


ORIGINAL ARTICLE



Impact of RBE variations on risk estimates of temporal lobe necrosis in patients treated with intensity-modulated proton therapy for head and neck cancer

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ABSTRACT

Background: Temporal lobe necrosis (TLN) is a potential late effect after radiotherapy for skull base head and neck cancer (HNC). Several photon-derived dose constraints and normal tissue complication probability (NTCP) models have been proposed, however variation in relative biological effectiveness (RBE) may challenge the applicability of these dose constraints and models in proton therapy. The purpose of this study was therefore to investigate the influence of RBE variations on risk estimates of TLN after Intensity-Modulated Proton Therapy for HNC.

Material and Methods: Seventy-five temporal lobes from 45 previously treated patients were included in the analysis. Sixteen temporal lobes had radiation associated Magnetic Resonance image changes (TLIC) suspected to be early signs of TLN. Fixed (RWD_{Fix}) and variable RBE-weighted doses (RWD_{Var}) were calculated using $RBE = 1.1$ and two RBE models, respectively. RWD_{Fix} and RWD_{Var} for temporal lobes were compared using Friedman's test. Based on RWD_{Fix} , six NTCP models were fitted and internally validated through bootstrapping. Estimated probabilities from RWD_{Fix} and RWD_{Var} were compared using paired Wilcoxon test. Seven dose constraints were evaluated separately for RWD_{Fix} and RWD_{Var} by calculating the observed proportion of TLIC in temporal lobes meeting the specific dose constraints.

Results: RWD_{Var} were significantly higher than RWD_{Fix} ($p < 0.01$). NTCP model performance was good (AUC:0.79–0.84). The median difference in estimated probability between RWD_{Fix} and RWD_{Var} ranged between 5.3% and 20.0% points ($p < 0.01$), with $V_{60GyRBE}$ and D_{Max} at the smallest and largest differences, respectively. The proportion of TLIC was higher for RWD_{Fix} (4.0%–13.1%) versus RWD_{Var} (1.3%–5.3%). For $V_{65GyRBE} \leq 0.03$ cc the proportion of TLIC was less than 5% for both RWD_{Fix} and RWD_{Var} .

Conclusion: NTCP estimates were significantly influenced by RBE variations. D_{max} as model predictor resulted in the largest deviations in risk estimates between RWD_{Fix} and RWD_{Var} . $V_{65GyRBE} \leq 0.03$ cc was the most consistent dose constraint for RWD_{Fix} and RWD_{Var} .

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Proton therapy; head and neck neoplasm; cerebral necrosis; toxicity; relative biological effectiveness; normal tissue complication probability

Background

The favorable physical properties of protons offer the ability to generate proton treatment plans with low entrance doses, high target volume conformity and a rapid dose fall-off beyond the target volume. This enables a reduction of delivered normal tissue doses and a potential clinical benefit over photon radiotherapy in terms of a lower risk of certain radiation induced side effects. The absorbed doses from protons are considered to be more biologically effective than absorbed doses from photons. The relationship between protons and photons is described by the proton relative biological effectiveness (RBE), which is defined as the ratio of doses required by photons and protons that result in the

same level of biological effect. Although the current clinical practice is to use a constant RBE of 1.1 to calculate the RBE-weighted doses (RWD) [1,2], it is well recognized that the proton RBE varies with fraction dose, Linear Energy Transfer (LET), biological endpoint and tissue (α/β) and other factors [2,3]. The 'true' RBE is therefore variable and the delivered biological dose distribution could deviate substantially from what was planned assuming a fixed RBE of 1.1. Several proton RBE models that take into account the RBE dependency on dose per fraction, LET and tissue α/β have been proposed [4–8]. When applying RBE models for calculation of variable RWD (RWD_{Var}), simulation studies have demonstrated both increased biologically dose in critical organs and reduced target doses compared to fixed RWD (RWD_{Fix}) [9–11].

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 Supplemental data for this article can be accessed [here](#).

Temporal lobe necrosis (TLN) is a potential radiation associated late effect which may occur in patients treated for head and neck cancer at the skull base. Commonly the diagnosis of TLN is based on characteristic image changes on Magnetic Resonance Images (MRIs) and graded according to severity of patient symptoms [12]. Radiation-associated brain image changes and brain necrosis has been described in a number of publications and numerous dose volume predictors and dose constraints for reducing risk of cerebral and TLN have been suggested [13–28]. To implement Normal Tissue Complication Probability (NTCP) models and dose constraints derived from different treatment techniques, different patient cohorts and/or modeling approaches without any form of validation, could in worst case result in clinical misjudgment of the risk of toxicity. In proton therapy, this is further challenged by the uncertainty and variability in proton RBE. The specific aims of the current study were therefore to (a) investigate the effect of RBE variations on NTCP estimates of TLN in skull base HNC previously treated with IMPT, and (b) to evaluate and compare the applicability of previously proposed dose constraints for limiting risk of TLN according to fixed and variable RBE weighted doses.

Material and methods

Patient data and endpoint definition

The patient data consisted of treatment plans from 45 patients selected from a database of 127 patients previously treated with passive scattering and/or pencil beam scanning proton therapy for HNC at the skull base [13]. In order to be included in the current analysis, the following criteria had to be met; treatment with Intensity Modulated Proton Therapy (IMPT), minimum prescribed dose of 60 GyRBE (RBE = 1.1), a minimum follow-up time of 24 months with at least one post-treatment MRI of ≥ 6 months from completion of IMPT. For all patients, the follow-up MRIs had routinely been reviewed for temporal lobe image changes (TLIC) assumed to be associated with TLN. The MRI findings were evaluated according to previously published recommendations for MRI-based diagnosis of radiation necrosis. The criteria included contrast-enhanced lesions located in previously irradiated regions visible on T1-weighted MRI sequences, and hyperintensity/edema visible on T2-weighted MRI sequences [29]. The initial diagnosis was verified through a second review of the MRIs and the MRI reports by two board certified radiation oncologists (GBG and SJF), whereas the clinical grading was based on a retrospective review of the patients' electronic medical records using the Common Terminology Criteria for Adverse Events (CTCAE 4.03) (Supplementary Table I) [12]. Asymptomatic TLIC is scored as Grade 1 according to CTCAE 4.03, and may further be considered as early signs of radiation associated TLN and lesions may evolve over time [29]. The initial TLIC was therefore used as endpoint for the NTCP model fitting and evaluation of the dose constraints associated with TLN.

Treatment

The IMPT treatment plans were based on noncontrast CT scans acquired with the patients immobilized in supine position using a 5-point thermoplastic mask. The CTV definitions were consensus-based. The temporal lobes were retrospectively contoured on the planning CT scans (guided by rigidly registered T1-weighted and T2-weighted MRI sequences when available) according to previously published guidelines [30]. Typically, beam arrangements consisted of one posterior beam and two lateral anterior oblique beams for bilateral neck treatments, and two lateral anterior and posterior oblique beams for unilateral treatments. Simultaneously integrated boost strategy was applied for all IMPT plans with multiple dose levels. All treatment plans were generated in the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA, USA).

Calculation of RBE-weighted doses

The patients' treatment plans and the corresponding planning CT were exported to an in-house developed Monte Carlo system [31–33] for accurate calculations of dose and dose-averaged LET (LET_d). The calculation of LET_d was performed using a step-by-step approach previously described by Cortes-Giraldo and Carabe (method 3) [34] and where LET_d was calculated from pre-generated tables for stopping power from GEANT4 [35]. The RWD_{var} was calculated using two different RBE models; the RBE model from McNamara *et al.* [6] and the RBE model from Wedenberg *et al.* [7]. Both the RBE models are based on the linear quadratic model and RBE is estimated based on the two functions RBE_{max} and RBE_{min} , which respectively describes extreme RBE at low and high doses (Supplementary material B). Both models take the LET_d , the tissue-specific parameter α/β for x-rays and dose as input variables. For calculation of the RWD_{var} , an α/β of 2.0 Gy was used for the temporal lobes [36], whereas the RBE model parameter values were taken from the original publications.

Selection of dose volume predictors and dose constraints

Dose volume predictors from previously published NTCP models for TLN were selected for evaluation according to fixed and variable RBE-weighted doses [16,25,37]. Dose volume constraints for 5% risk were those either previously recommended by international consensus guidelines or derived from the selected NTCP models (i.e., the estimated $TD_{5/5}$ from the original paper). Four of the dose constraints were proposed by international consensus guidelines including the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) [17], the International Consensus Guideline on Dose Prioritization and Acceptance Criteria for Radiotherapy Planning for Nasopharyngeal Carcinoma and the European Particle Therapy Network Consensus [38]. The dose volume predictors and dose constraints are displayed in Table 1. The $V_{70Gy} \leq 0.03$ cc was evaluated only for patients

Table 1. NTCP model predictors and dose constraints from the literature.

NTCP model predictor variables	Reference
D_{Max}	Kong <i>et al.</i> [16]
$D_{0.5cc}$	Wen <i>et al.</i> [25]
$D_{1.0cc}$	Kong <i>et al.</i> [16]
$D_{2.0cc}$	Feng <i>et al.</i> [37]
$V_{60.0}$	The European Particle Therapy Network consensus [38]
$V_{65.0}$	International Guideline on Dose Prioritization and Acceptance Criteria in Radiation Therapy Planning for Nasopharyngeal Carcinoma [18]
Dose constraints	
$D_{Max} \leq 72.0$ Gy*	Quantitative Analysis of Normal Tissue Effects in the Clinic [17]
$D_{0.5cc} \leq 65.05$ Gy	Wen <i>et al.</i> [25]
$D_{1.0cc} \leq 62.4$ Gy	Kong <i>et al.</i> [16]
$D_{2.0cc} \leq 60.3$ Gy	Feng <i>et al.</i> [37]
$V_{60.0} \leq 3.0$ cc*	The European Particle Therapy Network consensus [38]
$V_{65.0} \leq 0.03$ cc	International Guideline on Dose Prioritization and Acceptance Criteria in Radiation Therapy Planning for Nasopharyngeal Carcinoma [18]
$V_{70.0} \leq 0.03$ cc**	International Guideline on Dose Prioritization and Acceptance Criteria in Radiation Therapy Planning for Nasopharyngeal Carcinoma [18]

All the NTCP model predictors were photon-derived based on analysis of associations between TLN and temporal lobe dose distributions in patients treated with IMRT for nasopharyngeal cancer.

*Brain dose constraints in original publications, ** recommended for T3-T4 tumors nasopharyngeal cancers.

with T3–T4 tumors and diseases with skull base and/or intracranial involvement. All dose constraints were evaluated according to temporal lobe doses.

Statistical analysis and dose response modeling

Fixed and variable RBE-weighted doses for the temporal lobes were summarized using descriptive statistics and compared using Related Samples Friedman’s two-way analysis of variance by ranks (Friedman’s test).

To investigate the influence of RBE variations on the estimated probability of temporal lobe necrosis, RWD_{Fix} was used as input doses in NTCP model fitting with D_{max} , $D_{0.5cc}$, D_{1cc} , D_{2cc} , $V_{60GyRBE}$ and $V_{65GyRBE}$ as predictor variables. The NTCP model fitting was performed using univariate logistic regression analysis with robust estimation of standard errors to account for within-patient correlations of the temporal lobes. Bootstrapping ($n=1000$) was applied for internal model validation. Models were evaluated and compared using Nagelkerke’s R^2 , Brier score, Area Under the Receiver Operating Characteristic Curve (AUC) and Calibration intercept and slope. For each of the models, the probability of temporal lobe necrosis was estimated for RWD_{Fix} , RWD_{McN} and RWD_{Wed} using the formula

$$NTCP = \frac{1}{(1 + e^{-s})} \tag{1}$$

$$s = \beta_0 + \beta_1 x \tag{2}$$

where β_0 and β_1 are the model coefficients and x is the predictor variable. The differences in the estimated probabilities between RWD_{Fix} , RWD_{McN} and RWD_{Wed} were compared using two-sided paired Wilcoxon signed-rank test.

The applicability of the proposed dose constraints was evaluated by calculating the observed proportion of TLIC in temporal lobes with doses meeting the specific dose constraints associated with a 5% risk of temporal lobe necrosis. This was done separately for RWD_{Fix} , RWD_{McN} and RWD_{Wed} . For all statistical tests, p -values < 0.05 were considered significant. Bonferroni corrections were applied to adjust for multiple comparisons. All analyses were performed in R

version 4.0.2 [39]. Regression analysis and validation were performed using the package *rms* version 6.1-0 [40].

Results

Patient characteristics are displayed in Table 2. Three of the patients had bilateral temporal lobe image changes. After excluding the contralateral temporal lobes from patients with unilateral treatments, 75 temporal lobes, of which 16 with verified radiation associated image changes, were included in the analysis. Patient and TLIC outcomes for this cohort has previously been described [13].

Comparison of fixed and RBE-weighted doses

An example of the dose distribution for RWD_{Fix} , RWD_{McN} and RWD_{Wed} is displayed in Figure 1(a). The summary statistics of selected dose variables for the entire cohort are displayed in Figure 1(b–c) and according to TLIC status in Supplementary Table II. Overall, both RWD_{McN} and RWD_{Wed} was significantly higher than RWD_{Fix} ($p < 0.01$). The differences in median values between RWD_{Fix} and RWD_{Var} were typically in the range of 4 to 6 GyRBE for the high-dose indices with exception of D_{Max} , where the difference exceeded 8 GyRBE. There were only small and insignificant differences between RWD_{McN} and RWD_{Wed} , we therefore subsequently present only the results for RWD_{McN} . The median differences between RWD_{McN} and RWD_{Fix} in D_{max} and $D_{0.5cc}$ to the temporal lobes were 8.4 GyRBE (95% CI: 7.6–9.5 GyRBE) and 5.2 GyRBE (95% CI: 4.5–6.1 GyRBE), respectively, whereas the difference in temporal lobe D_{mean} between RWD_{McN} and RWD_{Fix} was 1.1 GyRBE (95% CI: 1.0–1.3 GyRBE) (Figure 1(b)). Similarly, the volume-dose indices were higher for the RWD_{Var} compared to RWD_{Fix} . The median difference between RWD_{McN} and RWD_{Fix} for $V_{40 GyRBE}$ and $V_{70 GyRBE}$ to the temporal lobe were 1.4 cc (95% CI: 1.2–1.6 cc) and 0.7 cc (95% CI: 0.4–1.2 cc), respectively (Figure 1(c)).

Table 2. Patient characteristics for those with ($n = 13$) and without ($n = 32$) image changes on the follow-up MRIs.

Parameter	No TLIC ($n = 32$) n (%)	TLIC ($n = 13$) n (%)	Total n (%)	p Value
Age, median (range)	44 (18–82)	54 (32–71)	46 (18–82)	ns
Sex				ns
Male	13 (40.6)	5 (38.5)	18 (40)	
Female	19 (59.4)	8 (61.5)	27 (60)	
Site				ns
Nasopharynx	11 (34.4)	8 (61.5)	19 (42.2)	
Sinonasal	8 (25.5)	4 (30.8)	12 (26.7)	
Parotid	8 (25.5)	–	8 (17.8)	
Other	5 (15.6)	1 (7.7)	6 (13.3)	
T-category				ns
T1–T2	9 (28.1)	2 (15.4)	11 (24.4)	
T3–T4	14 (43.8)	10 (76.9)	24 (53.3)	
Recurrence	7 (21.9)	1 (7.7)	8 (17.8)	
NA	2 (6.3)	–	2 (4.4)	
Surgery				ns
No	12 (37.5)	9 (69.2)	21 (46.7)	
Yes	20 (62.5)	4 (30.8)	35 (77.8)	
Chemotherapy				<0.05
No	10 (31.0)	–	10 (22.2)	
Yes	22 (68.8)	13 (100)	35 (77.8)	
Intracranial involvement				<0.01
No	23 (71.9)	3 (23.1)	26 (57.8)	
Yes	9 (28.1)	10 (76.9)	19 (42.2)	
Dose, median (range)	66 (60–70)	70 (60–70)	68 (60–70)	<0.05
Follow-up time, median (range)	60.0 (37–100)	49 (24–105)	59 (24–105)	ns
Latency time, median (range)	–	19 (9–33)	–	
CTCAE 4.03 grading				
Grade 1	–	11 (57.6%)	–	
Grade 3	–	2 (15.4%)	–	

Other site: Skin, Base of Skull. Follow-up time: from end of treatment to last available MRI. Latency time: from end of treatment to first MRI with image change. Significant tests: Chi-Square/Fisher exact test for categorical variables, Mann–Whitney for continuous variables.

The effect of RBE variations on NTCP

Of the six NTCP models, the model with $D_{0.5\text{cc}}$ as predictor had the best discrimination and calibration, however all model predictors were significantly associated with TLIC and all had good discriminative ability with corrected AUCs ranging from 0.785 to 0.838. The odds ratios, p -values and the result from the bootstrap validation of the models are displayed in [Supplementary Table III](#). For all the NTCP models, the estimated probabilities based on RWD_{McN} and RWD_{Wed} were approximately similar, however significantly higher than the estimated probability from RWD_{Fix} (all $p < 0.01$). Compared to RWD_{Fix} , the median increase in the estimated probabilities for RWD_{McN} and RWD_{Wed} were less than 10 percentage point for the majority of models and ranged between 5.3 and 8.1 percentage points for RWD_{McN} and between 5.3 and 8.0 percentage points for RWD_{Wed} . For the model with D_{Max} , however, the increase was 19.4 and 20.0 percentage points for RWD_{McN} and RWD_{Wed} , respectively ([Figure 2/Supplementary Figure 1](#)).

Evaluation of dose constraints according to fixed and variable RBE-weighted doses

In general, when dose constraints were met, the observed proportion of TLIC was higher for RWD_{Fix} than RWD_{McN} and RWD_{Wed} . For RWD_{Fix} , the observed proportion of TLIC ranged between 4.0% and 13.1%, with the highest proportion of TLIC for $V_{60\text{GyRBE}} \leq 3.0\text{cc}$. For RWD_{Var} , the observed proportion of TLIC ranged between 1.3% and 5.3%. For $V_{65\text{GyRBE}} \leq$

0.03 cc the proportion of TLIC was less than 5% for both RWD_{Fix} , RWD_{McN} and RWD_{Wed} ([Figure 3](#)).

Discussion

Although the variability in proton RBE is well recognized, a fixed RBE of 1.1 is standardly used in clinical practice. This practice is rationalized with the arguments that RBE models have significant uncertainties and lack validation in *in-vivo* studies and for clinical outcomes [2]. In the current study, we used treatment plans and outcome data from patients treated with IMPT for HNC at the skull base in order to explore how variations in RBE may influence temporal lobe dose distributions and hence the assessment of risk of developing radiation-induced TLN. We found that temporal lobe doses were systematically higher when calculated using variable RBE models compared to uniform scaling of the physical dose by a factor of 1.1. We further found that the resulting increase in NTCP varied depending on dose volume variable used in the model. Moreover, for the majority of dose constraints evaluated in this study, the RWD_{Fix} in general underestimated risk, while the RWD_{Var} were in line with the proposed dose thresholds.

Previous studies have addressed the potential effect of RBE variations in brain organs at risk (OARs) and reported comparable findings as in the current study. Yepes *et al.* [41], evaluated the effect of RBE variations in IMPT treatment plans using three different RBE models. They showed that RBE_{McN} and RBE_{Wed} predicted approximately similar, but in generally higher RBE than 1.1 in critical organs (and hence

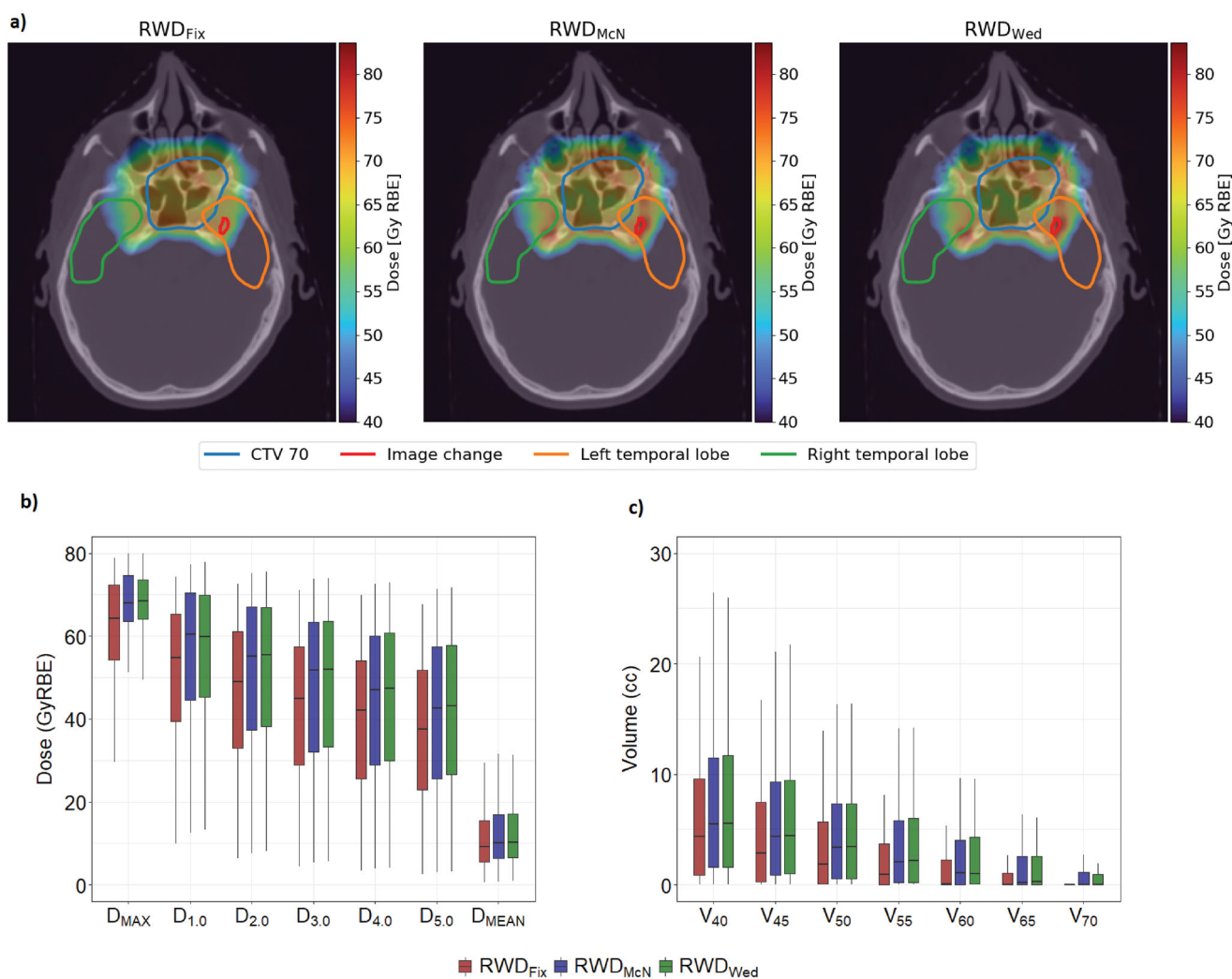


Figure 1. (a) Example of fixed and variable RBE weighted dose distributions. Note the high dose area in the contoured image change (red line) in the RWD_{var} dose distributions. (b–c) boxplots of selected dose volume indices for the temporal lobes. RWD_{Fix} : dose distribution calculated using a constant RBE of 1.1, RWD_{McN} : dose distribution calculated using the RBE model from McNamara et al. [6], RWD_{Wed} : dose distribution calculated using the RBE model from Wedenberg et al. [7]. CTV 70: prescribed dose 70 GyRBE (RBE = 1.1).

increased RWD_{var}), whereas the increase in RBE predicted by the repair-misrepair-fixation (RMF) model was less pronounced. Giantsoudi *et al.* [9] compared treatment plans from IMPT and passive scattering proton therapy (PSPT) and found that, although IMPT was superior to PSPT when evaluated according to RWD_{Fix} , increased maximum RWD_{var} of up to 6% in the brainstem was found for IMPT. Wedenberg *et al.* [11] compared dose distributions from photons, fixed and variable RBE weighted doses in treatment plans from three patients with brain tumors. They found higher doses in critical OARs and higher estimated NTCP for RWD_{var} compared to RWD_{Fix} .

The use of dose constraints across modalities is generally subject to uncertainties, and although all the evaluated dose constraints could be considered applicable in terms of RWD_{var} , only $V_{65GyRBE} \leq 0.03$ cc was applicable for RWD_{Fix} . This could indicate that, for IMPT, dose constraints specified in terms of the RBE models used in the current study could be clinically applicable in evaluating IMPT plans safely in terms of protection of temporal lobes from TLIC. Such constraints may very well be achievable and considered at the

time of plan optimization without compromising target dose. IMPT specific dose constraints for radiation induced brain toxicity are still generally lacking, however, based on analysis of a mixed patient cohort treated with IMPT and/or PSPT for skull base HNC, our group recently suggested that brain volume receiving 67 GyRBE (RBE = 1.1) should be ≤ 0.17 cc to limit risk of toxicity [13]. From treatments with PSPT alone, MacDonald *et al.* [19] reported a 15% risk of TLN if $V_{70GyRBE}$ to the temporal lobes exceed 1.7 cc.

In recent years, there has been a growing awareness of the potential of NTCP models as useful tools for plan evaluation and patient selection between different treatment modalities [42]. Our results suggest that the selection of dose volume predictor may not be straightforward in NTCP model fitting for proton therapy. Despite good performance and discriminative ability in the model with D_{Max} as predictor (AUC = 0.833), the deviations in risk estimates were more than twice as large as with any of the other dose volume predictors. Although D_{Max} previously has been suggested as predictor in NTCP models and is commonly used as dose constraints for treatment plan optimization- and evaluation,

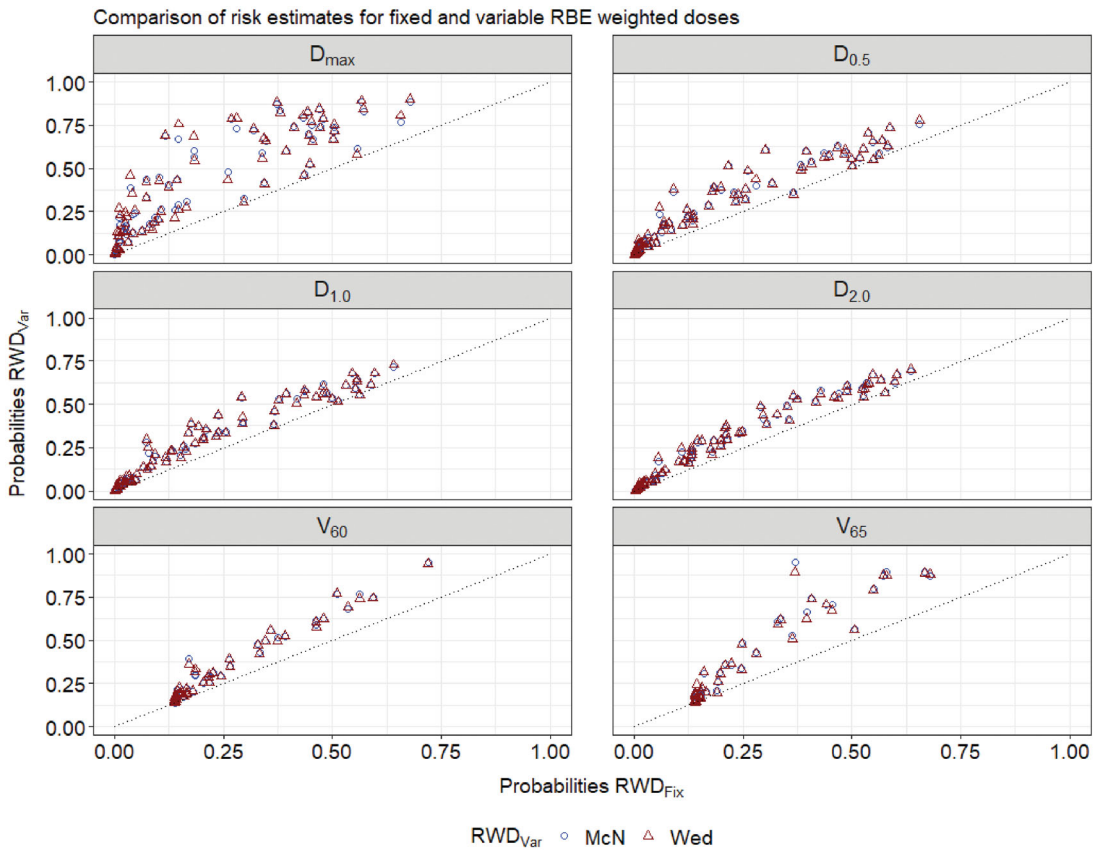


Figure 2. Scatter plot showing the difference in estimated probabilities between RWD_{Fix} and RWD_{Var} .

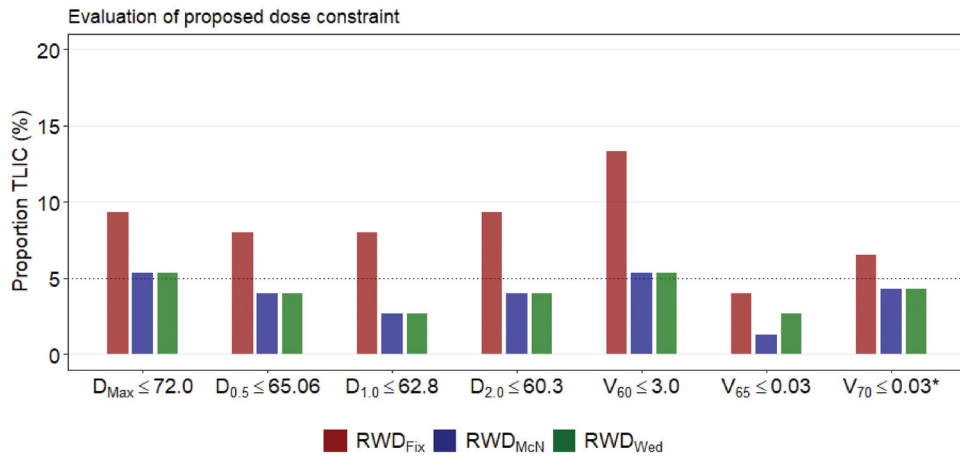


Figure 3. (a) Evaluation of the different dose constraints according to RWD_{Fix} , RWD_{McN} and RWD_{Wed} . Barplot of observed proportion of TLIC when the different dose constraints were met. *Dose constraint only evaluated for patients with T3–T4 disease and with skull base/intra cranial involvement. The dotted horizontal line represents the 5% level of observed TLIC in the data set. Dose and volumes in GyRBE and cc, respectively.

a different dose volume variable with lower predictive performance may in fact be preferable.

The RBE models from McNamara *et al.* [6] and Wedenberg *et al.* [7] have similarities in certain model assumptions and are partly based on analysis of the same data, which may explain the small differences in the estimated biological doses between the two. Further, Rørvik *et al.* [43] have previously showed that RWD_{var} vary greatly depending on RBE models used for dose calculations, mainly due to differences in model assumptions and data used for RBE model fitting. They found that low α/β combined with elevated LET lead to

the largest variations in biological dose, typically corresponding to late responding tissue at the distal edge of the target like in the current study. Therefore, in addition to the small cohort size and retrospective design, we consider the limited number of RBE models used in the analyses as the main limitation of this study. In future studies, including a wide range of different models and α/β values could better quantify the uncertainties in the assessment of risk of toxicity due to RBE variations.

In conclusion, we found systematically higher biologically effective temporal lobe doses with variable RBE models

compared to doses scaled by 1.1. For the majority of dose constraints evaluated in this study, the RWD_{Fix} in general underestimated risk, while the RWD_{Var} were in line with the proposed dose threshold associated with risk of temporal lobe necrosis. Dose volume predictors with near-maximum doses ($D_{0.5}$ – D_{2cc}) were less influenced by RBE variations than D_{max} . RBE variations may cause large uncertainties in assessment of risk of radiation induced toxicity. The result from the current study indicates that including RWD_{Var} as part of IMPT treatment plan evaluation may provide valuable clinical information in terms of temporal lobe protection and should be prospectively studied and validated.

Disclosure statement

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