Feasibility of relating LET differences to toxicity for Head & Neck proton therapy

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INTRODUCTION AND AIM

Variations of the relative biological effectiveness (RBE) of proton therapy with linear energy transfer (LET) are predicted from pre-clinical experiments and observations of brain lesions[1, 2]. However, RBE values may substantially vary for different clinical treatment sites and endpoints.

AIM

In this study, we aim to assess the feasibility of integrating LET into normal tissue complication probability (NTCP) models for patient-rated head and neck cancer toxicity.

METHOD

We analyzed 32 head and neck cancer patients treated with intensity modulated proton therapy (IMPT). Physical dose (D) and product of D and dose-weighted averge LET (D·LET) were calculated on weekly verification CTs and accumulated on the planning CT using the Raystation v9R Monte Carlo algorithm[3].

A multivariate Gaussian distribution is fitted to the dosimetric and D·LET parameters determining their standard deviations and covariance. From this distribution, patients can be sampled to create a realistic dataset of any number of patients with their dosimetric and D·LET parameters. Toxicity scores were simulated using NTCP models from the Dutch national proton therapy indication protocols[4] for xerostomia, dysphagia and tube feeding dependency. The biological equivalent dose used in the NTCP calculation was calculated assuming an RBE model with a linear dependency on LET. As the dependency of RBE on LET is not precisely known, the calculations were performed twice with slopes of 0.04 and 0.10 µm/keV.

A logistic regression analysis was used to test the hypothesis that the RBE depends on the LET in the simulated dataset by fitting the parameter c in the equation RBE = 1.0 + c · LET.[5] The simulation was performed 1.000 times for various sample sizes. The statistical power was calculated as the proportion of simulations for which c was larger than 0 with a two-tailed p-value < 0.05. All calculations were performed in Matlab 2018b.

RESULTS

The physical dose and D·LET parameters are shown in table 1 on the right.

The statistical power for various sample sizes and assumed RBE/LET dependencies are shown in figure 1 below. For a RBE / LET slope of 0.10 the required sample size for a power of 80% is upwards of 60.000 patients for all considered models. For a slope of 0.04 the required sample size for a power of 80% is higher than the highest considered dataset of 100.000 patients.

The Pearson correlation coefficient between physical dose and D·LET for all regions of interest considered in the NTCP models ranged from 0.89 to 0.95. This led to a high correlation between the biological dose calculated with a constant RBE of 1.1 or with a RBE depending on LET with a slope of 0.10 (figure 2).

	D [Gy]	LET [GykeV/µm]	D*LET [GykeV/µm]	Pearson R
Xerostomia				
Contralateral parotid gland	14.7	3.6	52.8	0.95
Dysphagia				
PCM superior	44.6	3.4	151.1	0.89
Oral cavity	11.1	4.7	52.1	0.95
Tube feeding dependence				
PCM superior	44.6	3.4	151.1	0.89
Contralateral parotid gland	14.7	3.6	52.8	0.95
Cricopharyngeal muscle	23.8	5.0	120.2	0.86

*Table 1: Average physical dose and D*LET of the parameters in the considered NTCP models and their Pearson correlation coefficient r. OAR LET is calculated by calculating by dividing the average D*LET by the average D.*

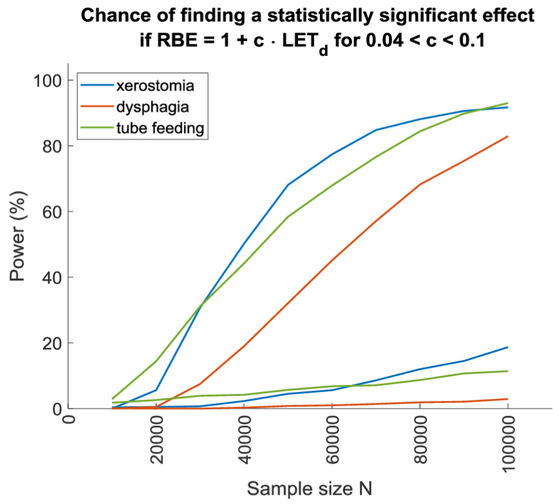

*Figure 1: The chance of finding an independently statistically significant relation (i.e. power) between patient-rated toxicities and the physical dose and additional biological dose (an unknown factor multiplied by dose and LET). For the simulations, two RBE models were assumed to give a lower and higher estimate of the power: RBE = 1.0 + 0.04 * LET and RBE = 1.0 + 0.10 * LET.*

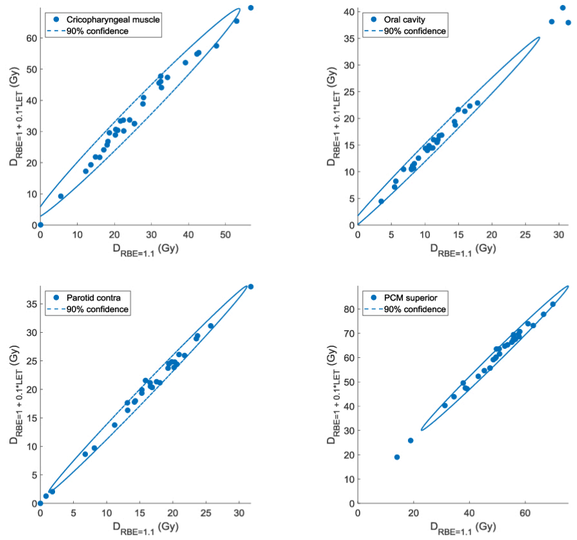

*Figure 2: The biological dose (D_{RBE}) for a variable RBE equal to 1.0 + 0.1 * LET plotted against the D_{RBE} for a constant RBE of 1.1 for different organs-at-risk. The lack of spread indicates a strong correlation between the two biological doses, indicating the LET for a certain ROI does not vary greatly among patients.*

CONCLUSIONS

- Directly relating LET to patient-rated head and neck cancer toxicity is not feasible for our current clinical practice.
- The high required number of patients is a consequence of the lack of variation of LET between patients. This is likely due to the protocolled treatment planning process.
- A potential solution is to perform a clinical trial in which LET optimization is applied with different weights on LET parameters as this could introduce more variation in LET between patients resulting in a higher statistical power.
- Imaging techniques which directly relate to radiation damage such as diffusion tensor imaging (DTI) for brain white matter or PSMA-PET scans for salivary glands can potentially help overcome this issue.
- Better understanding of the relation between RBE and LET is required to form clinical decisions when comparing plans with different LET and physical dose distributions. These decisions will become increasingly relevant when tools evaluating and optimizing LET distributions become clinically available.

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REFERENCES

[1] Paganetti H, Blakely E, Carabe-Fernandez A, Carlson DJ, Das IJ, Dong L, et al. Report of the AAPM TG-256 on the relative biological effectiveness of proton beams in radiation therapy. Med Phys. 2019;46(3):e53–78.
[2] Bahn E, Bauer J, Harrabi S, Herfarth K, Debus J, Alber M. Late contrast enhancing brain lesions in proton treated low-grade glioma patients: clinical evidence for increased periventricular sensitivity and variable RBE. Int J Radiat Oncol. 2020 Mar;
[3] Wagenaar D, Tran LT, Meijers A, Marmitt GG, Souris K, Bolst D, et al. Validation of linear energy transfer computed in a Monte Carlo dose engine of a commercial treatment planning system. Phys Med Biol. 2020 Jan 17;65(2):025006.
[4] Landelijk Platform Protonentherapie, Protonentherapie LP. Landelijk Indicatie Protocol Protonen Therapie Hoofd-halstumoren. 2017.
[5] Unkelbach J, Botas P, Giantsoudi D, Gorissen BL, Paganetti H. Reoptimization of Intensity Modulated Proton Therapy Plans Based on Linear Energy Transfer. Int J Radiat Oncol Biol Phys 2016;96:1097–106.

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