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Research Article

Correlation between Normal Tissue Complication Probability for Radiation Pneumonitis with Dosimetric Parameters: In-Silico Evaluation Based on Published Radiobiological Models

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Abstract:

Objectives: The first aim of this study is to evaluate the correlation between predicted normal tissue complication probability (NTCP) with dosimetric parameters. Then, the second goal is to evaluate the impact of published radiobiological models on NTCP prediction.

Methods: Ten lung cancer patients have been included in this study. The dose was calculated using anisotropic analytical algorithm(AAA). Dose volume histograms (DVH) for healthy lung (lungs minus target volume) were calculated. Then, the dosimetric parameters as mean lung dose (MLD) and V_{dose} values (% lung volume receiving more than a threshold dose in Gy) as V_{20} and V_{30}Gy were evaluated. The radiation pneumonitis (RP) was estimated using equivalent uniform dose (EUD) model, Lyman-Kutcher-Burman (LKB) model using radiobiological parameters assumed for AAA; and logistic fit using mean lung dose for RP (RP_{MLD}). The statistical correlation was evaluated using Spearman's correlation coefficient (ρ-value).

Results: The average NTCP values were higher with RP_{MLD} compared to EUD or LKB models, $p < 0.05$. The data showed a strong correlation between NTCP values with MLD.

Conclusions: For a given set of patients, we assessed the NTCP using published radiobiological parameters as well as the correlation between predicted NTCP with dosimetric parameters. The considerable impact of radiobiological model on the NTCP values urges to tune NTCP parameters. Therefore, the good correlation could suggest the use of mean lung dose in NTCP model.

Keywords: Mean Lung Dose; Normal Tissue Complication Probability; Radiation Pneumonitis

Introduction: The thoracic cancer radiotherapy irradiates the healthy lung surrounding the target, leading to risk of radiation as radiation pneumonitis (RP). In addition, the irradiation affects the lung function showing the need to the measure the quality of life (Qol) of patients [1]. Thus, the minimizing of dose to the healthy lungs is a one of the major objectives for chest radiotherapy treatment planning. The optimal plan would present lower toxicity for normal tissue while maximizing tumor control probability (TCP). The quality of radiotherapy treatment plans in terms of probability of TCP and normal tissue complication probability (NTCP) can be evaluated from dose distribution. Therefore, the knowledge of the relationship between the calculated dose and the risk of toxicity is the essential information to validate a radiotherapy treatment plans. For lung, the physical dose parameters as mean lung dose (MLD), volume-dose indices (V_{dose}) showing the percentage of healthy lung volume receiving a specific dose as V_5, V_{13}, V_{20} and V_{30}Gy could be used to validate a treatment plans. In addition, the estimation of the probability of developing RP can be estimated using NTCP radiobiological models [2-8]. Thus, NTCP prediction is based on physical dose distribution as could be calculated from dose volume histograms (DVH). The use of appropriate radiobiological models to estimate the TCP and NTCP is an important step to rank and compare radiotherapy plans for cost effectiveness. The first purpose of this paper is to evaluate the correlation between NTCP and dose parameters as MLD, V_{20} and V_{30}, since the MLD is the more accurate predictor for the incidence of RP [9]. The second aim is to evaluate the role played by the dosimetric

variables to predict NTCP. This is an interesting topic since radiotherapy plans could be compared using dosimetric and radiobiological criteria.

Methods:

Clinical cases and treatment planning: Ten patients with lung cancer have been included in this study. The patients were treated with postoperative 3D conformal radiation therapy (3DCRT) for Non-Small Cell Lung Cancer (NSCLC). A computed tomography (CT-scan) was done for each patient, then the images were loaded into the treatment planning system (TPS). Radiation oncologists delineated the target volumes including the security margins and the organs at risks (OARs). The virtual simulation for each patient was generated by a digitally reconstructed radiograph (DRR) and beam's eye view images. Next, treatment fields were superimposed on the DRR to assess the well adjustment to targets. The total dose prescribed to the PTV was 54-66 Gy with a daily dose of 1.8-2 Gy. The technique included five to eight beams of 6 MV photon.The dose constraints to the OARs are based on the international recommendations. The dose calculations were performed with heterogeneity correction using Anisotropic Analytical Algorithm (AAA) (version 13.5, Varian Eclipse™ TPS). In AAA, three sub-sources are modeled, including primary photons, extra-focal photons and electron contamination [10-14].

Radiobiological modeling: The dose-response models describe the response probability as a function of dose. A sigmoid curve usually is assumed, characterized by the steepness of the slope and the dose required to obtain a 50% probability of response (TD_{50}). Firstly, the cumulative DVHs were calculated, and then converted into differential dDVH to compute the NTCP. The healthy lung volume was defined excluding the target tumor volume as (healthy lung-PTV). To account for variations in dose per fraction in different sub-volumes, with changes in fractionation schedules, total physical dose corresponding to each DVH bin, Di, was converted into biological equivalent physical dose of 2 Gy fractions using linear quadratic (LQ) model [15]:

$$LQEDi = Di\ [1+(Di/nf)/(\alpha/\beta)\ ]\ /\ [1+2/(\alpha/\beta)] \quad (1)$$

where (nf) is the number of fractions.

The RP as late effect was evaluated and the $\alpha/\beta = 3$ Gy was taken from quantitative analysis of normal tissue effects in the clinic (QUANTEC) recommendations [16].

For comparative purposes, the NTCPs for lung were calculated using Lyman-Kutcher-Burman (LKB) model [2-4] and Equivalent Uniform Dose (EUD) model proposed by Gay-Niemierko (GN) [6,7]. In addition, the RP formulation for calculating the RP risk based on the MLD was also used [16-17].In fact, the GN model is solely the new definition of the LKB model, in which the power-law exponent 'n' is replaced by 'a = 1/n', and these two models have not basic physical/ radiobiological differences.

EUD is defined as:

$$EUD = \left(\sum_i v_i LQED_i^a \right)^{1/a} \quad (2)$$

where v_i is the fractional organ volume receiving a dose D_i and 'a' is a tissue specific parameter that describes the volume effect. For a = 1, the power law-based EUD becomes the arithmetic mean dose, typical for parallel organs. When a < 1, it weighs more on the low dose region, typical for target volumes. In contrast, when a > 1, it weighs more on the high dose region, typical for serial organs. Using GN model, the NTCP is defined as:

$$NTCP_{GN} = \frac{1}{1+\left(\frac{TD_{50}}{EUD}\right)^{4\gamma_{50}}} \quad (3)$$

where TD_{50} is the tolerance dose for 50% complication rate of the normal organ. The γ_{50} describes the slope of the dose-response curve.

Using LKB model, the NTCP is defined as:

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

$$t = (EUD - TD_{50})/(m.TD_{50}) \quad (5)$$

where TD_{50} is the tolerance dose for 50% complication rate of the normal organ. The parameter m represents the slope of the sigmoid dose response curve.

The radiobiological parameters used in this study were adapted for AAA and the endpoint of the study was grade ≥ 2 of RP. For EUD model the parameters were respectively (TD_{50} = 29.19 Gy,a = 1.0 and γ_{50} = 2.0). For LKB, the parameters were taken from Hedin *et al*. 2013 [18]: TD_{50} = 29.19 Gy,n = 0.99 and m = 0.374.

The RP risk using mean lung dose (RP_{MLD}) is calculated as [16,17]:

$$RP_{MLD} = \frac{\exp(b_0 + b_1.MLD)}{1+\exp(b_0 + b_1.MLD)}$$

(6)

The values of parameters were b_0 = -3.87, b_1 = 0.126 Gy^{-1}.

Statistical analysis: The same CT-scan for each patient was used to generate a treatment plan. Then NTCP were evaluated for the same patient and the same plan using NTCP models. Thus, there is a relationship for each patient between the dosimetric parameters and NTCP values. In this case, the dosimetric data used as input to estimate NTCP show a repeated NTCP calculation for the same patient. The statistical correlation between predicted NTCP with dosimetric parameters calculated with AAA, was evaluated using Spearman's correlation coefficient (ρ-value) [19].

Results:

Assessment of normal tissue complication probabilities: The EUD values were lower than MLD predicting lower effective dose to the healthy lung. Thus, GN and LKB models predicted lower NTCP values, compared with RP_{MLD}. The average values (%) for NTCP were respectively: 0.1, 4.7 and 9.8 using GN, LKB and RP_{MLD}. However, to conclude about which is the better prediction, one should consider the most accurate DVH and radiobiological parameter setting. The radiobiological parameters are still a critical issue since their values are dependent on the dose calculations algorithms which are continuously changing through the years.

Correlation between NTCP and dosimetric parameters: The RP_{MLD} formulation showed a strong correlation with MLD, with $\rho > 0.7$. Figure 1 shows the NTCP values as a function of dosimetric parameters. Table 1 shows the ρ-values from Spearman's test. It can be seen that the RP_{MLD} showed a significant and strong correlation with NTCP, as mentioned by previous literature studies [8,9]. Thus, the relationship between MLD and NTCP is a key information. The accuracy in calculating dose by commercial photon dose calculation algorithms integrated in a TPS is a critical issue, since the available algorithms have some limitation to calculate the dose distribution for lung. The over/under estimation of dose would over/under estimate the NTCP and thus the real correlation between MLD and NTCP rates. In the same line, one of the important limit of the radiobiological models is the available radiobiological parameters, as mentioned above. The former NTCP models were initially proposed for photon treatment without heterogeneity correction or with 1D density correction. The re-use of these models for more modern proton dose calculation algorithms as AAA or type 'c' algorithms as Acuros XB should be used with caution to avoid the underestimation of NTCP. It should be also noted that the beam configuration in 3DCRT treatment planning significantly affects the DVH shape; and consequently the dosimetric and radiobiological evaluations.

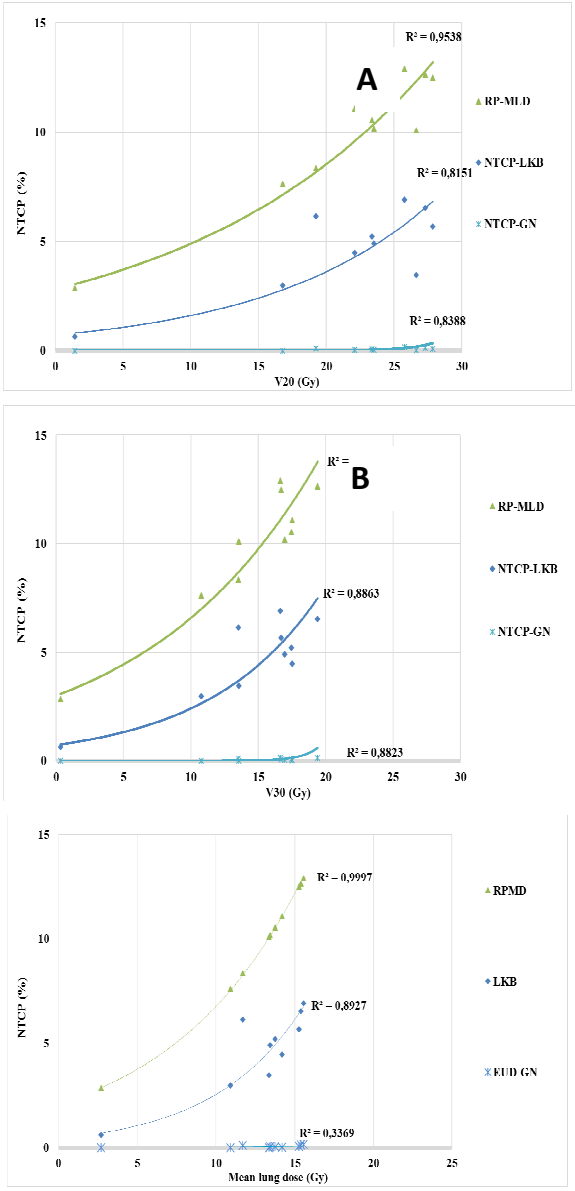

Figure 1: Complication probability values as a function of dosimetric parameters. The panels A and B show NTCP values as a function of V_{20}Gy and V_{30}Gy. The panel C shows NTCP values as a function of MLD. The NTCP were calculated from RP_{MLD}, LKB and GN models.

Models	MLD		V_{20}Gy		V_{30} Gy	
	ρ	p-value	P	p-value	P	p-value
RP_{MLD}	0.95	< 0.001	0.75	0.009	0.74	0.01
$NTCP_{LKB}$	0.76	0.01	0.6	< 0.001	0.53	< 0.001
$NTCP_{GN}$	0.76	0.01	0.57	< 0.001	0.47	< 0.001

Table 1: Spearman's correlation coefficient (ρ-value) and p-values, resulting from the correlation between NTCP with dosimetric parameters as MLD, V_{20} and V_{30} Gy

Comparison between predicted toxicity with NTCP rates: Figure 2 shows the NTCP values from RP_{MLD} as well as NTCP rates from QUANTEC review as a function of MLD. It can be seen that the NTCP values from RP_{MLD} shows a strong correlation with NTCP rates. Conversely, the NTCP values from GN and LKB models showed a smaller correlation, as shown in table 1. Considering NTCP values from RP_{MLD} as more correlated with observed NTCP rates, the radiobiological parameters from literature, do not translate the relation between calculated MLD dose and NTCP values, since the same DVHs were used as input. However, to conclude about which is the better NTCP estimation, one should correlate the predicted NTCPs with measured Qol [1]. In addition, the relative predictive capabilities of models could be statistically assessed using receiver operating characteristics (ROC) curves. A higher area under the ROC curve indicates a more accurate model, the accurate model has area = 1.

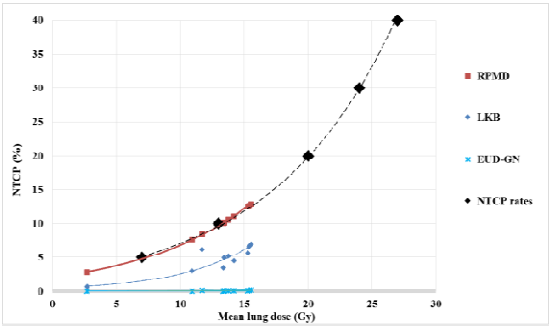

Figure 2: The NTCP values as a function of MLD. The NTCP values were calculated by RP_{MLD}, as well as NTCP rates taken from QUANTEC report.

Impact of NTCP models on treatment effectiveness prediction: The magnitude of the estimation of treatment effectiveness depends on radiobiological models' predictions and their parameters, as input for in-silico evaluation. Since the estimates of the absolute NTCP values from GN and LKB models are extremely low, due to EUD << TD_{50}, the reduction of EUD value, rather than NTCP would better reflect the "expected" benefit. Thus, if the objective is to select the optimal plan, the EUD dose concept is a robust translation of the dose distribution and could be used as radiobiological guide to select the patients. In addition, EUD could be correlated, in-silico, with NTCP. Figure 3 shows the NTCP from RP_{MLD} and LKB as a function of EUD.

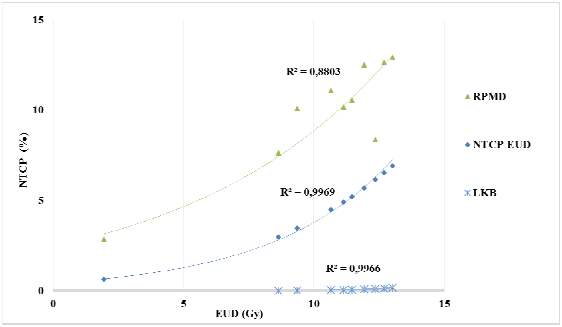

Figure 3: NTCP values from RP_{MLD} and LKB as a function of EUD

Need to measure Qol to tune radiobiological parameters for NTCP models: NTCP data from RP model using MLD showed the best correlation with NTCP rates taken from QUANTEC. Thus, these results suggest to use the recommended MLD as the dose tolerance limit, and to use it in NTCP model to better estimate the NTCP. In addition, the EUD concept translates the DVH in a unique value in (Gy). The EUD reduction could confirm a true dose reduction when comparing radiotherapy plans. Moreover, the EUD can be used as indicator to estimate the potential benefit to select optimal plan. However, a calibration of the parameter 'a' should be carried out to better estimate the NTCP. The considerable impact of radiobiological models on the radiotherapy outcomes as well as medical-decision making urges to measure specific (CTCAE scale) and Qol using, for example, EQ-5D, to tune the parameters of NTCP models [20,21]. This can be applied in the NTCP models by relating the clinical data (eg. lesion size, histology, case type, treatment technique, complication grading, health status, surgery, chemotherapy, base-line organ function). We suggest a sample size (n > 10 cases) to improve the sensitivity of the NTCP models, as well as the use of statistical methods as bootstrap simulation to evaluate the correlation and estimate the needed sample size to confirm the results.

Discussion: Numerous studies have evaluated the most accurate dosimetric parameter from DVH that can be used topredict the RP [8,9,22]. They reported that the MLD had a significant correlation on NTCP prediction. However, the novelty of this study is to alter that taking into account of the MLD from more accurate dose calculation algorithm on NTCP modeling showed a significant correlation with NTCP rates taken from QUANTEC report [16,17]. When considering the strong correlation represents the better NTCP prediction, a readjusting of radiobiological parameters should be taken in consideration for each dose calculation algorithm types, irradiation techniques as IMRT, stereotactic, etc. Thus, it is essential to compare predicted NTCP with Qol for any treatment delivery techniques. The objective is to avoid the over/under estimation and better correlate NTCP prediction with dosimetric parameters.

In this radiobiological study, we compared NTCP values from RP, GN and LKB models. Both GN and LKB models demonstrated low NTCP values using the same DVH and $TD_{50,}$ compared to RP_{MLD}. It can be seen from figures 1 and 2 that RP risk increases slowly with MLD and V_{dose}. As a result, it would be difficult to define a safe threshold. The main cause of this inconsistency would be that V_{dose} is a single point from DVH. Contrarily, the MLD and EUD use all the dose bins from DVH. This finding suggests the use of the MLD in NTCP models for RP prediction. The difference between NTCP values from different models depend on radiobiological parameter setting. This confirms that, the choice of NTCP model could influence the medical decision making.

Precaution about radiobiological parameters: The probability and the severity of the toxicity depends on the MLD/EUD values that could be translated into NTCP. Thus, increasing MLD/EUD could increase the NTCP and severity. In this study, the available parameters for AAA were used, assuming they are adapted for this comparison, i.e. to severe late effects. However, it is relevant to mention that for the previous radiobiological modeling studies, done on lung cancer, the TD_{50} = 24.5 Gy, without heterogeneity correction and TD_{50} = 29.19 Gy has been re-estimated for AAA. This is a sensitive issue, since NTCP depends on TD_{50} value. It should be clear that, using more adapted radiobiological parameters is the optimal approach to compare, *in silico*, the radiotherapy outcomes, and correlate with Qol calculation. In this regard, it is important to mention that there are some limits that may influence the interpretation of the predicted results. Firstly, the choice of 'a=1/n' influences the EUD values. Thus, using the same DVH, but with different values of 'a', the NTCP values would be different. In this study, a = 1 for EUD model and n = 0.99 for LKB model were used leading to EUD < MLD. Tucker *et al*, 2012, showed the effective dose computed from the LKB model using n = 0.41 may provide a better dosimetric parameter for predicting RP risk [23]. Secondly, the relationship between dosimetric parameters and NTCP might differ among different patient populations. It cannot be excluded that RP correlate with MLD. In this context, the appropriate and more accurate DVH are necessary to better calculate dosimetric data. In addition, the radiobiological parameters well adapted for each dose calculation model are suitable. However, recommending MLD or V_{dose} limits are challenging since there are no clear consistent thresholds for low grade. However, to limit the risk of RP to ≤ 15-18% the MLD should be ≤ 15-20 Gy with conventional fractionation. Nevertheless, the V_{20} and V_{30} Gy should be respectively, V_{20}< 30% and V_{30}< 20% [24].

Conclusion: We assessed the correlation between NTCP values with dosimetric parameters as MLD, V20 and V30 Gy. The DVH was calculated from more accurate dose calculation algorithm as AAA.The results obtained from NTCP confirmed a probably strong correlation with MLD, with $\rho >$ 0.7. However, a large cohort (n > 10) is needed to better estimate the correlation. In addition, the considerable impact of radiobiological models and parameters setting on the NTCP prediction urges to measure Qol to tune the parameters of NTCP models for more advanced dose calculation algorithms and delivery techniques.

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