Radiotherapy and Oncology 132 (2019) 142–147

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Modeling radiation pneumonitis of pulmonary stereotactic body radiotherapy: The impact of a local dose–effect relationship for lung perfusion loss

Jothybasu Selvaraj [a,1], Joos Lebesque [a,1], Andrew Hope [b], Matthias Guckenberger [c,d], Maria Werner-Wasik [e], Heike Peulen [a], Meredith Giuliani [b], Frederick Mantel [c], José Belderbos [a], Inga Grills [f], Jan-Jakob Sonke [a,*]

[a] Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [b] Department of Radiation Oncology, University of Toronto and Princess Margaret Cancer Center, Canada; [c] Department of Radiation Oncology, University of Wuerzburg, Germany; [d] Department of Radiation Oncology, University Hospital Zurich, University of Zurich, Switzerland; [e] Department of Radiation Oncology, Thomas Jefferson University Hospital, Philadelphia; and [f] Department of Radiation Oncology Beaumont Hospital, Royal Oak, USA

ARTICLE INFO

Article history:
Received 29 May 2018
Received in revised form 6 November 2018
Accepted 16 December 2018
Available online 9 January 2019

Keywords:
SBRT
NTCP
Radiation pneumonitis
Perfusion loss
Local dose–effect relations

ABSTRACT

Purpose: To investigate if a local dose–effect (LDE) relationship for perfusion loss improves the NTCP model fit for SBRT induced radiation pneumonitis (RP) compared to conventional LDEs.
Methods and materials: Multi-institutional data of 1015 patients treated with SBRT were analyzed. Dose distributions were converted to NTD with $\alpha/\beta = 3$ Gy. The Lyman–Kutcher–Burman NTCP model was fitted to the incidence grade $\geq$2 RP by maximum likelihood estimation with mean lung dose (MLD), equivalent uniform doses (EUD) using three LDE functions (power-law (EUD_{power}), logistic with 2 free parameters ($EUD_{log\text{-}free}$) and logistic with fixed parameters describing local perfusion loss ($EUD_{Perfusion}$)) and volume above a threshold dose (V_x). Models were compared with the Akaike weights (Aw) derived from the Akaike information criteria (AIC).
Results: The median time to grade $\geq$2 RP was 4.2 months and plateaued after 17 months at 5.4%. A strong dose–effect relationship for RP incidence was observed. The $EUD_{Perfusion}$ based NTCP model had the lowest AIC. The Aw were 0.53, 0.19, 0.11, 0.11, 0.05 for the $EUD_{Perfusion}$, V_x, MLD, $EUD_{log\text{-}free}$ and EUD_{power} LDEs respectively.
Conclusion: A LDE for perfusion loss provided modest improvement in NTCP model fit for SBRT induced radiation pneumonitis.
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Stereotactic body radiotherapy (SBRT) is now considered as the standard of care for early-stage medically inoperable non-small-cell lung cancer (NSCLC) patients [1,2]. Toxicity is low in most prospective and retrospective studies, but radiation pneumonitis (RP) has serious clinical implications. In order to optimize radiation therapy and counsel patients, it is important to determine the normal-tissue complication probability (NTCP) of RP before treatment [3]. However, in contrast to conventionally fractionated (CF) radiotherapy (RT), data to derive accurate NTCP models for SBRT are scarce and hampered by the relatively low incidence of toxicity observed in SBRT [4].

Several NTCP models mostly based on CF-RT have been developed to predict the risk of RP in lung. These models use dose–volume histogram (DVH) reduction methods such as mean lung dose (MLD), V_{20} (volume of lung receiving more than 20 Gy) and the equivalent uniform dose (EUD). Several groups found that in lung SBRT, as in CF-RT, MLD is a reasonable predictor of radiation pneumonitis [5–7].

Lung has a parallel tissue architecture consisting of several independently functioning sub-units (FSUs). The DVH reduction methods described above, effectively apply a dose–effect relation for FSU damage. Accurately deriving such a dose–effect relationship through NTCP modeling of RP incidence is statistically challenging due to the increased number of degrees-of-freedom. As it is not possible to measure the damage to every single FSU, surrogates such as perfusion loss, ventilation and tissue density changes are used in the literature to find the local dose–effect relation. Single-photon emission computed tomography (SPECT) scans can be used to quantify the loss of local perfusion of the lung, which correlates with the loss of local lung ventilation [8,9] and thus can be considered a good surrogate for lung function. There is a strong evidence of a dose–effect relation for lung perfusion loss after CF-RT in lung cancer patients [10,11]. Recently, our group

* Corresponding author at: Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands.
E-mail address: j.sonke@nki.nl (J.-J. Sonke).
[1] Both authors contributed equally to this manuscript.

https://doi.org/10.1016/j.radonc.2018.12.015
0167-8140/

has established a logistic local dose–effect relation for perfusion loss in SBRT with SPECT imaging [12].

The aim of this study was to investigate if inclusion of a local dose–effect (LDE) relationship for perfusion loss improves the NTCP model fit for SBRT induced radiation pneumonitis (RP) compared to conventional LDEs.

Methods and materials

Patient cohort

DICOM datasets of 1015 early-stage NSCLC patients or patients with pulmonary metastases, treated with online image-guided SBRT between 1998 and 2010 at five international institutions (Netherlands Cancer Institute, Princess Margaret Cancer Center, Thomas Jefferson University, William Beaumont Hospital and University Hospital Wurzburg) were available for this study. Each institute contributed between 2.5% and 61% of the number of patients. Immobilization, motion assessment, treatment planning and image guidance were performed according to respective institutional protocols. Patients were followed after SBRT according to each institution's protocol and radiation pneumonitis was scored according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 3.0. This has been comprehensively described in a prior publication [4].

Several fractionation schemes were used at these institutes [4], with 54 Gy in 3 fractions, 48 Gy in 4 fractions being the dominant schedules used in 58% and 17% of patients respectively. Twenty-five patients were treated synchronously to 2 or more lesions. Details of the treated patients included can be found in Table 1.

Table 1
Patient, tumor and treatment characteristics.

Parameter	Value (%)
Patient (Tumor)	1015 (1041)
Male gender (%)	543 (53.5)
Median (IQR) age (y)[α]	74 (67–80)
Median (IQR) tumor diameter (cm)[β]	2.2 (1.6–3.1)
T-stage (%)[γ]	
T1	664 (63.8)
T2	247 (23.7)
T3	3 (0.3)
T4	1 (0.1)
Metastasis	118 (11.3)
Lobe (%)[δ]	
RUL	352 (33.8)
RML	41 (3.9)
RLL	197 (18.9)
LUL	289 (27.8)
LLL	160 (15.4)
WHO performance score (%)[ε]	
0	226 (26.2)
1	486 (47.9)
2	214 (21.1)
3	26 (2.6)
Charlson comorbidity index (%)[ζ]	
0	61 (6.0)
1–2	195 (19.1)
3–4	235 (23.1)
5–6	243 (23.9)
≥7	241 (23.7)
FEV1 predicted (%)[η]	
<70%	382 (37.6)
≥70%	468 (46.1)
Median (IQR) number of fractions[α]	3 (3–4)
Median (IQR) fraction dose (Gy)[α]	18 (12–18)
Median (IQR) BED (α/β = 10 Gy) (Gy)[α]	151 (106–151)
Median (IQR) Follow up (months)	23.4 (11.4–40.6)

[α] 1 missing.
[β] 2 missing.
[γ] 8 missing.
[δ] 2 missing.
[ε] 23 missing.
[ζ] 40 missing.
[η] 165 missing.

DVH reduction methods

DVHs (both lungs minus GTV) were derived from the normalized total dose (NTD; equal to the equivalent dose delivered at 2 Gy per fraction (EQD2)) distributions using the LQ model with an α/β ratio of 3 Gy [13–15]. For the synchronously treated tumors, the dose values were first converted to NTD and summed and the DVH was calculated for the lungs minus both GTVs.

Following the general parallel NTCP model described by Seppenwoolde et al. [14] a dose–effect relation quantifies the fraction of FSUs damaged locally. The summation of these local responses gives the overall response parameter, which can be used to calculate an Equivalent Uniform Dose (EUD), i.e., the uniform dose producing the same overall response parameter (biological effect) as that of the non-uniform dose.

The local dose–effect relationship can have any arbitrary shapes. Here we consider the following relationships. A sigmoidal local dose–effect relation according to a logistic function (EUD_{log}) defined as:

$$EUD_{\log} = D_{50}\left(\left\{1/\left[\sum_{i=1}^{N}\frac{1}{1+(D_{50}/D_i)^k}\cdot\frac{V_i}{V_{total}}\right]\right\}-1\right)^{-1/k} \quad (1)$$

where D_i is the dose in the i^{th} bin in the differential DVH, V_i the volume in the corresponding bin, V_{total} the total volume of the structure of interest, N the number of bins in the DVH, D_{50} the local dose for 50% damage and k the steepness parameter of the local dose–effect curve, respectively. We fitted the data using free values for D_{50} and k resulting in $EUD_{log\text{-}free}$ and the D_{50} and k values from SPECT data fit according to Table S1, resulting in $EUD_{Perfusion}$.

In case $D_{50} \to \infty$, Eq. (1) reduces to the well-known power-law local dose–effect relationship (EUD_{power}) defined as:

$$EUD_{power} = \left(\sum_{i=1}^{N} D_i^{1/n}\frac{V_i}{V_{total}}\right)^n \quad (2)$$

where $n = 1/k$. For the special case of a linear local dose–effect relation ($n = 1$), EUD_{power} for lungs minus GTV equals the MLD.

For a local dose–effect relation according to a step-function at x, no EUD can be calculated. Instead we take the overall response parameter, i.e., the volume receiving doses $\geq x$:

$$Vx = \sum_{i=1}^{N}\begin{cases} 0 & \text{if } D_i < x \\ \frac{V_i}{V_{total}} & \text{if } D_i \geq x \end{cases} \quad (3)$$

NTCP calculation

NTCP models were derived to predict RP grade ≥2. The NTCP was calculated using the DVH reduction methods described above assuming a sigmoid relationship between these parameters and NTCP:

$$NTCP = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} e^{-\frac{x^2}{2}}dx \quad (4)$$

$$\text{where } t = \frac{EUDpower - TD_{50}}{m.TD_{50}},\quad t = \frac{EUD_{\log} - TD_{50}}{m.TD_{50}} \text{ or } t = \frac{V_x - V_{50}}{m.V_{50}}$$

and TD_{50} (V_{50}) the dose (volume) required for 50% complication rate and m is the slope of the sigmodal NTCP curve.

A random model with a fixed but unknown overall NTCP value π independent of dose was used to test whether there is a dose–effect relation at all, i.e.: NTCP = π.

Statistics

Maximum-likelihood estimation (MLE) was used to select the best-fit model parameters of different NTCP models of RP grade $\geq$2 with the CERN MINUIT function minimization package [16]. The model fits were evaluated with the Hosmer–Lemeshow goodness-of-fit test [17] using the commonly used number of ten groups. The null hypothesis is that the model is fit and thus smaller *p*-values indicate inferior goodness of fit. The 95% confidence intervals (CI) of the estimated parameters were found using the profile-likelihood method. Nested models were compared using the deviance test with $\alpha = 0.05$. Other models were compared based on the Akaike weights (Aw) derived from the Akaike information criteria (AIC) [18]. The Aw of a particular model can be interpreted as the probability that this is the best model, in the AIC sense, given the data and the set of candidate models [19].

Results

The incidence of RP grade $\geq$2 in the patients included in this study is given in Fig. 1. With a median follow-up time of 23.4 months, the median time to toxicity was 4.2 months and plateaued after 17 months at 5.4%.

Best-fit parameters obtained for different DVH reduction methods are given in Table 2, along with Aw and goodness of fit *p*-value. Comparing the models, the $EUD_{Perfusion}$ had the highest Aw. The fixed D_{50} and *k* based on perfusion loss were not significantly different from the optimized D_{50} and *k*. The V_x model was found to be the next best model with Aw = 0.19. Both the MLD and $EUDlog_{-free}$ models had Aw = 0.11 while EUD_{power} was the dose–effect model with the lowest Aw of 0.05. Comparing the $EUD_{log\text{-}free}$ model with the simpler nested models $EUD_{Perfusion}$, EUD_{power} and MLD with the deviance test, yielded p-values of 0.67, 0.06 and 0.14 respectively. Similarly, the deviance test comparing EUD_{power} and MLD model yielded $p = 0.53$. Therefore the models with 3 and 4 free parameters (the EUD_{power} and EUD_{log} model, respectively) did not fit the data significantly better than the simpler models with 2 free parameters (the MLD and $EUD_{Perfusion}$ models). This is consistent with the overlapping CIs of the extra parameters. Furthermore, based on the *p*-values obtained from the Hosmer–Lemeshow test, only the random model showed evidence of poor goodness-of-fit with a $p < 0.05$, for all the other models there is no evidence to reject the null hypothesis. This model also has an Aw of $4.3E^{-3}$, indicating that the random model has a very low probability to be the best model.

The optimized NTCP models and 95% CIs along with the incidence or RP grade $\geq$2 and corresponding 95% CIs are shown in Fig. 2. Note that both the LDE parameters impact the horizontal axis and consequently how the RP incidences project into the various sub-plots. From this figure it can be seen that $EUD_{Perfusion}$ fits

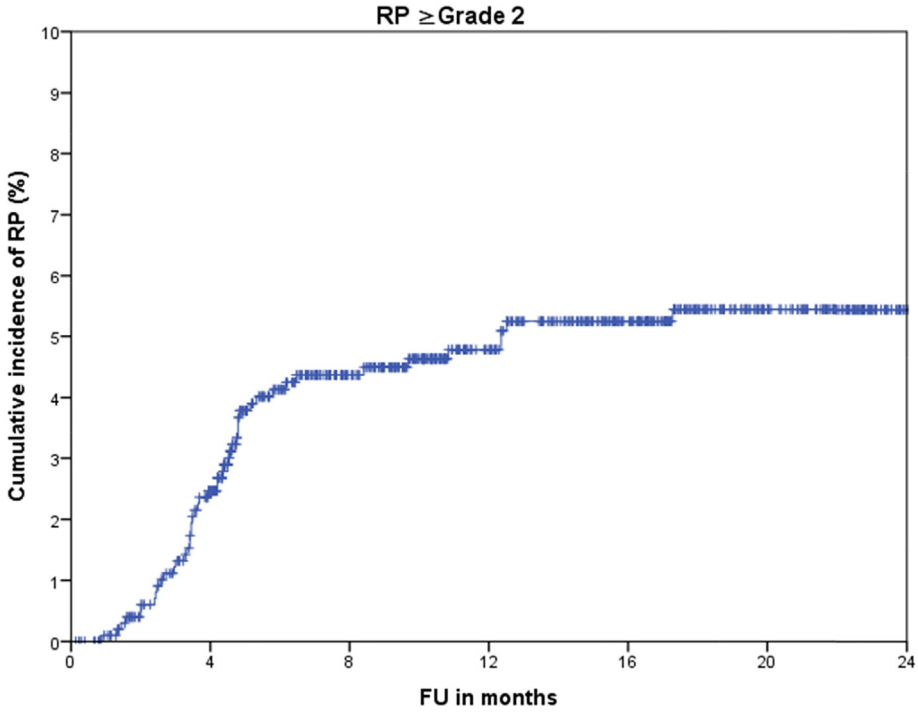

Fig. 1. Kaplan–Meier estimates of cumulative RP $\geq$grade 2 incidence.

Table 2
Best-fit model parameters with 95% CI with their corresponding MLLs, AIC, Aw and Hosmer–Lemeshow's *p*-values.

Model	TD_{50} (Gy)/V_{50}(%)	*M*	$n/D_{50}/x/\pi$	*k*	MLL	AIC	Aw	*p*
MLD	47.3(33.0–124.0)	0.49(0.43–0.57)	1.0 (fixed)		−192.1	388.1	0.11	0.87
EUD_{power}	28.1(7.2–213.9)	0.50(0.42–0.58)	1.5(0.5–8)		−191.9	389.7	0.05	0.31
$EUD_{Perfusion}$	24.9(19.1–46.9)	0.38(0.31–0.49)	28.7(fixed)	2.2(fixed)	−190.5	385	0.53	0.45
$EUD_{log\text{-}free}$	17.8 (4.0–64.8)	0.25(0.07–0.53)	16.0(3.4–91.0)	5.0(0.4–8)	−190.1	388.1	0.11	0.67
V_x	42.4(30.4–91.0)	0.47(0.41–0.55)	20.0(2.8–43.4)		−190.5	387	0.19	0.61
Random			0.05(0.04–0.06)		−196.3	394.6	4.3E−3	1.04E−4

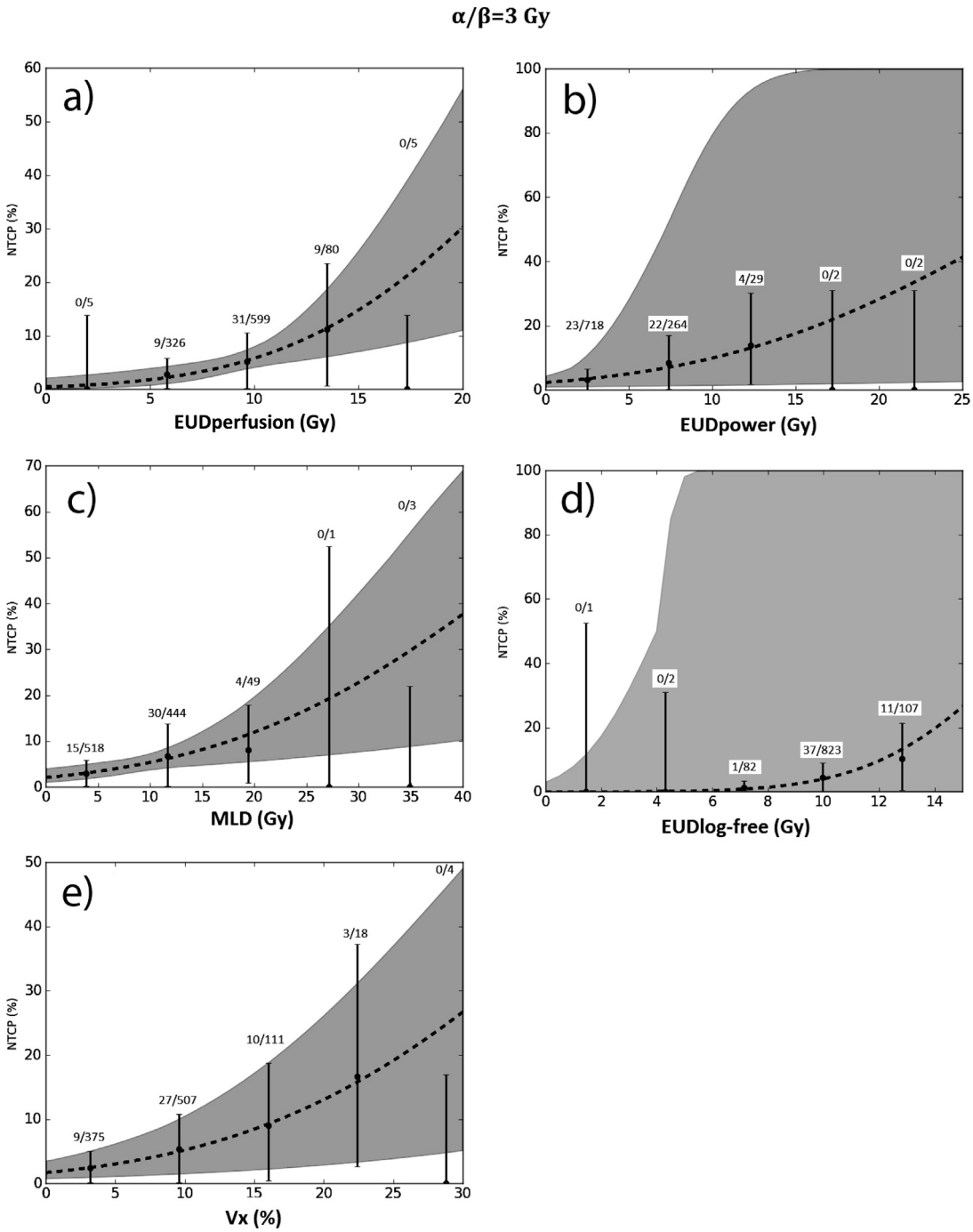

Fig. 2. Dose–response (NTCP) curves for the $EUD_{Perfusion}$ (a), EUD_{power} (b), MLD (c), $EUD_{log\text{-}free}$ (d), and V_x (e) DVH reduction methods. Note the differences in scale of both x and y axis in the different sub-plots.

the RP incidence rates quite well with small CI especially for the lower doses. MLD and V_x also provide good fits with somewhat larger CI. EUD_{power} and $EUD_{log\text{-}free}$, on the other hand, have much larger CIs. Note that the CI shown for V_x, EUD_{power} and $EUD_{log\text{-}free}$ are projections of a multi-dimensional CI as the uncertainty of the LDE parameters (x for V_x, n for EUD_{power} and D_{50} and k for $EUD_{log\text{-}free}$) impacts the 'scaling' of the horizontal EUD axis.

The local dose–effect relations for various models used in this study are shown in Fig. 3. For lower local NTDs, EUD_{power} models the highest effect followed by MLD, $EUD_{Perfusion}$ and $EUD_{log\text{-}free}$. For higher doses the effect order is reversed. V_x has a binary response swapping at 20 Gy.

Discussion

The incidence of radiation pneumonitis was investigated in a large multi-institutional database of patients with pulmonary lesions treated with SBRT using a variety of fractionation schedules. The median time to RP grade ≥2 was 4.2 months and plateaued after 17 months at 5.4%. Significant dose–effect relations for RP were found. The NTCP model based on a LDE for perfusion loss (and implicitly for the loss of functional subunits) outperformed NTCP models based on traditional LDEs. The resulting relation between the parameter $EUD_{Perfusion}$ and the incidence of RP (Fig. 2A) could enable the clinician to estimate reliably the proba-

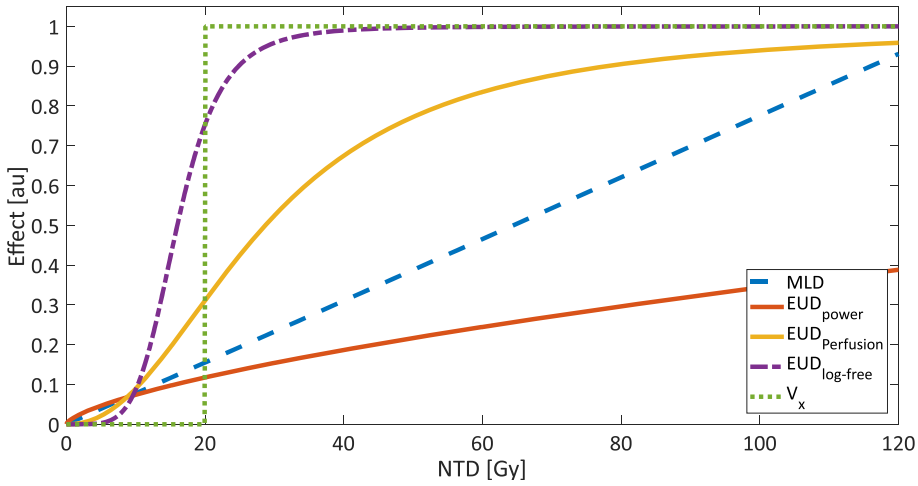

Fig. 3. Local dose–effect relations for different models used in this study. The MLD, EUD_{power} were normalized to the population mean $EUD_{Perfusion}$ which is 8.7 Gy, i.e., at a local NTD of 8.7 Gy the effect of MLD, EUD_{power} are the same as the effect of $EUD_{Perfusion}$.

bility of RP from the dose distribution of a new SBRT patient. And to shape the dose distribution in order to limit this probability to less than 5% by limiting the $EUD_{Perfusion}$ to values below 10 Gy.

Differences between the various NTCP models were modest with an Aw of 0.53 for the optimal model $EUD_{Perfusion}$ and Aw ranging from 0.05 to 0.19 for the alternative models. This indicates that the normalized probability [19] that $EUD_{Perfusion}$ is to be preferred over a competing model ranges from 0.73 to 0.91 The Hosmer–Lemeshow p-values were >0.05 for all dosimetric models thus not rejecting the 'null-hypothesis' that the models fit the data. Only for the random model $p < 0.05$ meaning the random model couldn't fit the data well demonstrating the presence of dose–effect relation for RP in SBRT.

The LDE relationship for perfusion loss $EUD_{Perfusion}$ saturates for NTD > 70–100 Gy with a D_{50} of 28.7 Gy. Similar saturation is described by the $EUD_{log\text{-}free}$ model but at a considerably lower D_{50} of 16 Gy. The V_x model models a binary response with optimal value of 20 Gy, which is frequently used in CF-RT as well [20]. CIs of the D_{50} and x model parameters, however are relatively wide, overlapping with the D_{50} of the $EUD_{Perfusion}$ LDE model. The EUD_{power} LDE model with optimal parameter $n = 1.5$ also exhibits a reduced incremental effect with increasing dose but saturation cannot be captured by a power-law. Liu et al. [21] found similarly n-values >1 for CF-RT.

The reported TD_{50} values and the steepness parameter m in the literature for CF-RT for the MLD based NTCP model for RP grade ≥2 is close to 30 Gy and 0.35 respectively [14,22]. These values are considerably lower than the values found in this study, namely $TD_{50} = 47$ Gy and m = 0.49 and outside the CIs. Interestingly, the $EUD_{Perfusion}$ model has values very similar to CF-RT with $TD_{50} = 25$ - Gy and m = 0.38. Borst et al. [5] did not find significant differences in MLD based NTCP model parameters between CF-RT and SBRT with $TD_{50} = 25$ Gy and $m = 0.5$. A possible explanation could be the relatively low fraction doses in their SBRT cohort (4 and 10 Gy for the largest sub-groups).

This study has various limitations. The low incidence of RP grade ≥2 associated with the small target volumes and low lung exposure limits the accuracy of estimated NTCP models especially at higher dose levels. This is further challenged by the difficulty to accurately score RP in a patient population with a high incidence of co-morbidities like chronic obstructive pulmonary disease (COPD) which has the same clinical symptoms and treatment as RP. While possible miss-classifications would impact the goodness of fit of the model, it is unlikely to have a considerable impact on the Akaike Weights of the various dose–effect relationships. In this work, toxicity was scored using CTC v3.0 in which grade 2 is defined as symptomatic pneumonitis/pulmonary infiltrates not interfering with activities of daily living (ADL). CTC v4.0 defines grade 2 as symptomatic pneumonitis, indicating medical intervention and limiting instrumental ADL. Therefore CTC v4 would have provided a more robust grading system. Moreover, 25% of RP events were scored later than 6 months after treatment up to 17 months after treatment. While RP traditionally is scored up to 6 months, with the prolonged inflammatory response in SBRT, no clear time thresholds for RP events is established. On the other hand, pulmonary fibrosis has very similar symptoms as RP (dry cough, shortness of breath) and consequently, at least some of the RP events in this study might have been suffering from fibroses instead. The optimal model parameters for the perfusion loss LDE relationship were used, ignoring their confidence interval reflecting the uncertainty of the parameters in the comparison with traditional LDEs. Moreover, the LQ model was applied to convert physical dose into NTD. The validity of the LQ model for high doses per fraction might be questioned. On the other hand, the $EUD_{Perfusion}$ LDE model saturates at higher doses making the NTCP model robust against possible inaccuracies of the LQ model. NTDs were calculated with $\alpha/\beta = 3$ Gy which might not be the correct value. However, evaluation with $\alpha/\beta = 1.3$ Gy, i.e., the value that aligned the perfusion loss LDE between CF-RT and SBRT, provided very similar results (Supplementary material). Due to the limited number of events, this study only modeled the association between radiation dose and RP, ignoring clinical factors such as cardiac comorbidities [23] or pretreatment interstitial lung disease [24]. Conceptionally, such factors could be included as dose modifying factors into the LKB model [25]. Similarly, differences between institutions were not analyzed giving both the limited number of events and large variability in the number of patients contributed per institution. Finally, this manuscript represents a retrospective analysis and results should be validated in an independent dataset.

In summary, strong dose–effect relations were found for grade ≥2 RP incidence following SBRT for pulmonary lesions in a large multi institutional analysis. The $EUD_{Perfusion}$ model with local dose–effect parameters based on local perfusion loss based on SPECT imaging modestly improved the prediction of RP in SBRT over conventional LDEs. With $EUD_{Perfusion} \leq 14.8$ Gy, the estimated risk of grade ≥2 RP is ≤15%.

Acknowledgements

The authors would like to thank Maddalena Rossi and Hong Ye for support in data management.

Conflict of interest statement

This work was sponsored in part by a research grant from the Dutch Cancer Society (NKI 2009-4568). This research was partially supported by Elekta through a research grant. This work and these data, however, 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.2018.12.015.

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