stage NSCLC (excluding studies with conventional fractionation) generally estimated α/β ratios larger than 10 Gy. For example, Chi and colleagues observed a higher degree of correlation between isocenter BED and TCPs from published studies, when α/β ratios >10 Gy were used for the BED calculation [26]. The Spearman's correlation coefficients used to quantify the strength of the dose–response relationship were remarkably similar and stable over a broad range of α/β values from 20-50 Gy. While Chi et al.'s analysis relied on heterogenous literature data with non-consideration of study sizes and tumor diameters, it is interesting that the stability of the biologically effective dose–response relationship over a broad range of α/β values exhibits some parallels to our findings.

Tai et al. [28] obtained a best-fit estimate of $\alpha/\beta = 15.9 \pm 1.0$ Gy by fitting a regrowth TCP model to 196 published actuarial TCPs at 1, 2, 3 and 5 years follow-up from different institutions. Their model is similar to our cure rate model in that tumor cell regrowth after SBRT is taken into account, thereby effectively reducing the TCP as follow-up time increases. However, Tai et al.'s analysis relied on single- and multi-institutional data from the literature and included the pooling of metastases and hepatic tumors together with NSCLC in one of the datasets. A subsequent meta-regression analysis by Liu et al. [27], again applying a regrowth TCP model to 1-, 2-, 3- and 5-year TCP values from published clinical studies, yielded $\alpha/\beta = 20.7 \pm 1.0$ Gy. However, in contrast to our work and the model used by Tai et al. [28], the regrowth model applied by Liu et al. [27] contained a correction term accounting for tumor cell repopulation already during SBRT treatment which would effectively increase the α/β ratio and possibly explain the slightly larger value found by these authors. Consistent with this argument, when we accounted for treatment duration as a covariate in the cure rate model in an additional analysis, we obtained larger estimates for α/β with median at 17.4 Gy and 95% HPDI 4.0–29.2 Gy. Longer treatment duration was thereby associated with lower TCP (median $b_{duration} = 0.0415$ day^{-1}), although not "significantly" (95% HPDI = [−0.1892, 0.2428]). Besides treatment duration, we did not evaluate additional covariates in the cure rate model, the major reason being that such variables possibly affecting the dose–response relationship (e.g. smoking during treatment) were completely or to a large extent missing in the combined database. Furthermore, any sort of competing risk was treated as censored and thereby causally unrelated to the occurrence of local progression – an assumption often made in TCP modelling. While these assumptions pose major limitations to our

Table 2
Parameter estimates of the Bayesian model for two different choices of the prior distribution of α/β (Eqs. (7.1) and (7.2)). For modelling, tumor size l was standardized to mean 0 and standard deviation 1. HPDI: Highest posterior density interval.

Prior distribution	$\alpha/\beta \sim U(-10, 30)$			$\alpha/\beta \sim LN(2.33, 0.68^2)$		
Parameter	Mean	Median	95% HPDI	Mean	Median	95% HPDI
α/β [Gy]	16.4	16.0	[5.6, 28.6]	13.0	12.0	[4.7, 26.6]
α [Gy^{-1}]	0.0242	0.0244	[0.010, 0.0372]	0.0207	0.0203	[0.0087, 0.0349]
b_0	1.251	1.242	[0.324, 2.215]	1.166	1.157	[0.255, 2.143]
b_l [cm^{-1}]	0.224	0.226	[0.0703, 0.369]	0.2255	0.2278	[0.0686, 0.3679]
κ	1.560	1.559	[1.292, 1.825]	1.560	1.560	[1.292, 1.826]
η	−5.909	−5.898	[−6.763,−5.115]	−5.909	−5.896	[−6.761,−5.123]

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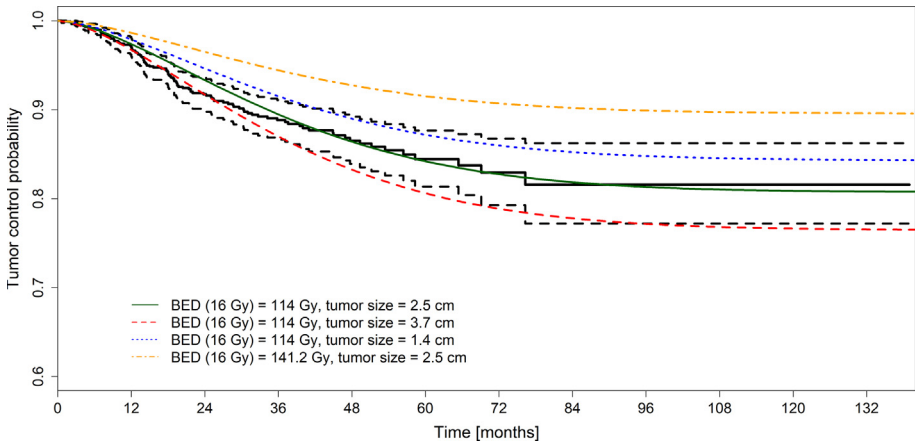

Fig. 4. Kaplan–Meier plot of the data with 95% confidence bands (black) compared to four different fits of the Bayesian cure rate model (colored). The choice for the BED and tumor size represent the mean values and one standard deviation differences in our sample. For each fit the median posterior parameter values obtained for the uniform prior on α/β given in Table 2 were used. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

analysis, we at least were able to incorporate tumor diameter as the probably most important modifier of the dose–response relationship in all our models.

In the studies discussed above the isocenter dose was used for dose–response modelling which is approximately close to the maximum dose. While we confirm here a previous result [9] that using near maximum doses results in a substantially better fit of the logistic dose–response curve than SBRT prescription doses, we also show that the average of both improves the model fit further (Table 1). It is likely that isocenter doses overestimate the delivered dose to the tumor and hence the biological effect, which would result in a correspondingly larger α/β ratio, consistent with what we observed (Tables 1 and Supplementary Table C2).

A possible limitation of our models is that they do not account for redistribution of cells in the cell cycle, intratumoral hypoxia and the role of reoxygenation. These factors have been included in a recent modeling study of Jeong et al. [19] who derived an α/β estimate of 2.8 Gy with 95% CI of 0.4–4.4 Gy for early stage NSCLC across a large range of fractionation schedules pooled from the literature. If the α/β ratio of hypoxic cells is proportionately larger than the α/β ratio of normoxic cells [14], the presence of hypoxic cells would effectively result in an overestimation of the α/β ratio, especially with very hypofractionated SBRT that may not cause optimal reoxygenation. Therefore our estimated α/β ratio might be unreliable for transforming between SBRT and conventional fractionation schedules.

In conclusion, only weak evidence for the LQ-L over the LQ formalism together with most probable α/β ratios larger than 10 Gy implies that the simple LQ formalism likely remains adequate for comparing different SBRT treatment schedules in terms of biological effectiveness. While using the conventional $\alpha/\beta = 10$ Gy for such calculations is still consistent with our data, consideration of α/β ratios between 12 and 16 Gy appears slightly better supported.

Acknowledgments

This research was partially supported through an Elekta research grant with five institutions being members of the Elekta Lung Research Group. Dr. Grills reports grants from Elekta during the conduct of the study. Dr. Hope reports grants and nonfinancial support from Elekta during the conduct of the study. Dr. Sonke has received research grants and royalties from Elekta Oncology, Ltd., and he holds patents with royalties paid to Elekta. Dr. Guckenberger reports grants from Elekta during the conduct of the study. The remaining authors declare no conflict of interest. This work and these data are the intellectual property of the individual group members and their sponsoring institutions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.07.008.

References

[1] Song CW, Park H, Griffin RJ, Levitt SH. Radiobiology of stereotactic radiosurgery and stereotactic body radiation therapy. In: Levitt SH, Purdy JA, Perez CA, Poortmans P, editors. Technical Basis of Radiation Therapy. Springer-Verlag Berlin Heidelberg; 2012. p. 51–61. doi:10.1007/174.

[2] Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: Are more than the 5 Rs involved ? Int J Radiat Oncol Biol Phys 2014;88:254–62. https://doi.org/10.1016/j.ijrobp.2013.07.022.

[3] Shibamoto Y, Miyakawa A, Otsuka S, Iwata H. Radiobiology of hypofractionated stereotactic radiotherapy: what are the optimal fractionation schedules? J Radiat Res 2016;57:i76–82. https://doi.org/10.1093/jrr/rrw015.

[4] Siva S, Callahan J, Macmanus MP, Martin O, Hicks RJ, Ball DL. Abscopal effects after conventional and stereotactic lung irradiation of non-small-cell lung cancer. J Thorac Oncol 2013;8:e71–2. https://doi.org/10.1097/JTO.0b013e318292c55a.

[5] Zhang H, Wan C, Huang J, Yang C, Qin Y, Lu Y, et al. In vitro radiobiological advantages of hypofractionation compared with conventional fractionation: early-passage NSCLC cells are less aggressive after hypofractionation. Radiat Res 2018;190:584–95. https://doi.org/10.1667/RR14951.1.

[6] Park C, Papiez L, Chichuan Z, Story M, Timmerman R. Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy. Int J Radiat Oncol Biol Phys 2008;70:847–52. https://doi.org/10.1016/j.ijrobp.2007.10.059.

[7] Wang JZ, Huang Z, Lo SS, Yuh WTC, Mayr NA. A generalized linear-quadratic model for radiosurgery, stereotactic body radiation therapy, and high-dose rate brachytherapy. Sci Transl Med 2010;2:39ra48. https://doi.org/10.1126/scitranslmed.3000864.

[8] Astrahan M. Some implications of linear-quadratic-linear radiation dose-response with regard to hypofractionation. Med Phys 2008;35:4161–72.

[9] Guckenberger M, Klement RJ, Allgäuer M, Appold S, Dieckmann K, Ernst I, et al. Applicability of the linear-quadratic formalism for modeling local tumor control probability in high dose per fraction stereotactic body radiotherapy for early stage non-small cell lung cancer. Radiother Oncol 2013;109:13–20. https://doi.org/10.1016/j.radonc.2013.09.005.

[10] Shuryak I, Carlson DJ, Brown JM, Brenner DJ. High-dose and fractionation effects in stereotactic radiation therapy: analysis of tumor control data from 2965 patients. Radiother Oncol 2015;115:327–34. https://doi.org/10.1016/j.radonc.2015.05.013.

[11] Santiago A, Barczyk S, Jelen U, Engenhart-Cabillic R, Wittig A. Challenges in radiobiological modeling: can we decide between LQ and LQ-L models based on reviewed clinical NSCLC treatment outcome data? Radiat Oncol 2016;11:67. https://doi.org/10.1186/s13014-016-0643-5.

[12] Brown JM. The biology of SBRT: LQ or something new? Int J Radiat Oncol Biol Phys 2018;101:964. https://doi.org/10.1016/j.ijrobp.2018.02.038.

[13] Fowler JF. Linear quadratics is alive and well: In Regard to Park et al. (Int J Radiat Oncol Biol Phys 2008;70:847–852). Int J Radiat Oncol Biol Phys 2008;72:957. https://doi.org/10.1016/j.ijrobp.2008.06.1929.

[14] Carlson DJ, Stewart RD, Semenenko VA. Effects of oxygen on intrinsic radiation sensitivity: a test of the relationship between aerobic and hypoxic linear-quadratic (LQ) model parameters. Med Phys 2006;33:3105–15. https://doi.org/10.1118/1.2229427.

[15] Tomé WA. Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy: In Regard to Parks et al. (Int J Radiat Oncol Biol Phys 2008;70:847–852). Int J Radiat Oncol Biol Phys 2008;72:1620. https://doi.org/10.1016/j.ijrobp.2007.10.059.

[16] Guckenberger M, Andratschke N, Alheit H, Holy R, Moustakis C, Nestle U, et al. Definition of stereotactic body radiotherapy: principles and practice for the treatment of stage I non-small cell lung cancer. Strahlenther Onkol 2014;190:26–33. https://doi.org/10.1007/s00066-013-0450-v.

[17] Guckenberger M, Allgäuer M, Appold S, Diekmann K, Ernst I, Ganswindt U, et al. Safety and efficacy of stereotactic body radiotherapy for stage I non-small-cell lung cancer in routine clinical practice: a patterns-of-care and outcome analysis. J Thorac Oncol 2013;8:1050–8.

[18] Klement RJ, Allgäuer M, Appold S, Dieckmann K, Ernst I, Ganswindt U, et al. Support vector machine-based prediction of local tumor control after stereotactic body radiation therapy for early-stage non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2014;88:732–8. https://doi.org/10.1016/j.ijrobp.2013.11.216.

[19] Jeong J, Oh JH, Sonke J-J, Belderbos JSA, Bradley JD, Fontanella AN, et al. Modeling the cellular response of lung cancer to radiation therapy for a broad range of fractionation schedules. Clin Cancer Res 2017;23:5469–79. https://doi.org/10.1158/1078-0432.CCR-16-3277.

[20] Chen M-H, Ibrahim JG, Sinha D. A new Bayesian model for survival data with a surviving fraction. J Am Stat Assoc 1999;94:909–19.

[21] Klement RJ, Allgäuer M, Andratschke N, Blanck O, Boda-Heggemann J, Dieckmann K, et al. Bayesian cure rate modeling of local tumor control: evaluation in stereotactic body radiotherapy for pulmonary metastases. Int J Radiat Oncol Biol Phys 2016;94:841–9. https://doi.org/10.1016/j.ijrobp.2015.12.004.

[22] Cooner FC, Banerjee S, Carlin BP, Sinha D. Flexible cure rate modeling under latent activation schemes. J Am Stat Assoc 2007;102:560–72. https://doi.org/10.1198/016214507000000112.

[23] Kruschke J. Doing Bayesian data analysis: a tutorial introduction with R. Academic Press; 2010.

[24] Cameron E. On the estimation of confidence intervals for binomial population proportions in astronomy: the simplicity and superiority of the Bayesian approach. Publ Astron Soc Aust 2011;28:128–39. https://doi.org/10.1071/AS10046.

[25] Stuschke M, Pöttgen C. Altered fractionation in radiotherapy. Front Radiat Ther Oncol 2010;42:150–6. https://doi.org/10.1159/000262470.

[26] Chi A, Wen S, Liao Z, Fowler J, Xu J, Nguyen NP, et al. What would be the most appropriate alpha/beta ratio in the setting of stereotactic body radiation therapy for early stage non-small cell lung cancer. Biomed Res Int 2013;2013:. https://doi.org/10.1155/2013/391021391021.

[27] Liu F, Tai A, Lee P, Biswas T, Ding GX, El Naqa I, et al. Tumor control probability modeling for stereotactic body radiation therapy of early-stage lung cancer using multiple bio-physical models. Radiother Oncol 2016;122:286–94. https://doi.org/10.1016/j.radonc.2016.11.006.

[28] Tai A, Liu F, Gore E, Li XA. An analysis of tumor control probability of stereotactic body radiation therapy for lung cancer with a regrowth model. Phys Med Biol 2016;61:3903–13. https://doi.org/10.1088/0031-9155/61/10/3903.

Please cite this article as: R. J. Klement, J. J. Sonke, M. Allgäuer et al., Estimation of the α/β ratio of non-small cell lung cancer treated with stereotactic body radiotherapyα/β ratio of NSCLC treated with SBRT –>, Radiotherapy and Oncology, https://doi.org/10.1016/j.radonc.2019.07.008