Article:
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Table 2: voxelised LET studies ('Group A'), key methods & analysis

First author, year	Level of analysis	Type of image registration between dose/LET and follow-up imaging	Physical dose and LET calculation methods	Statistical method	Interactions and clinical factors considered	Model linking dose and LET: literature-based or fitted?	Accounting for nested nature of voxel-data (inter-patient radiosensitivity)
Peeler, 2016	Voxel	Rigid	MC^2 (in-house) Monte Carlo system used to calculate dose and track-averaged LET (LET_t).	Generalised linear model using probit link function to relate dose and LET with binary presence of image change.	Mean dose, max. dose, mean LET_t, max. LET_t (all within the CTV), age, time between surgery and radiation.	Fitted model: voxel-wise probability of image change ~ (1.2* LET_t)+ (0.14*Dose) – 11.2 (with probit link function)	No
Giantsoudi, 2016	Structure	Assumed rigid	TOPAS Monte Carlo simulations of dose and dose-averaged LET (LET_d) scored in units of keV/mm/(g/cm^3).	Wilcoxon signed-rank test comparing LET and model-based RBE values / RBE-weighted dose between the target volume and the outlined region of change.	None	Literature-based models: Wilkens [40] and Carabe-Fernandez [41] LET-based RBE models (both based on the linear-quadratic dose-response), with a fixed α/β value of 2.1 Gy.	N/A
Fossum, 2017	Structure	N/A	Graphics processing unit (GPU) Monte Carlo calculations of dose and dose-averaged LET (LET_d).	Qualitative: the location of RBE adjusted dose hotspots predicted by the LET-based model was qualitatively compared to the location of reported toxicities	None	Literature-based model: Beltran [42] RBE = 1.1*(0.08* LET_d + 0.88)	N/A
Roberts, 2019	Structure	Rigid	GPU Monte Carlo calculations of dose and dose-averaged LET (LET_d).	Wilcoxon signed rank test comparing volumetric overlap between the regions of image change (binary measure) and isodose regions evaluated either RBE=1.1 or the variable RBE model.	Univariate analyses evaluating patient-specific factors, dose, and proton-specific parameters were conducted. No further details provided.	Literature-based model: Beltran [42]RBE = 1.1*(0.08* LET_d + 0.88)	N/A
Eulitz, 2019	Voxel	Deformable	TOPAS Monte Carlo simulations of dose and of track-averaged LET (LET_t).	10 logit models for presence of image change (binary measure) in a voxel were built based on dose, LET, Periventricular Region (PVR) contour, interaction terms dose*LET and dose*PVR.	Intercorrelation among the variables was tested by calculating the Spearman rank coefficient.	Fitted model: voxel-wise probability of image change ~ -13.9+(0.113*Dose)+(1.37*LET)+(2.43*PVR) (with logit link function)	No

Bolsi, 2020	Structure	Not reported	LET_d distributions (considering only primary protons in water) were calculated analytically according to Wilkens & Oelfke [40].	Dose–volume metrics for dose and LET_d distributions were compared between patients with toxicity vs the rest of the cohort with the Kruskal-Wallis test.	None	None: physical doses and LET_d distributions were evaluated separately. Maximum and mean values of dose average LET_d were considered for the PTV and the vascular structures.	N/A
Ödén, 2020	Structure	Rigid	Monte Carlo simulations using research version of RayStation v6 (RaySearch Laboratories, Sweden). LET_d was calculated as the unrestricted LET on voxel level in unit density tissue with dose-averaging method "C" from [43].	Qualitative: the location of RBE weighted dose hotspots predicted by the LET-based model was qualitatively compared to the location of reported toxicities.	None	Literature-based models: Wedenberg [44] and McNamara [45] LET-based RBE models (both based on the linear-quadratic dose-response), with volume dependent α/β values considered (2Gy for normal tissue).	N/A
Wang, 2020	Structure	Deformable	TOPAS Monte Carlo simulations of dose and of dose-averaged LET (LET_d).	Biological effective D0.5cc (dose to 0.5 cm^3 of rib volume), using constant and LET_d-dependent RBE, compared between ribs with and without fractures. Logistic regression model relating BED0.5 and the binary outcome of fracture.	None	Literature-based model: McMahon [46]RBE $= 1+0.055* LET_d$	No
Bahn, 2020	Voxel	Rigid	FLUKA Monte Carlo simulations of dose and of dose-averaged LET (LET_d). LET_d calculations were based on mass stopping power and all charged	Logistic regression linking dose, dose-LET product, and ventricular proximity (binary; VP = 1: distance ≤4 mm; VP = 0: distance >4 mm), to the probability of a voxel being the origin of an imaging lesion.	None	Fitted model: voxel-wise probability of lesion origin (POLO) ~ 26.3 + (0.19*Dose) + (0.018*LET*Dose) + (1.19*VP) (with logit link function) $\mathrm{RBE} = 1 + 0.0947 * \mathrm{LET}_d$	No

			particles, such as secondary protons and heavier hadrons, were taken into account.				
Bertolet, 2021	Voxel	Deformable	Dose-averaged LET (LET_d) distributions were calculated according to an analytical algorithm where primary plus secondary protons and alpha particles were considered [47].	For each patient, one-sided Kolmogorov-Smirnov tests were performed to compare the cumulative distribution of LET_d in voxels with and without image-changes.	Inter-patient variability: for each patient, difference between average LET in image change area and average LET in dose-matched region without image change. Age, gender, time elapsed between end of treatment and MRI, and CTV / beam - specific factors were also considered.	Fitted model: voxel-wise probability of image change (based on effective cell survival under the linear quadratic model) = $(1 - \exp(-\alpha\ \mathrm{LET}_d * \mathrm{Dose} - \beta\ \mathrm{LET}_d * \mathrm{Dose}^2))^{N_0}$ Where N_0 is the number of cells in a voxel and the following dependencies on LET_d were assumed: $\alpha(\mathrm{LET}_d) = 0.011 + 0.033\mathrm{LET}_d$ and $\beta(\mathrm{LET}_d) = 0.0015$	Yes, for initial LET_d analysis – patient-specific radiosensitivity accounted for by comparing voxels within individual patients. No, for model of image change probability.
Niemierko, 2021	Voxel	Not reported	TOPAS Monte Carlo simulations of dose and of dose-averaged LET (LET_d). LET_d was density corrected and calculated for protons only.	Principal analysis: Nested (2-level) mixed-effects logistic regression to relate (voxel-wise) presence of necrosis to dose and LET (random intercept by patient, random coefficient on voxel's LET, unstructured covariance of random effects). Separate models were fitted for CNS and for head and neck tumours.	Inter-patient variability: for each patient, difference between average LET in necrotic region and average LET in dose-matched non-necrotic region. Meta-analysis methodology to estimate average difference over all patients, and to assess study het-erogeneity (ie, interpatient variation) using the I-squared statistic.	Fitted model: Voxel-wise probability of necrosis ~ -14.7+(0.18*Dose)+(-0.84*LET) (logit link function) NB: When the nested structure of the data was explicitly accounted for using the 2-level mixed effects model, no LET effect was evident (but dose effects remained significant).	Yes - patient specific radiobiology was considered using multi-level mixed effects modelling
Yang, 2021	Structure	N/A	GPU Monte Carlo calculations of dose and dose-averaged LET (LET_d).	Dose Volume LET Histogram (DLVH) developed, for analysing adverse events (rectal bleeding). Dose and LET incorporated as independent variables.	None	N/A: DVLH lines used to represent the percentage volume of a structure that had a dose of at least *d* Gy and an LET of at least *l* keV/mm	No
Skaarup, 2021	Voxel	Deformable	MCNPX Monte Carlo simulations of dose and of LET	Nested generalized linear mixed regression to relate dose and LET to variation in image	None	Fitted model:	Yes - patient specific radiobiology

			(LET definition not specified).	signal. This was done separately for the three MRI modalities: T1, T2 FLAIR and FA images.		$\text{Follow-up}_{i,j,n} = a * \text{Baseline}_{i,n} + b * \text{f}(\text{dose}_{i,n}) + c * \text{LET}_{i,n} * \text{f}(\text{dose}_{i,n}) + \alpha_{i,j}$ where the i-subscript refers to an individual patient, the j-subscript refers to the different follow-up sessions for that patient, the n-subscript refers to a specific voxel for the patient. Follow-up and Baseline represent the image voxel values of the scans, f(dose) represents a function of the dose for that voxel. Different fit parameters were obtained for different imaging modalities.	was considered using multi-level mixed effects modelling