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Angaben zur Veröffentlichung / Publication details:

Klement, Rainer J., Michael Allgäuer, Nicolaus Andratschke, Oliver Blanck, Judit Boda-Heggemann, Karin Dieckmann, Marciana Duma, et al. 2016. "Bayesian cure rate modeling of local tumor control: evaluation in stereotactic body radiation therapy for pulmonary metastases." *International Journal of Radiation Oncology*Biology*Physics* 94 (4): 841–49. https://doi.org/10.1016/j.ijrobp.2015.12.004.

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Bayesian Cure Rate Modeling of Local Tumor Control: Evaluation in Stereotactic Body Radiation Therapy for Pulmonary Metastases

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Supplementary material for this article can be found at www.redjournal.org.

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Summary

We applied 2 Bayesian cure rate models to a sample of 770 patients with pulmonary metastases treated with stereotactic body radiation therapy in order to predict tumor control probability, while accounting for censored observations. Both of the models yielded stable posterior model parameter estimates, indicating their identifiability. In practice, application of such models to the clinical setting could allow for adaption of treatment doses, depending on whether local control should be achieved in the short or longer term.

Purpose: Most radiobiological models for prediction of tumor control probability (TCP) do not account for the fact that many events could remain unobserved because of censoring. We therefore evaluated a set of TCP models that take into account this censoring.

Methods and Materials: We applied 2 fundamental Bayesian cure rate models to a sample of 770 pulmonary metastasis treated with stereotactic body radiation therapy at German, Austrian, and Swiss institutions: (*1*) the model developed by Chen, Ibrahim and Sinha (the CIS99 model); and (*2*) a mixture model similar to the classic model of Berkson and Gage (the BG model). In the CIS99 model the number of clonogens surviving the radiation treatment follows a Poisson distribution, whereas in the BG model only 1 dominant recurrence-competent tissue mass may remain. The dose delivered to the isocenter, tumor size and location, sex, age, and pretreatment chemotherapy were used as covariates for regression.

Results: Mean follow-up time was 15.5 months (range: 0.1-125). Tumor recurrence occurred in 11.6% of the metastases. Delivered dose, female sex, peripheral tumor location and having received no chemotherapy before RT were associated with higher TCP in all models. Parameter estimates of the CIS99 were consistent with the classical Cox proportional hazards model. The dose required to achieve 90% tumor control after 15.5 months was 146 (range: 114-188) Gy_{10} in the CIS99 and 133 (range: 101-164) Gy_{10} in the BG model; however, the BG model predicted lower tumor control at long ($\gtrsim$20 months) follow-up times and gave a suboptimal fit to the data compared to the CIS99 model.

Conclusions: Biologically motivated cure rate models allow adding the time component into TCP modeling without being restricted to the follow-up period which is the case for the Cox model. In practice, application of such models to the clinical setting could allow for adaption of treatment doses depending on whether local control should be achieved in the short or longer term. © 2016 Elsevier Inc. All rights reserved.

Introduction

The challenge in radiation therapy (RT) is optimizing the therapeutic window, which is the difference between the tumor control probability (TCP) and the normal tissue complication probability (NTCP) for a given dose, fractionation schedule, and eventually other covariates. However, a problem with most current modeling of radiation therapy outcomes lies in the ignorance of latency parameters that determine the time course of the events, so that many events could remain unobserved because of censoring. Consequently, current TCP and NTCP models bear the risk of under- and overestimating these probabilities, respectively, when events occur late after the average follow-up period of the study cohort.

Early work accounting for censoring in radiobiological data was made in the 1980s and 1990s, notably by Taylor et al (1, 2), as well as Bentzen and Thames (3), and aimed at the prediction of late NTCPs. These studies utilized phenomenological relations between the covariates and the observed outcomes either in the form of the Cox proportional hazards (CPH) model (1, 2) or a mixture model (3-5) that was based on earlier work by Farewell (6). Contrary to the CPH model, the mixture model naturally allows for the probability of never experiencing the event of interest whereas the probability of experiencing the event at time t is described by a so-called conditional latency distribution $F(t)$ ("conditional" because it depends on the probability that a subject is in the population that will experience the event at some point in the future). Another mixture model was later applied by Tucker et al as a modification of the Lyman NTCP model for predicting radiation pneumonitis risk among 576 non-small cell lung cancer patients (7).

Such mixture models belong to a broader class of cure rate models that theoretically should provide a more

realistic description of outcomes after RT than the CPH model since the latter can give the implausible result that the outcome of interest will always occur at a certain time if the last patient surviving experiences the event at that time. However, similar to the CPH model, the mixture models used in the studies described above are purely phenomenological and lack a straightforward biological interpretation. A variety of mechanistic cancer cure rate models has been developed more recently. These incorporate mathematical descriptions that link the putative latent biological processes responsible for the event of interest to the observed data. However, to the best of our knowledge, no study has yet attempted to use these models for radiobiological outcome data.

In addition, all the previous modeling studies described above were done using frequentist techniques such as maximum likelihood estimation. There are several drawbacks associated with the frequentist paradigm when analyzing outcome data of cancer patients such as: (*1*) Uncertainty estimates of model parameters often rely on asymptotic arguments that might be hard to derive or do not necessarily hold; (*2*) there is no straightforward and intuitive way to compare models, especially when models are non-nested; (*3*) there is no natural way to use prior information from already conducted clinical trials to incorporate in modeling new data. The Bayesian paradigm offers natural solutions to these problems (8).

In this work we applied and compared 2 fundamental mechanistic cure rate models using a large dataset of pulmonary metastases treated with SBRT. The models we adopt are the Bayesian cure rate model developed by Chen, Ibrahim and Sinha (9), subsequently named the "CIS99 model", and a mixture model similar to the classical model developed by Berkson and Gage (BG model) in 1952 (10). These models were chosen because most cure rate models in the literature are modifications of one of them. Along these lines we also conducted a classical frequentist analysis using the CPH model since it is the most popular model for fitting censored time-to-event data (11).

Methods and Materials

Patients

This analysis is based on a retrospective multi-institutional database of SBRT for lung metastases (12). 715 Patients were treated for a total of 964 lesions at 23 German, Austrian and Swiss institutions, mostly academic centers, between 1998 and 2011. This analysis was approved by the Ethics committee of the University Hospital Heidelberg (S-280/2014).

In the current study we included only patients with complete information on physical treatment planning parameters, resulting in 580 patients with a total of 770 lesions.

Tumor control probability

While TCP is usually defined as the probability that no clonogenic cells survive the treatment we are here interested in the clinically more relevant probability that no detectable tumor regrowth occurs until a given time, denoted by TCP*. TCP* depends both on the number of clonogens left intact after RT (which itself can depend on the RT schedule and other covariates) as well as the time that it takes for any remaining clonogen to grow into a clinically detectable tumor. The CIS99 and BG model describe these latent processes differently.

CIS99 model

Let n denote the number of metastases in our sample and, for the ith metastasis, let t_i denote the time of last follow-up and v_i the censoring indicator taking the value 1 if t_i is a failure time and 0 if it is right censored. N_i will refer to the number of clonogenic cancer cells left after RT treatment of metastasis i. The N_i clonogens are assumed to follow a Poisson distribution with mean θ_i that depends on the covariates through $\theta_i \equiv \theta_i(\beta_0 + \mathbf{x}_i^T\boldsymbol{\beta}) = \exp(\beta_0 + \mathbf{x}_i^T\boldsymbol{\beta})$, where $\mathbf{x}_i^T = (x_{i1}, \ldots, x_{ip})$ is the vector of the p covariates for the ith metastasis ($i = 1,\ldots,n$) and $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_p)^T$ the corresponding vector of regression coefficients. θ is called the cure parameter since it determines the expected number of clonogens remaining after treatment and thus the probability of "curing" the patient. Let Z_{ij} denote the random time for the jth clonogen to produce a detectable tumor and thus cause relapse of the ith metastasis, $i = 1,\ldots n$, $j = 0,\ldots,N_i$ and $P(Z_{i0} = \infty) = 1$ (so that for $j = 0$ the patient is cured from the tumor). These latent failure times Z_{ij} can then be linked to the observed failure time T_i of metastasis i if we define T_i by the random variable $T_i = \min\{Z_{ij},\ 0 \le j \le N_i\}$. Assuming the Z_{ij} are independent and identically distributed with a common distribution function $F(t) = 1 - S(t)$ that does not depend on the number of clonogens N_i we can write down TCP* for metastasis i as

$$\begin{aligned} TCP_i^*(t) &= P(\textit{no new detectable tumor by time } t) \\ &= P(N_i = 0) + P(Z_{i1} > t, \ldots, Z_{iN_i} > t, N_i \ge 1) \end{aligned} \quad (1)$$

Using $P(N|\theta) = \frac{\theta^N}{N!}\exp(-\theta)$ and $\theta = \theta(\mathbf{x})$ one can evaluate this expression further to obtain

$$\begin{aligned} TCP_i^*(t, \mathbf{x}) &= \exp(-\theta) + \sum_{k=1}^{\infty} S(t)^k \frac{\theta^k}{k!}\exp(-\theta) \\ &= \exp(-\theta + \theta S(t)) = \exp(-\theta(1 - S(t))) \end{aligned} \quad (2)$$

Equation (2) expresses TCP^* as a function of both the follow-up time, entering through the latent survival function $S(t)$, and the covariates $\mathbf{x}$, entering through regression on the cure parameter $\theta(\mathbf{x})$. We model $S(t)$ as a Weibull distribution with parameters ρ and η, so that $S(t) = \exp(-t^\rho e^\eta)$ (13). From Eq 2, it also follows that $TCP^*(\infty, \mathbf{x}) \equiv P(N = 0) = \exp(-\theta(\mathbf{x}))$ which is called the cure rate (8), corresponds to the classical definition of TCP

as the probability that no clonogenic cells survive the treatment and in practice is given by the fraction of metastases that never will regrow after very long follow-up.

BG model

The BG model differs from the CIS99 model in that it assumes that there is only 1 latent dominant event, eg, 1 dominant relapse-competent tissue mass, so that N_i is modeled through a Bernoulli distribution depending on θ which is the probability of activation so that the cure rate is given as $1-\theta$. Furthermore, regression is now performed on η, the Weibull scale parameter, whereas θ is a random variable specified by a uniform prior on (0,1). Thus this model is similar to the original mixture model of Berkson & Gage (10), only differing in the use of a Weibull instead of an exponential survival distribution. It differs from the older studies of Bentzen et al (3, 5) and Taylor et al (1, 2) in which logistic regression was performed on θ. Regressing on η, however, ensures that the model is identifiable and yields proper posteriors even with improper priors with an appropriate link (13). We specify the link through $\eta(\mathbf{x})=\beta_0+\mathbf{x}_i^T\boldsymbol{\beta}$. The probability of no relapse at time t is given as the sum of the probability that a patient is "cured" ($N_i=0$) and the probability that a relapse-competent tissue mass remained but has not yet developed into a new detectable tumor:

$$\begin{aligned} TCP_i^*(t,\mathbf{x}) &= P(\textit{no new detectable tumor by time } t) \\ &= P(N_i=0)+P(Z_{i1}>t, N_i=1) \\ &= 1-\theta+S(t)\theta = 1-\theta(1-S(t)) \end{aligned} \quad (3)$$

Note that the dependence on the covariates now is in the latent survival function through $\eta(\mathbf{x})$.

Estimation of model parameters

We use a Bayesian framework to estimate the set of model parameters given as $\Omega=\{(\theta_i(\boldsymbol{\beta}))_{i=1,\ldots,n},\rho,\eta\}$ in case of the CIS99 model or $\Omega=\{\theta,\rho,(\eta_i(\boldsymbol{\beta}))_{i=1,\ldots,n}\}$ in case of the mixture model, respectively. Briefly, Bayesian parameter estimation involves computing the joint posterior probability density function of all model parameters given the observed data. This is accomplished via Bayes theorem which states that

$$P(\Omega|D)\propto P(D|\Omega)\times P(\Omega) \quad (4)$$

where the observed data have been collected into $D=\{(t_i,\upsilon_i,\mathbf{x}_i)_{i=1,\ldots,n}\}$, with t_i denoting the time of last follow-up, υ_i the censoring indicator and $\mathbf{x}_i$ the vector of covariates, and $P(\Omega)$ is the joint prior probability density of the model parameters. $P(D|\Omega)$ is the likelihood function of the observed data that has been made independent of the latent data N_i through marginalization (13, 14). Following Cooner et al (13), an expression for $P(D|\Omega)$ is given by

$$P(D|\Omega)=\prod_{i=1}^{n}\left[-\frac{d}{dt_i}\log S(t_i)\right]^{\upsilon_i} TCP_i^*(t_i) \quad (5)$$

Specifying a prior probability density for the model parameters and using expression (5) for the data likelihood we are able to draw samples from the posterior density $P(\Omega|D)$ using Markov Chain Monte Carlo (MCMC) methods. To build a model we use uninformative priors for the model parameters. A full description of the priors and MCMC procedure is provided in the supplementary material.

Covariate selection

The dose calculating algorithm varied between institutions and over time (unknown for 13%; pencil beam for 36%; CCC for 31%; AAA for 15%; and MC for 5% of patients). Therefore the isocenter dose was used for modelling because it is approximately the maximum planning target volume dose which has been shown to vary the least between different dose calculation algorithms compared to other dose statistics such as mean and minimum doses (15). Doses were converted to biologically effective doses at the isocenter (BEDiso) using an α/β ratio of 10 Gy. The BEDiso has been shown to correlate better with TCP than the dose surrounding the planning target volume (16). Any potential differences that might exist between metastases of different primary sites were neglected based on our previous work showing no significant differences in their radio-sensitivity (17). Further treatment and patient-specific covariates were considered for modeling if they were known for a minimum of 80% of patients (Table 1); the missing values were estimated using multiple imputation by chained equations with the R package mice (18) (see Supplementary Material; available online at www.redjournal.org). Before entering the model, binary covariates were rescaled to ± 0.5 and continuous covariates were standardized to have mean 0 and standard deviation 0.5 (19).

Model comparison

Model comparison was based on the logarithm of the pseudomarginal likelihood (LPML) measurement which is a numerically stable cross-validated leave-1-out measurement of model fit and suitable for comparison of Bayesian survival models (8). LPML is based on the conditional predictive ordinate (CPO) statistic which, for the *i*th metastasis, is given as the survival probability density for this metastasis' observed failure or censoring time, respectively, given all the other observations with metastasis i removed. The individual CPO values, and thus the LPML measurement, can be approximated from the Markov chain output, and greater values indicate a better model fit. Calculation details are provided in the supplementary material.

Results

Treatment details of this cohort are given in Table 1. Median and mean follow-up time was 11.3 and 15.5 months,

Table 1 Treatment characteristics of the 770 metastases

Characteristic	Number	Mean	Median (range)
Age (y)	770	64	67 (6.4-100)
Baseline Karnofsky index	606		90 (40-100)
Sex (total males and females)	770		
Males	479		
Females	291		
Maximum tumor diameter (cm)	680	2.3	2.0 (0.4-9.4)
Tumor location	660		
Peripheral	538		
Central	122		
Follow-up time (months)	770	15.5	11.3 (0.1-125)
Local control	770		
Yes	681		
No	89		
Number of fractions	770		3 (1-14)
Prescribed dose (Gy) per fraction	770	15.1	12.5 (3-33)
Maximum (isocenter) dose (Gy) per fraction	770	20.1	19.2 (3.2-42.0)
BED at PTV periphery (Gy_{10})	770	88.3	84.4 (22.5-180)
BED at isocenter (BED_{ISO}) (Gy_{10})	770	143	138 (24.3-309)
Dose inhomogeneity (PTV minimum/maximum dose) (%)	770		80 (55-105)
Chemotherapy prior to SBRT	703		
Yes	352		
No	351		

Abbreviations: BED = biologically effective dose; BED_{ISO} = biologically effective doses at the isocenter; PTV = planning target volume; SBRT = stereotactic body radiation therapy.

respectively (range: 0.1-125 months). A large range of irradiation doses and fractionations was used. Most treatments were planned with inhomogeneous dose distributions: planning target volume encompassing doses were most frequently 80% (median: 33.8%) and 60% (median: 20.1%) of the maximum dose. Details for this cohort are available elsewhere (17).

A summary of the posterior estimates for the model parameters is given in Table 2. BED_{ISO} was the most influential predictor of TCP in all models, followed by sex and chemotherapy prior to SBRT: female sex, peripheral tumor location, and having received no chemotherapy before RT were associated with improved prognosis. Survival curves and model fits for males and females are shown in Figure E1 (available online at www.redjournal.org). Interestingly, tumor size had a negligible influence on TCP. The regression coefficients and their standard deviations in the CIS99 model closely mirrored those of a frequentist CPH model (Table 2). Accordingly, the fitted curves of the CIS99 and the CPH model were very similar (Fig. E1; available online at www.redjournal.org).

Figure 1 shows a Kapan-Meier plot for all treated metastases. The red solid and blue solid lines show the predictions of the CIS99 and BG model, respectively; the 95% highest posterior density (HPD) intervals are indicated by dashed and dashed-dotted lines, respectively (Fig. 1). The prediction for the dose required to achieve 90% tumor control (TCD90), after 15.5 months, the mean follow-up times of our sample were 146^{+42}_{-34} Gy_{10} (CIS99) and 133^{+31}_{-31} Gy_{10} (BG model). As evident from Figure 1, the models started to differ from approximately 20 months follow-up. This difference is expressed in a lower cure rate predicted by the BG model (48^{+15}_{-16}% vs 63^{+11}_{-12}% in the CIS99 model); it also becomes apparent from Figure 2A which is a 3-dimensional perspective of TCP depending on follow-up time and dose. An enlarged view (Fig. 2B) from a different perspective confirms the similarity of both models for short follow-up times. Tables 3 and 4 provide some quantitative TCP estimates for both models; note that the uncertainties on these estimates increase for low doses and long follow-up times, reflecting the scarcity of data points in these ranges.

Table 2 Posterior model parameter estimates for the CIS99 and BG model and frequentist estimates for a Cox proportional hazards model with their *P* values derived from likelihood ratio tests

Variable	CIS99 model			BG model			Cox PH model		
	Mean	SD	95% HPD interval	Mean	SD	95% HPD interval	Mean	SE	*P* value
β_0 (Intercept)	−0.94	0.25	(−1.38 to −0.50)	−5.85	0.44	(−6.74 to −5.01)			
β_1 (BED_{iso})	−0.88	0.26	(−1.40 to −0.36)	−1.10	0.31	(−1.69 to −0.48)	−0.87	0.26	.0008
β_2 (tumor diameter)	−0.05	0.24	(−0.42 to 0.51)	0.07	0.23	(−0.39 to 0.50)	0.05	0.24	.83
β_3 (peripheral/central tumor)	0.49	0.27	(−0.04 to 1.00)	0.28	0.35	(−0.39 to 0.96)	0.50	0.27	.06
β_4 (no chemo/chemo prior to RT)	0.46	0.23	(0.01 to 0.93)	0.68	0.29	(0.12 to 1.24)	0.45	0.24	.05
β_5 (female/male)	0.61	0.25	(0.13 to 1.09)	0.70	0.30	(0.11 to 1.29)	0.59	0.24	.02
β_6 (Age)	−0.11	0.24	(−0.60 to 0.35)	−0.34	0.26	(−0.86 to 0.17)	−0.12	0.24	.61
θ				0.52	0.08	(0.37-0.68)			
η	−5.77	0.43	(−6.60 to −4.86)						
ρ	1.66	0.15	(1.36-1.98)	1.52	0.15	(1.25-1.82)			

Abbreviations: BED_{iso} = biologically effective doses at the isocenter; BG = Berkson and Gage (model); CIS99 = Chen, Ibrahim, and Sinha (model); HPD = highest posterior density; SD = standard deviation; SE = standard error; PH = proportional hazards.

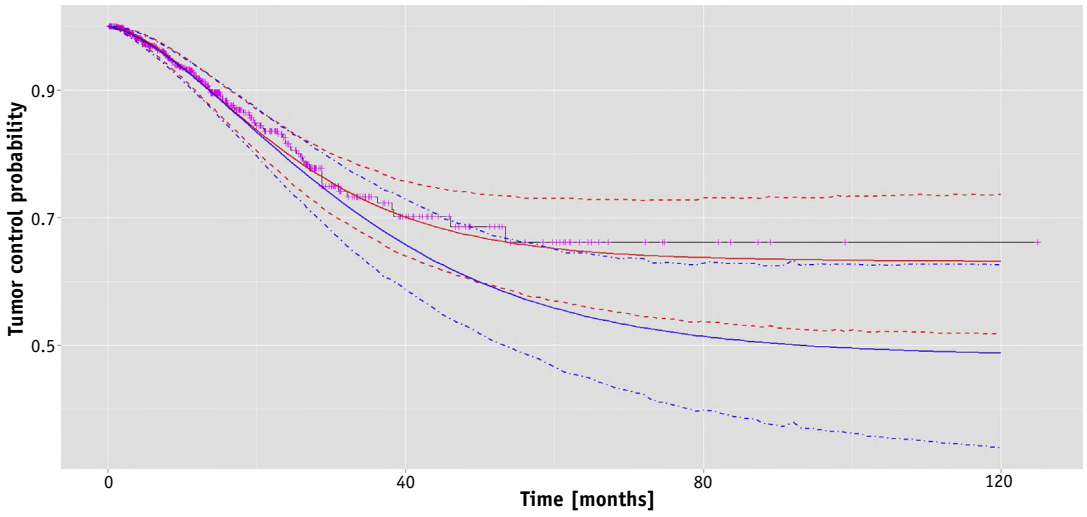

Fig. 1. Kaplan-Meier plot of metastases data (solid line = censored observation indicated by a magenta point) and predictions of the CIS99 model (red solid line) and BG model (blue solid line) together with their 95% HPD intervals (dashed and dash-dotted lines, respectively). *Abbreviations:* BG = Berkson and Gage (model); CIS99 = Chen, Ibrahim and Sinha (model); HPD = highest posterior density. A color version of this figure is available at www.redjournal.org.

Consistent with the visual impression from Figure 1, the CIS99 model provided a better overall fit to the data as judged by the LPML measurement (LPML = −507.3 *versus* −509.4). The cure rate in the CIS99 model as a function of delivered dose is shown in Figure E2 (available online at www.redjournal.org). To achieve a 90% probability of cure, the model predicts that doses exceeding 278 Gy_{10} would have to be applied.

Discussion

Due to rapid technological progress, SBRT achieves high local control rates with concurrently low toxicity rates. Consequently, many patients are expected to live long enough to be considered "cured" from their tumor. An obstacle for modeling TCP outcomes for such patients lies in the uncertainty associated with short follow-up times; cure rate models specifically aim at taking into account such uncertainty and provide a way to make predictions of TCP beyond the follow-up period. Unfortunately their usage within radiation oncology has so far been restricted to a few papers mainly concerned with predicting NTCP. An application to the prediction of TCP, after SBRT for lung tumors in particular, has not yet been reported.

Here we focused on 2 fundamental cure rate models that incorporate biological mechanisms of failure through mathematical distributions, specifying the number of latent factors remaining after radiation therapy and different scenarios in which a specific number of these factors are activated and cause relapse (13). The BG model, which has a form similar to that of the mixture model proposed by Berkson and Gage in 1952 (10), assumes that there is a certain probability of cure after SBRT; otherwise 1 latent factor remains whose progression toward a clinically detectable tumor depends on the dose that has been delivered during treatment. The CIS99 model, on the other hand, assumes that the number of latent factors is equal to the number of surviving clonogens which follows a Poisson distribution with parameter depending on the dose delivered during treatment.

The Poisson assumption has a long tradition in radiobiological modeling. From in silico experiments Tucker et al (20) have inferred that this assumption might underestimate the tumor control probability by as much as 15% in protracted fractionation schedules in which significant interfraction tumor cell repopulation occurs, although the cell division probability applied in these experiments has been criticized as unrealistically high (21). Furthermore, Poisson statistics should be appropriate whenever a small number of fractions with large single doses such as in SBRT is applied (20).

As the CIS99 model provided a better fit to the data than the BG model, we concluded that the Poisson assumption describes the actual reality better than a Bernoulli distribution. However, a variety of biologically motivated models exist that have not been tested here, but may describe the data even better. Furthermore, cure rate models not necessarily have to yield improvements over more simplistic ones. Taylor and Kim for example showed that the preference for a mixture cure rate or the Cox proportional hazards model depended on the goal of the inference and the specificities of the dataset such as follow-up times, number of censored observations and latency times for the event (2). In our case, the CIS99 and the classical CPH model were found to be equivalent in their ability to identify prognostic covariates and describe the survival curve. This is not surprising given that the survival function of the CIS99 model (Eq 2) yields a proportional hazards structure $h^*(t,\boldsymbol{x}) = \theta(\boldsymbol{x})f(t)$ (8), so that the covariates enter

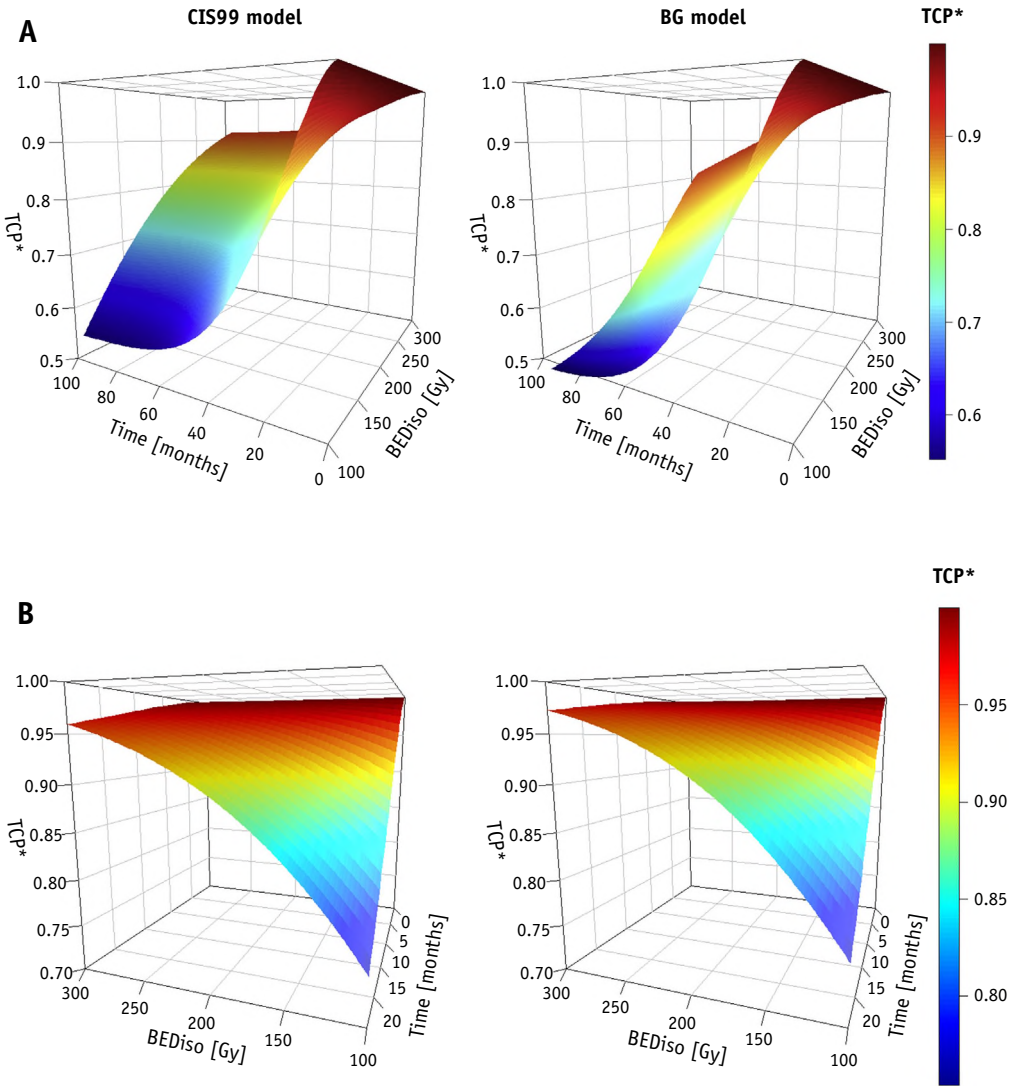

Fig. 2. (A) Illustration of the dependency of tumor control probability from follow-up time and dose. To illustrate the dose dependency, all other covariates were set to their mean (continuous variables) or midpoint (binary variables) values, respectively. Note that for doses between 150 and 200 Gy_{10}, the BG model predicts lower TCP for long follow-up times than the CIS99 model (see also Fig. 1 and Tables 3 and 4). (B) Enlargement of panel A from a different perspective. Note the similarity of both models within 24 months' follow-up time. *Abbreviations:* BED_{iso} = biologically effective doses at the isocenter; BG = Berkson and Gage model; CIS99 = Chen, Ibrahim and Sinha; TCP = tumor control probability.

in the same functional form as in the CPH model (except for the intercept term). However, the survival function of the classical CPH model is not specified and has to be approximated using secondary estimators (11), is discrete and only changes at the failure times. This makes this model less flexible and unable to make predictions beyond the last follow-up time. For example, let us assume that the 1 metastasis from the plateau of the survival curve, which has received the smallest amount of dose, would not have been censored but recurred at a hypothetical next follow-up visit at 126 months so that the last observation is now a "failure." In such a scenario, the CIS99 and BG models still give meaningful predictions of cure probability beyond the last follow-up point (49% and 24%, respectively), whereas in the CPH model TCP at the last follow-up time drops to a value that depends on the approximation used (0% with Kalbfleisch-Prentice or 45% with Breslow approximation [Fig. E3; available online at www.redjournal.org]).

On the other hand, removing the plateau in our data by deleting the last 20 observation times decreased the cure rate estimate of the CIS99 model from 63% (range: 51%-74%) to 35% (range: 0%-67%) and that of the BG model from 48% (range: 32%-63%) to 31% (range: 9%-51%) but did not significantly change model estimates concerning much shorter time periods such as the TCD90 estimate at 15.5 months (Fig. E4; available online at www.redjournal.org). This is consistent with the findings of Taylor and Kim (2), showing that long follow-up observations are essential in order to derive reliable cure rate estimates. However, the Bayesian paradigm would naturally allow

Table 3 TCP predictions (in %) for the CIS99 model*

Time (months)	BED_{iso} (Gy)						
	100	120	140	160	180	200	220
3	$98.7^{+0.7}_{-0.8}$	$98.9^{+0.6}_{-0.6}$	$99.1^{+0.5}_{-0.5}$	$99.3^{+0.4}_{-0.5}$	$99.4^{+0.4}_{-0.4}$	$99.5^{+0.3}_{-0.4}$	$99.6^{+0.3}_{-0.4}$
6	$96.2^{+1.5}_{-1.7}$	$96.8^{+1.3}_{-1.3}$	$97.4^{+1.1}_{-1.0}$	$97.8^{+1.0}_{-1.0}$	$98.2^{+0.9}_{-1.0}$	$98.5^{+0.8}_{-0.9}$	$98.7^{+0.8}_{-0.9}$
9	$92.9^{+2.4}_{-2.5}$	$94.1^{+1.9}_{-1.9}$	$95.1^{+1.6}_{-1.7}$	$96.0^{+1.5}_{-1.6}$	$96.6^{+1.5}_{-1.6}$	$97.2^{+1.5}_{-1.6}$	$97.7^{+1.4}_{-1.5}$
15	$85.4^{+4.0}_{-4.1}$	$87.8^{+3.1}_{-3.2}$	$89.9^{+2.9}_{-2.9}$	$91.6^{+2.8}_{-2.9}$	$92.9^{+2.9}_{-3.0}$	$94.1^{+2.9}_{-3.0}$	$95.0^{+2.8}_{-3.1}$
21	$78.1^{+5.5}_{-5.8}$	$81.6^{+4.4}_{-4.5}$	$84.6^{+4.1}_{-4.2}$	$87.1^{+4.2}_{-4.3}$	$89.2^{+4.3}_{-4.4}$	$90.9^{+4.2}_{-4.7}$	$92.3^{+4.2}_{-4.8}$
30	$69.2^{+7.4}_{-7.3}$	$73.9^{+5.8}_{-6.1}$	$77.9^{+5.7}_{-5.7}$	$81.4^{+5.7}_{-6.1}$	$84.3^{+6.1}_{-6.2}$	$86.8^{+6.1}_{-6.6}$	$88.8^{+6.1}_{-6.7}$
40	$62.8^{+8.7}_{-8.6}$	$68.2^{+7.1}_{-7.2}$	$73.0^{+6.0}_{-7.0}$	$77.1^{+7.1}_{-7.3}$	$80.6^{+7.3}_{-7.7}$	$83.6^{+7.5}_{-8.0}$	$86.1^{+7.5}_{-8.3}$
60	$57.1^{+10.7}_{-10.8}$	$63.1^{+9.3}_{-9.4}$	$68.4^{+8.7}_{-9.1}$	$73.1^{+8.8}_{-9.2}$	$77.1^{+9.1}_{-9.5}$	$80.6^{+9.3}_{-9.6}$	$83.5^{+8.8}_{-10.1}$

Abbreviations: BED_{iso} = biologically effective doses at the isocenter; CIS99 = Chen, Ibrahim and Sinha model; TCP = tumor control probability.
* To illustrate dose dependency, all other covariates were set to their mean (continuous variables) or midpoint (binary variables) values, respectively.

incorporating prior knowledge from other datasets that could improve the cure rate estimates in such situations (Fig. E4; available online at www.redjournal.org); this is not the case for frequentist analysis (8).

A major limitation of cure rate models is their identifiability (ie, whether or not the fitted model parameters are unique in describing the observed data) (22, 23). A model is nonidentifiable if the model output is the same for 2 or more distinct sets of model parameters. In the context of cure models it would thus not be possible to distinguish a high incidence of tumor recurrence and a long tail of the latency distribution that delays this recurrence from a low incidence of recurrence and a short tail of the latency distribution. As a rough check for the identifiability of a cure rate model the Kaplan-Meier plot should have a clear horizontal plateau at long follow-up (2). Identifiability problems can also arise with Bayesian analyses when the choice of parameter priors yields improper posteriors. However, the analytical form of the regression link function in our models has been shown to yield identifiable model parameters even with improper priors (13). Furthermore, although nonidentifiability would be detectable through instable parameter estimates, the MCMC error of our parameter estimates indicated good convergence, and a sensitivity analysis using widely dispersed initial parameter values yielded very similar posterior estimates.

Our analysis revealed some insights into the possible mechanisms of failure. Chemotherapy prior to RT was significantly associated with higher probability of failure, which within the context of the CIS99 model would mean that chemotherapy increases the number of clonogenic cells surviving radiation. A plausible mechanism is a chemotherapy-mediated adaptation to oxidative stress and improved DNA repair capacity (24). The fact that males had a higher probability of relapse than females could be related to some life style factors such as smoking. Unfortunately, smoking status was not assessed in the database.

As expected, dose was the strongest predictor of tumor control. The isocenter dose was used because it was the best estimate available for the dose actually delivered to the tumor given the various dose calculation algorithms that were used across institutions and years. In Table 1 in the study by Haedinger et al (15), it can be seen that the maximum dose to the gross tumor volume, which is approximately the isocenter dose, changed nonsignificantly by, on average, −3.7% (±4.7%) when pencil beam plans were recalculated using a collapsed cone algorithm. We checked the impact of such effects on our results by decreasing all physical isocenter doses that were derived from pencil beam-calculated plans before calculating BED_{ISO}. The amount of reduction was a random number following a normal distribution with mean and SD of −3.7% and 4.7%, respectively, of the isocenter dose. This had no

Table 4 TCP predictions (in %) for the BG model*

Time (months)	BED_{iso} (Gy)						
	100	120	140	160	180	200	220
3	$98.6^{+0.7}_{-0.9}$	$98.9^{+0.6}_{-0.7}$	$99.1^{+0.5}_{-0.6}$	$99.3^{+0.4}_{-0.5}$	$99.5^{+0.4}_{-0.4}$	$99.6^{+0.3}_{-0.4}$	$99.7^{+0.3}_{-0.3}$
6	$96.2^{+1.6}_{-1.8}$	$97.0^{+1.3}_{-1.3}$	$97.6^{+1.0}_{-1.1}$	$98.1^{+1.0}_{-1.0}$	$98.5^{+0.8}_{-0.9}$	$98.8^{+0.7}_{-0.9}$	$99.0^{+0.6}_{-0.8}$
9	$93.2^{+2.3}_{-2.6}$	$94.6^{+1.8}_{-2.0}$	$95.7^{+1.5}_{-1.7}$	$96.6^{+1.5}_{-1.5}$	$97.3^{+1.3}_{-1.5}$	$97.8^{+1.2}_{-1.5}$	$98.3^{+1.1}_{-1.4}$
15	$86.4^{+3.8}_{-4.2}$	$89.1^{+2.9}_{-3.3}$	$91.2^{+2.6}_{-2.8}$	$93.0^{+2.5}_{-2.8}$	$94.3^{+2.5}_{-2.9}$	$95.4^{+2.5}_{-2.7}$	$96.3^{+2.3}_{-2.7}$
21	$79.6^{+5.2}_{-5.7}$	$83.1^{+4.2}_{-4.4}$	$86.2^{+4.0}_{-3.8}$	$88.8^{+3.7}_{-4.2}$	$90.9^{+3.8}_{-4.2}$	$92.6^{+3.7}_{-4.3}$	$94.0^{+3.6}_{-4.2}$
30	$70.3^{+6.8}_{-7.4}$	$74.7^{+6.0}_{-5.9}$	$78.7^{+5.5}_{-5.7}$	$82.3^{+5.6}_{-6.0}$	$85.4^{+5.7}_{-6.4}$	$88.0^{+5.9}_{-6.5}$	$90.2^{+5.9}_{-6.5}$
40	$62.3^{+8.0}_{-8.6}$	$66.7^{+6.9}_{-7.7}$	$71.2^{+7.0}_{-7.2}$	$75.5^{+7.4}_{-7.5}$	$79.4^{+7.8}_{-8.3}$	$82.8^{+8.1}_{-8.7}$	$85.8^{+8.0}_{-9.1}$
60	$53.5^{+10.3}_{-10.7}$	$56.6^{+9.1}_{-9.3}$	$60.3^{+8.4}_{-8.9}$	$64.6^{+9.0}_{-9.2}$	$68.9^{+10.3}_{-10.1}$	$73.2^{+11.4}_{-11.1}$	$77.2^{+11.4}_{-12.6}$

Abbreviations: BED_{iso} = biologically effective doses at the isocenter; BG = Berkson and Gage (model); TCP = tumor control probability.
* Compare to Table 3.

impact on either the model parameter estimates (mean posterior values remaining the same) or the TCD90 estimates (only the 95% highest posterior density interval changing slightly). Thus, we conclude that, even if the pencil beam plans had overestimated the physical doses delivered to the isocenter, the expected impact on our results would be negligible. Nevertheless, our analysis might be limited by the treatment planning and delivery uncertainties associated with 235 (31%) single fraction treatments. For these one would also expect a higher radioresistance due to missing interfractional re-oxygenation of hypoxic areas that provide niches for stem cells (25). The flattening of the dose-response curve and the very high dose of 278 Gy_{10} needed to achieve 90% TCP in the CIS99 model (Fig. E2; available online at www.redjournal.org) suggests that in approximately 10% or more of the lesions, viable clonogens remain despite extremely high doses and may be a consequence of this effect. Consistently, single-fraction SBRT seems to fail in approximately 20% of patients irrespective of applied doses (16). The prognostic significance of BED_{ISO} for TCP in our sample indicates, however, that sufficient re-oxygenation occurs with 3 and more fractions, independent of tumor size for which no influence was detected.

Conclusions

From a clinical perspective, there are broad applications for the modelling methods and results of this study. Treatment of metastatic disease may serve multiple different purposes in clinical practice and irradiation doses could be adapted accordingly. In oligometastatic patients, cure is the goal of the treatment and irradiation doses need to be selected in order to achieve long-term local tumor control. However, long-term progression-free survival and overall survival are achieved in only a few patients, and less aggressive and potentially less toxic irradiation doses could be selected in patients with very high risk for systemic progression (26). In contrast, SBRT in the oligo-progression situation, progression of a few de-differentiated metastases during otherwise effective systemic treatment, may serve a different purpose. Systemic progression will develop in most patients within a short time of 6 to 12 months due to further development of resistance (27, 28). Consequently, irradiation doses could be adapted and reduced for short- or intermediate-term local tumor control.

References

1. Taylor JM, Withers HR, Vegesna V, et al. Fitting the linear-quadratic model using time of occurrence as the end-point for quantal response multifraction experiments. *Int J Radiat Biol* 1987;52:459-468.
2. Taylor JM, Kim DK. Statistical models for analysing time-to-occurrence data in radiobiology and radiation oncology. *Int J Radiat Biol* 1993;64:627-640.
3. Bentzen SM, Thames HD, Travis EL, et al. Direct estimation of latent time for radiation injury in late-responding normal tissues: Gut, lung, and spinal cord. *Int J Radiat Biol* 1989;55:27-43.
4. Schultheiss TE, Thames HD, Peters LJ, et al. Effect of latency on calculated complication rates. *Int J Radiat Oncol Biol Phys* 1986;12:1861-1865.
5. Bentzen SM, Thames HD, Overgaard M. Latent-time estimation for late cutaneous and subcutaneous radiation reactions in a single-follow-up clinical study. *Radiother Oncol* 1989;15:267-274.
6. Farewell VT. A model for a binary variable with time-censored observations. *Biometrika* 1977;64:43-46.
7. Tucker SL, Liu HH, Liao Z, et al. Analysis of radiation pneumonitis risk using a generalized Lyman model. *Int J Radiat Oncol Biol Phys* 2008;72:568-574.
8. Ibrahim JG, Chen MH, Sinha D. Bayesian Survival Analysis. New York: Springer; 2001.
9. Chen MH, Ibrahim JG, Sinha D. A new Bayesian model for survival data with a surviving fraction. *J Am Stat Assoc* 1999;94:909-919.
10. Berkson J, Gage RP. Survival curve for cancer patients following treatment. *J Am Stat Assoc* 1952;47:501-515.
11. Harrell FE Jr. Regression Modeling Strategies. 2nd ed. New York: Springer; 2015.
12. Sterzing F, Streblow J, Scherer K, et al. SBRT for lung metastases: A pooled analysis of 651 patients and 868 lesions of the German Working Group Stereotactic Radiotherapy. *Int J Radiat Oncol Biol Phys* 2014;90:S31.
13. Cooner FC, Banerjee S, Carlin BP, et al. Flexible cure rate modeling under latent activation schemes. *J Am Stat Assoc* 2007;102:560-572.
14. Chen MH, Harrington DP, Ibrahim JG. Bayesian cure rate models for malignant melanoma: A case-study of Eastern Cooperative Oncology Group trial E1690. *Appl Stat* 2002;51:135-150.
15. Haedinger U, Krieger T, Flentje M, et al. Influence of calculation model on dose distribution in stereotactic radiotherapy for pulmonary targets. *Int J Radiat Oncol Biol Phys* 2005;61:239-249.
16. Guckenberger M, Klement RJ, Allgäuer M, 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.
17. Guckenberger M, Klement RJ, Allgäuer M, et al. Local tumor control probability modeling of primary and secondary lung tumors in stereotactic body radiotherapy [published online September 15, 2015]. *Radiother Oncol* http://dx.doi.org/10.1016/j.radonc.2015.09.008.
18. Van Buuren S, Groothuis-Oudshoorn K. Mice: Multivariate imputation by chained equations in R. *J Stat Softw* 2011;45:1-67.
19. Gelman A. Scaling regression inputs by dividing by two standard deviations. *Stat Med* 2008;27:2865-2873.
20. Tucker SL, Thames HD, Taylor JM. How well is the probability of tumor cure after fractionated irradiation described by Poisson statistics? *Radiat Res* 1990;124:273-282.
21. Hoang T, Tsodikov A, Asselain B, et al. A parametric analysis of tumor recurrence data. *J Biol Syst* 1996;4:391-403.
22. Li CS, Taylor JM, Sy JP. Identifiability of cure models. *Stat Probab Lett* 2001;54:389-395.
23. Hanin L, Huang LS. Identifiability of cure models revisited. *J Multivar Anal* 2014;130:261-274.
24. Landriscina M, Maddalena F, Laudiero G, et al. Adaptation to oxidative stress, chemoresistance, and cell survival. *Antioxid Redox Signal* 2009;11:2701-2716.
25. Keith B, Simon MC. Hypoxia-inducible factors, stem cells, and cancer. *Cell* 2007;129:465-472.
26. Milano MT, Katz AW, Zhang H, et al. Oligometastases treated with stereotactic body radiotherapy: Long-term follow-up of prospective study. *Int J Radiat Oncol Biol Phys* 2012;83:878-886.
27. Weickhardt AJ, Scheier B, Burke JM, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small cell lung cancer. *J Thorac Oncol* 2012;7:1807-1814.
28. Iyengar P, Kavanagh BD, Wardak Z, et al. Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. *J Clin Oncol* 2014;32:3824-3830.