

Does variable RBE affect toxicity risks for mediastinal lymphoma patients? NTCP-based evaluation after proton therapy treatment.

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Short Title

Impact of protons' variable RBE on toxicity risks for mediastinal lymphoma patients

Abstract

Introduction: Mediastinal lymphoma (ML) is a solid malignancy affecting young patients. Modern combined treatments allow obtaining good survival probability, together with a long life expectancy, and therefore with the need to minimize treatment-related toxicities. We quantified the expected toxicity risk for different organs and endpoints in ML patients treated with intensity-modulated proton therapy (IMPT) at our centre, accounting also for uncertainties related to variable RBE.

Methods: Treatment plans for ten ML patients were recalculated with a TOPAS-based Monte Carlo code, thus retrieving information on LET and allowing the estimation of variable RBE. Published NTCP models were adopted to calculate the toxicity risk for hypothyroidism, heart valve defects, coronary heart disease and lung fibrosis. NTCP was calculated assuming both constant (i.e. 1.1) and variable RBE. The uncertainty associated with individual radiosensitivity was estimated by random sampling α/β values before RBE evaluation.

Results: Variable RBE had a minor impact on hypothyroidism risk for 7 patients, while it led to significant increase for the remaining three (+24% risk maximum increase). Lung fibrosis was slightly affected by variable RBE, with a maximum increase of $\approx 1\%$. This was similar for heart valve dysfunction, with the exception of one patient showing an about 10% risk increase, which could be explained by means of large heart volume and D_1 increase.

Discussion: The use of NTCP models allows for identifying those patients associated with a higher toxicity risk. For those patients, it might be worth including variable RBE in plan evaluation.

Introduction

Mediastinal lymphoma (ML) is a type of malignancy affecting young patients. Modern combined treatments allow obtaining a good survival and a long life expectancy [1]. Consequently, aiming at preserving a good life quality, concerns are raised associated with medium- and long-term treatment-related toxicity risks.

ML treatment protocols often include radiotherapy in combination with chemotherapy. In this context, the major concerns are associated with the dose released to the heart and to the lungs, as well as to the thyroid. Modern photon radiotherapy techniques (i.e. intensity-modulated radiotherapy, IMRT) allow significantly improved sparing of such organs at risk (OARs) compared to the past. Pencil beam scanning proton therapy (PT) represents nowadays an additional treatment option for those patients, especially in selected cases that turn out more challenging for IMRT [2,3]. In fact, the higher spatial selectivity offered by protons' depth-dose profile translates into an enhanced OAR sparing potential. Consequently, depending on the anatomy of the patient and location of the target, those cases might be identified for which PT would result in a substantial sparing of sensitive OARs compared to IMRT. For instance, ML patients with a target spanning the right or both sides of the heart could fall in this category [4].

Despite the potential advantages offered by PT in selected ML cases, a limited number of studies are available, mainly focusing on dosimetric aspects [5,6]. However, according to the modern criteria for patient-allocation, a more

appropriate patient selection should span from accompanying dosimetric data with toxicity risks, supported by the use of normal tissue complication probability (NTCP) models [7,8]. Most NTCP models are typically non-linear sigmoid functions of one or more parameters, thus it is not granted that a significant dose sparing would also result in a significantly lower toxicity risk [9]. An exception is represented by linear models, which also have been proposed in the past [10,11].

For patients receiving PT the question has been raised whether NTCP evaluation should take into account protons' relative biological effectiveness (RBE, i.e. the ratio of photon to proton doses that are needed to observe the same biological effect [12]). While a constant RBE=1.1 is currently adopted in PT (i.e. protons are assumed to be always 10% more effective than photons), it is known from radiobiology that RBE differ from such constant value, depending on a number of physical (e.g. dose, LET [linear energy transfer], fractionation) and biological (e.g. endpoint, oxygenation) parameters. Different models have been proposed to describe such variable RBE (detailed reviews can be found in [13,14]), and several papers analysed the potential impact of RBE variations on NTCP estimation for different target localizations [15–21]. Recently, different groups tried to identify RBE effects in treated patients. Advanced imaging techniques and voxel-level analysis were adopted trying to find an association between variable RBE and image changes, with discordant results [22–25]. Overall, those works support the need to start including variable RBE in the clinics, at least for plan evaluation [26–28].

Here we present the results of an NTCP study on ML patients treated with pencil beam scanning intensity-modulated proton therapy (IMPT) at our centre. NTCP models for thyroid, heart and lung toxicity were employed to attribute a risk to each patient. This was done both assuming both constant (i.e. 1.1) and variable RBE. Variations in terms of sensitivity to fractionation are also taken into account by repeated random sampling α/β values for each patient. For each patient, results in terms of absolute NTCP and NTCP variation due to variable RBE are presented.

Methods

Patients and Treatment Planning

Ten patients (3 male and 7 female, median age 31 ± 10 years old, ranging from 15 to 49 years old) affected by ML who underwent PT treatment, were included in the study. Those patients correspond to the last ten 10 ML treated at our institution without boost when this study started. All patients were treated according to international lymphoma radiation oncology group guidelines after induction chemotherapy regimens [4,29]. Patients' and treatment characteristics are reported in Table 1.

Details on the treatment planning procedure were provided elsewhere [30]. In summary, all patients were treated in a supine position in deep inspiration breath-hold (DIBH). An active breathing coordinator (ABC) system (Elekta Instrument AB, Stockholm, Sweden) was employed, allowing forced breath-hold. On the DIBH simulation CT, two anterior-oblique fields were employed

for the treatment of mediastinum, with one or two additional posterior beams when it was required due to posterior extension of the target and/or to contribute to the irradiation of the cervical nodes (details on beam arrangement are reported in Table 1). The average target size was $263 \pm 84 \text{ cm}^3$ (range 78-384 cm^3). Multi-field optimization was planned with the Raystation (Raystation V9B, RaySearch Laboratories, Sweden) treatment planning system. A Monte Carlo engine was used for both optimization and final dose calculation. A dose grid of $2 \times 2 \times 2 \text{ mm}^3$ was employed. Each plan was planned by min-max robust optimization, with 3.5% range and 6 mm setup uncertainties, to guarantee target coverage by the 95% isodose in the worst-case scenarios.

LET and variable RBE model

Variable RBE was calculated with the parametric model proposed by McNamara et al [31], according to which RBE is a function of fraction dose, dose-average LET and α/β . For this purpose, the nominal plans were recalculated with a previously in-house validated Monte Carlo code [32] based on TOPAS [33] (TOPAS version 3.7). This allowed retrieving the dose-average LET information at a single-voxel level. In line with the recent recommendations [34,35], we report that the LET is obtained by means of a volumetric scoring with the standard TOPAS scorer, according to which the LET is calculated by dividing the energy deposited by the step length. A scaling to take into account the density of each voxel as retrieved from CT

imaging is also performed. The α/β ratio reflects the different sensitivities of cells to fractionation, and a large range of possible α/β values has been reported [36]. To account for the model sensitivity to this parameter [13], a procedure was set up for a random sampling of α/β values. Few literature data are available concerning linear-quadratic dose-response curves for the OARs and endpoints of interest. Accounting for the scarcity of data and for the fluctuations observed, we attributed a mean $\alpha/\beta=3$ to the three OARs. A standard deviation of 1.5 was estimated from confidence intervals available in the literature [37,38]. The sampling distribution was then truncated bilaterally to zero, to avoid negative α/β values [20]. For each patient, the random sampling procedure was repeated 1000 times. For each run, a variable RBE dose was obtained according to the sampled α/β , and the corresponding NTCP was computed.

NTCP analysis

NTCP models available from the literature were employed to attribute toxicity risks to every single patient. For consistency, among the several published models for thoracic OARs, we selected those derived from lymphoma patients. Three different logistic models were adopted to evaluate NTCP for hypothyroidism [39], heart valve dysfunction [40] and lung fibrosis [41]. The linear model for coronary heart disease (CHD) proposed by van Nimwegen was also employed [42], assuming that the relative risk (expressed as rate ratio, i.e. **the ratio between the number of patients reporting toxicity when receiving a**

given dose and patients not receiving radiotherapy) increases as a linear function of the mean heart dose (MHD). Details on model parameters are reported in Supplementary Table S1.

For each patient, NTCP values for the selected OARs and endpoints were calculated for the nominal plan as well as accounting for variable RBE. For the latter, results are summarised using box plots, reflecting how variations in radiosensitivity (i.e., a different α/β value) affect the variable RBE dose and thus the toxicity risk. Additionally, a ΔNTCP (i.e. $\text{NTCP}_{\text{varRBE}} - \text{NTCP}_{1,1}$) was calculated. NTCP is reported in the following as percentage points.

Replanning strategy

For one patient (patient 6) we investigated a different planning strategy, trying to mitigate the risk of heart toxicity, which was well above average as better described in the following. According to the specific NTCP model adopted, the heart D_1 is the only parameter that could be modified by the planning. To this purpose, we calculated two additional plans for this patient, by including an objective in the cost function, in order to reduce the heart D_1 , without compromising target coverage. Replan 2 differs from Replan 1 only for a higher weight to the new objective.

Results

Dosimetric parameters were analysed for the three OARs of interest. Figure 1 shows average dose and LET values for thyroid, heart and left lung, calculated

for the 10 patients included in the study. The boxplots indicate that both higher average dose and inter-patient variability are associated with thyroid compared to lung and heart. In terms of LET, the highest values with a median of about 3 keV/ μm are again observed for thyroid. LET is on average lower for the heart and left lung, but it shows larger variability among patients.

The dosimetric parameters employed for NTCP calculations are reported in Table 2. The results of the NTCP analysis are collected in Figure 2. For each patient, the NTCP associated with the nominal plan is shown (circles), together with the NTCP resulting from variable RBE (boxplots). Concerning the thyroid (Figure 2A), we observe that, for 7 over 10 patients, variable RBE has minor to no impact on the risk of hypothyroidism. For some patients (i.e. ID 6, 8, 9, 10) there is no increase due to variable RBE, while nominal plans are associated with the same NTCP value. These are in fact female patients, for which the NTCP model predicts a higher baseline risk compared to males. At the same time, the dosimetric parameter of the NTCP model (i.e. thyroid V_{30}) is zero both for nominal and variable RBE plans (Table 1), leaving unaffected the baseline NTCP. A significant effect of variable RBE is instead registered in patients 3, 4 and 5 (again female patients). Figure 3 reports the dose distribution with constant and variable RBE for one of these patients (i.e. patient 4), together with the thyroid DVH and LVH (LET-volume histogram).

In this case, the thyroid V_{30} is well above zero in nominal plans (range 7.5-38.4%) and a further increase is observed due to variable RBE (range 26.3-53.4%). The largest effect is observed for patient 5, for whom NTCP goes up

by about 24%. The large impact of variable RBE for these patients is associated with the specific shape of the DVH, showing a steep fall-off at about 30 Gy. Variable RBE moves the fall-off to higher doses, with a significant increase in terms of V_{30} . To show this behaviour with more details, in Supplementary Material S2 we report the thyroid DVH for patient 5 obtained with constant and variable RBE.

When looking at the NTCP for lung fibrosis (Figure 2B), it is obvious how variable RBE only slightly affects the risk of toxicity. This is a consequence of RBE leading to a minor increase in the dosimetric parameters (i.e. heart M_{30} , left lung V_5 , see also Table 1). Overall, we observe fluctuations in NTCP values between about 3% and 11.6%, as a consequence of the inter-patient lung V_5 variability.

Concerning heart toxicity, we considered two different models and endpoints. Figure 2C indicates that the risk for heart valve dysfunction fluctuates around 2% for all patients but for patient 6. For this endpoint, the NTCP model is based on three variables (heart D_1 , heart and lung volumes), their interplay defining the risk. The NTCP increases for increasing D_1 and heart volume, while it goes down for large lung volume. This explains why patients 2 and 6, having similar heart D_1 , show such large differences in NTCP. In fact, according to this model, it is the large lung volume of patient 2 that plays a “protective” role. Moreover, the larger heart volume, also increasing the risk, is associated with patient 6. Despite the increase in heart D_1 due to variable RBE is similar to that observed for other patients, the combination of model

parameters for patient 6 return an NTCP belonging to steep part of the risk function. Therefore, even small D_1 variations are associated with large NTCP differences. The NTCP as a function of D_1 for patient 6 is reported in Supplementary Material S2, where we also show how variations in heart volume have a strong impact on the predicted risk.

Trying to mitigate toxicity risks, we dedicated additional effort to the analysis of patient 6, which is associated with the largest risk of heart valve dysfunction. A replanning was performed, as described in the Methods. The heart D_1 decreased from the 39.9 Gy(RBE) of the nominal plans to 37.6 and 36.2 Gy(RBE) for Replan 1 and 2, respectively. Figure 4 collects the NTCP associated with constant and variable RBE. The figure shows that assuming a variable RBE, by including a specific objective in the cost function, we were able to lower the NTCP from 31% to 24% and to 21% for Replan 1 and 2, respectively. A similar trend was observed for constant RBE. The D_{95} for the target volume (ITV_{40}) was lowered from 39.9 Gy(RBE) to 39.2 and 38.4 Gy(RBE) for the two additional plans. This indicates that target coverage obviously decreased, but acceptance criteria were met also for the new plans.

Finally, the risk for CHD was computed according to the linear model by van Nimwegen et al [42] and is reported in Figure 3D expressed as RR. Due to the dependence on MHD, the resulting RRs are quite scattered. At the same time, variable RBE has a direct effect on increasing MHD and thus the toxicity risk: the higher the nominal MHD, the higher the impact of variable RBE.

Based on the results discussed above, we collected the information presented so far in the scatter plot of Figure 5. Here, we show Δ NTCP as a function of the difference in terms of dosimetric parameters between variable RBE plans (median RBE values were employed) and nominal ones. Each symbol refers to a single patient, while colours identify the OAR. First, the scatter plot indicates that in most of the cases we recorded a limited effect of variable RBE on dosimetric predictors, and therefore a minor NTCP variation. However, the figure also shows how the variation of similar size in terms of heart D_1 or thyroid V_{30} can result in much different Δ NTCP.

Discussion

NTCP models are becoming increasingly employed as a tool for plan evaluation in modern-RT. Their use is of particular interest when comparing different RT techniques since they allow translating dosimetric parameters into an expected toxicity risk, a non-obvious step due to the non-linear nature of most of the models [7,43]. For PT, this is also true when considering the impact of variable RBE, which overall leads to higher biological doses, eventually associated with an increased risk of toxicity [15–19,21]. Here we applied several NTCP models to investigate the impact of variable RBE on young patients treated for ML with IMPT.

Different NTCP models have been proposed in the last decades, among which we decided to adopt models derived from lymphoma patients. Such models were obtained with patients treated with photons, and the risk estimation might

be sub-optimal when they are applied to PT. This is currently an unavoidable approximation, due to the scarcity of NTCP models derived from PT patients. This represents a potential criticism to our approach, which is nevertheless similar to that adopted by other [6,7,20,44,45]. Unfortunately, the availability of proton-derived NTCP models, as well as of photon models validated on proton patients, is very limited. Studies have been published, indicating that photon NTCP models can be robustly applied to predict toxicity in head and neck patients treated with protons [7]. More in general, the model-based approach [7–9] recommends the use of available models to select patients for proton therapy, based on the gain in toxicity risks. While few dedicated studies were published in the last years, there are no PT-derived NTCP models for the endpoints included in our study.

Overall, our data indicate that, for the analysed cohort of ML patients, toxicity risks for thyroid and heart are comparably low, with a few exceptions (i.e., patients 3, 4, 5 for hypothyroidism, patient 6 for heart valve dysfunction). Remarkably, the risk increase due to variable RBE seems to be significant only for those patients having a higher risk for the nominal plan. Similarly, the uncertainties in the α/β values seem not to markedly affect the risk estimation. Again, an exception is represented by the cases listed above, also showing a larger dependence on the α/β ratio. NTCP values show larger inter-patient fluctuations when looking at lung fibrosis, falling in any case below 8% for 9/10 of the patients, with a weak dependence on RBE and on the α/β ratio.

Finally, a slightly different trend is observed for the RR of CHD, due to the linear dependence on the MHD.

In this context, the analysis of NTCP for heart valve dysfunction deserves a specific comment. According to Hoppe et al [46], while the MHD correlates with the dose to cardiac substructures for conventional RT, this is not always the case for highly conformal techniques. The model by Cella et al adopted in this study is based on the heart D_{\max} as dosimetric parameter, resulting from the analysis of a cohort of patients treated with 3D conformal RT. In that study, a correlation was observed between MHD and D_{\max} ; the MHD reported by Cella et al was equal to 23.2 Gy(RBE), well above the 2.9 Gy(RBE) observed in our patients. This could indicate that, due to the lower MHD observed with IMPT, the application of such a model to PT patients could provide a conservative overestimation of the NTCP for this specific endpoint.

Recently, Dabaya et al [4] proposed practical guidelines for the treatment of adult ML patients with PT, which provides support in identifying patients to be selected for PT, as well as in guiding planning strategy. When selecting NTCP models for our analysis, we detected a discrepancy among the dose metrics proposed in that work compared to those employed by NTCP models developed for ML patients and employed for our analysis (Table 1). Left lung V_5 is indeed present in both guidelines and risk models. A similar thyroid parameter is also employed (V_{25} and V_{30} in [4] and in [39], respectively). However, we observed that the heart D_{\max} and M_{30} , while not being included in the guidelines, are variables used for predicting the risk of heart valve

dysfunction [40] (for which heart and lung volumes also play a role) and lung fibrosis [41], respectively. The analysis of patient 6 summarized in Figure 4 indicates that, by including the heart D_1 in the optimization cost function we were able to reduce the risk of heart toxicity, without compromising target coverage. This could be a practical approach for patients associated with a higher risk of cardiac toxicity, according to the model by Cella et al [40].

Interesting indications concerning the role of model parameters also emerge from Figure 5. The scatter plot associates, for each patient and each OAR, the difference in terms of dosimetric parameters used by the NTCP models with the corresponding Δ NTCP. While for the majority of patients a limited NTCP increase is observed, there are a few notable cases to be discussed. While the increase in heart D_1 is limited to a few Gy(RBE), and the Δ NTCP is also well below 5%, for patient 6 the same D_1 increase corresponds to an enhanced toxicity risk above 10%. Larger effects of RBE are registered for thyroid V30. Interestingly, two patients show a similar increase in the order of 14 Gy, but the corresponding NTCP is increased by about 1% for one of them (patient 7) and by about 15% for the other (patient 4). Due to the non-linear NTCP functions, a given ΔD can correspond to very different Δ NTCP, depending on which portion of the NTCP function is interested (e.g. the initial and final low slope regions, or the high gradient intermediate one). Thus, even though a direct quantification of Δ NTCP between a reference photon plan and proton plan is beyond the purpose of this work, these data show that only considering dosimetric parameters may not be sufficient to estimate a proper risk increase

when accounting for variable RBE. Efficient patient-selection criteria could therefore consider including variable RBE in plan evaluations.

To our knowledge, this is the first study combining variable RBE with NTCP evaluation for ML patients treated with IMPT. Previously, Tseng et al published a dosimetric analysis including variable RBE [5], while Scorsetti et al performed an NTCP evaluation on nominal plans [6], without considering variable RBE. Overall, the results reported by both the studies are in line with our results, where a comparison is possible. In [6] different NTCP models were employed compared to the one used in this study. Specifically, those models were not derived from ML clinical studies. Therefore we believe that our choice was more appropriate for this specific case. However, none of the models employed here or used in [6] has been so far externally validated on patients treated with protons, which would contribute to identifying the most suitable models for this type of analysis.

It is known that combined radiotherapy and chemotherapy treatments may increase the risk of toxicities [47,48]. This is not taken into account in the present analysis, since neither of the NTCP models employed includes chemotherapy as a co-variable. The development of additional models in the future could contribute to investigating this aspect.

Among the limitations affecting our analysis there are the comparably low numbers of patients included. However, this is a representative cohort of patients treated at our institutions. Nevertheless, specific cases of interest such

as the ones discussed might emerge when considering a larger number of patients.

Concerning RBE modelling, several approaches are available in the literature, parametric models being usually employed for proton RBE. The choice of the McNamara model [31] was motivated by the fact that, among parametric models, it was developed by fitting the largest dataset of experimental RBE data. It has also been adopted by a large number of studies, making it easier to compare results obtained by different groups. Current RBE models were developed mostly based on experimental clonogenic survival data. This represents a general limitation when such models are adopted for NTCP analysis, since RBE might differ for endpoints associated with normal tissue toxicities. While more suitable RBE models might become available in the future, current RBE models are expected to provide reasonable hints on the potential impact of variable RBE, and were therefore adopted in several studies [15–21].

For female ML patients, there is also concern for an increased risk of secondary breast cancer [4]. Previous reports indicate that IMPT is associated to a risk reduction compared to photon RT [6]. Such results were obtained assuming a RBE=1.1. Importantly, patient age at treatment, which in the present study only influenced the risk of lung fibrosis (Table S1), would also modulate the risk of cancer induction. Investigations of variable RBE effects on secondary cancer risk estimation are currently on going in our group, on the

base of a recently published RBE model for mutation induction [49], and will be object of separate publications.

Conclusions

In this study we performed a dosimetric and NTCP analysis for ML patients treated with IMPT, comparing nominal plans with that obtained with variable RBE. Our data indicate that, when translated in terms of toxicity risk, the impact of variable RBE is limited, with the exception of a few patients, being associated with a higher nominal risk. Non-linearity effects of NTCP models also suggest that looking only at the biological dose increase might not be sufficient to properly assess variable RBE effects.

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Figure Captions

Figure 1. Boxplot summarizing the distribution of average dose (left) and LET (right) for the ten patients included in the study, for the three selected OARs. For each patient, the average dose and LET associated with the nominal plan have been calculated by considering all voxels belonging to the selected ROI. The boxplots have been obtained based on the 10 patients included in the study, and thus show inter-patient variability in the parameters of interest.

Figure 2. Comparison of nominal vs variable RBE NTCP prediction for the selected OARs and endpoints. For each panel, circles indicate the nominal NTCP, while boxplots reflect the variability associated with variable RBE and random sampling of α/β values.

Figure 3. Dose distribution obtained with constant (a) and variable RBE (b) for patient 4, who was associated with a high thyroid dose. The plan consists of 3 beams (2 anterior + 1 posterior) as indicated in Table 1. The dose-average LET distribution is also reported (c), together with the dose difference (constant – variable RBE) (d). The bottom row shows the DVH (e) and LVH (i.e. LET

volume histogram) (f) for the thyroid, which is the ROI displayed in the dose distributions. In (e) both the constant (solid line) and the variable RBE (dotted line) DVH are shown.

Figure 4. Comparison of nominal plans vs Replan 1 and 2, obtained with an additional heart D1 objective in the optimization cost function. Circles indicate the NTCP for constant RBE, while boxplots reflect the variability associated with variable RBE and random sampling of α/β values. Boxplots were obtained by sampling 100 α/β values.

Figure 5. Scatter plot of ΔNTCP as a function of the difference in terms of dosimetric parameters (ΔV_x or ΔD_1) employed by the NTCP models. Each symbol indicates a patient, while the colours are associated with the three OARs investigated.