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Table 1: all clinical studies, key details and findings

First author, year	Primary tumour	Cohort considered in statistical modelling; number (n) of patients reported for outcome under consideration	Image changes / patient effects studied	Authors' view: have they found clinical evidence for variable RBE?
Group A: voxelised analyses of patient effects versus physical dose and LET				
Giantsoudi, 2016	Paediatric medulloblastoma	Subset of 10/111 proton cases who developed image changes (4 symptomatic, 6 asymptomatic). 6 randomly selected proton patients without image changes also studied. Protons: n=10/111 (PS)	All areas of MRI radiographic changes were considered. Additional details not provided. Reported time to injury (from the start of the irradiation to the first image change) ranged from 7.9 to 17.8 months.	No: "Differences in RBE and LET, among the three patient groups, were not statistically or clinically significant."
Peeler, 2016	Paediatric ependymoma	Subset of 14/34 proton cases who developed image changes. Protons: n=14/34 (PS)	Image changes were determined as T2-weighted FLAIR hyperintensity, with or without enhancement on T1-weighted post-contrast scans. The earliest timepoint with changes was considered (further details on image change time-course are not given).	Yes: "Our correlation of changes on MR images after proton therapy with increased LET constitutes the first clinical evidence of variable proton biological effectiveness."
Fossum, 2017	Head and neck cancer	11 consecutive proton cases, all with reported toxicities. Protons: 11/11 (IMPT)	Physician-reported toxicity and patient-reported outcomes. Toxicity was assessed: 11-16 days post-treatment, plus 3, 6 and 12 months later.	Maybe: "The correlation between higher LET and RBE and toxicity in the oral cavity and oropharynx was strong. For higher LET and RBE in regions such as the brain or mandible, the correlation was not as strong. Higher LET and RBE did not always result in unwanted toxicities. These initial observations should be considered exploratory."
Roberts, 2019	Paediatric brain tumours	30 proton patients treated within a specific window were evaluated. 7 developed post-treatment radiologic changes (5 of these were symptomatic). Protons: n=7/30 (PBS)	Image changes were identified from T1-weighted images post contrast and T2-weighted FLAIR images. In patients with multiple follow-up MRI scans, the scan with the maximal imaging changes was selected for analysis. Timing is not reported for image change onset, but the average time to symptom onset was 126 days (range 73-178 days).	Yes: "Within our paediatric brain tumour population treated with spot-scanning proton therapy, our BD [Biologic Dose] model demonstrated superior volumetric overlap with posttreatment T2 changes compared with the TPD [Treatment Planning Dose] model."
Bahn, 2020	Glioma (grade I / II)	Subset of 23/110 proton patients who exhibited at least one contrast-enhancing brain lesion (CEBL) Protons: n=23/110 (IMPT)	Contrast-enhancing brain lesions (CEBLs) were identified using T1-weighted post-contrast MR. Follow-up scans were taken ~3 monthly, but only the smallest 30% of CEBLs were used for model building.	Yes: "Our findings provide clinical evidence for a relative biological effectiveness that increases significantly with linear energy transfer and an increased tissue sensitivity in proximity to the ventricular system."

			Further details on CEBL time-course are not given.	
Eulitz, 2019	Glioma (grade II / III)	6 proton patients treated within a specific window were evaluated, all showed treatment related changes confirmed using histology (4/6) or radiological diagnosis (2/6). Protons: n=6/6 (PS)	Image changes were identified from T1-weighted post-contrast MR. The earliest timepoint with changes was considered (inter-patient variation of 6 -24 months post-treatment).	Yes: "The modelled tissue tolerance dose TD15 decreased with increasing LET, which indicates a variable proton RBE that increases with LET."
Bolsi, 2020	Paediatric craniopharyngioma	16 proton patients treated within a specific window (with >1 year of follow-up) were analysed. Of these, two developed radiation-induced cerebral vasculopathy (RICV). Protons: n=2/16 (PBS)	For one patient, RICV was identified by clinical presentation (and confirmed by MRI) 2 years after irradiation. The other patient was asymptomatic but MR imaging revealed a stenosis of the right internal carotid artery, 14 months after irradiation.	Maybe: "For children with and without RICVs, quantitative analysis showed a significant correlation with LET_d average/maximum values in vascular structures, whilst no correlation was found on dosimetric parameters"
Ödén, 2020	Schwannoma (grade I), meningioma (grade I) and frontal oligoastrocytoma (grade II)	3 proton patients with suspected radiation-induced toxicities were identified. Protons: n=3 (PBS)	Suspected radiation-induced toxicities (brainstem complications and unilateral blindness) were established based on clinical evaluations and consecutive MRIs at follow-up: T2-weighted FLAIR and/or T1-weighted contrast enhancement sequences. Toxicities presented 5-9 months after irradiation.	Maybe: "Although a direct causality between RBE and toxicity cannot be established in a study of this size and design, the analysis indicates that it is unlikely to have been caused by setup and range errors, whereas high LET_d and RBE values could be associated with the observed toxicities."
Wang, 2020	Breast cancer	Subset of 13/203 proton patients with rib fractures. Proton: n=13/203 (PS and PBS)	Rib fractures contoured on original plan from follow-up CT scans. The median time from the end of treatment to the first noted fracture was 15 months (range 7-42).	Maybe: "The increased rib fracture rate seen in our trial is probably associated with the increased LET_d and RBE at the distal edge of proton beams."
Bertolet, 2021	Meningioma	31/93 proton patients treated within a specific window exhibited abnormal follow-up images. 5 patients were excluded due to data calculation issues. Protons: n = 31/93 For the data analysis: Protons: n=26/93 (PBS)	Regions showing hyperintensity on T2 weighted-FLAIR were labelled as 'image change areas (ICA)'. Intervals between end of treatment and ICA identification ranged from 2 to 61 months, with a median of 17 months. No significant changes in ICA were observed for at least 2 years.	Maybe: "11 [of 26] patients showed higher LET_d in imaging change regions than in group of voxels with the same dose. This group of patients had significantly shallower targets for their treatment than the other 15 and used fewer beams and angles. …This study points towards the possibility of areas with imaging change are more likely to occur in regions with high dose or in those areas with lower dose but increased LET_d… However, most of the patients did not show spatial correlation between their image changes and the LET_d values, limiting the cases for the possible role of high LET as a toxicity inductor".
Niemierko, 2021	Head and neck, skull base, or	64/179 proton patients treated within a specific window exhibited necrosis. 50 of these were available for analysis: 27 with	Determination of necrosis was based on multiple factors including neuro-radiologist interpretation, serial imaging	No: "Our data analysis… did not show a correlation between regions of toxicity and proton LET using 4 different analysis methods. Our data analysis is

	intracranial tumours	extracranial tumours, 23 with intracranial (CNS) tumours. Protons: n = 64/179 For the data analysis: Protons: n=50/179 (45 PS, 5 stereotactic beamline)	(T1-weighted sequences with and without contrast, T2-weighted-FLAIR, and DWI) and, in 7 cases, surgery. Details on necrosis time-course are not provided.	unique in that we considered variations in patient specific radiosensitivity by analysing each patient separately using dose-matched voxels… and by explicitly accounting for the hierarchical structure of voxel data. Our study suggests that interpatient variability in radiosensitivity is significant and thus potentially overshadows the LET effect. Nevertheless, our results cannot rule out a correlation between brain necrosis and LET (RBE)."
Skaarup, 2021	Paediatric brain cancer	6 paediatric brain cancer patients treated using protons; 5 had images suitable for analysis. Protons: n=5 (PS)	Quantitative image changes were considered for a variety of MR techniques: T1-weighted sequences with contrast, T2-weighted FLAIR and fractional anisotropy images (the latter stemming from diffusion tensor imaging, or DTI). The following approximate follow-up timepoints were considered: 2 months, 5 months, 8 months and 11 months (after the end of radiotherapy).	No: "the number of patients accrued in our project is too small to draw firm conclusions… We observe substantial patient to patient variation in the internal model fits (i.e. sensitivity to dose and LET)… inter-patient variation in radiation sensitivity may be a stronger factor than variation in biological effect across clinical proton beams".
Yang, 2021	Prostate cancer	9 proton patients treated within a specific window who developed rectal bleeding were identified (cases), and 48 proton patients treated at the same time who did not develop rectal bleeding (controls). Model validated in a further 8 cases and 13 controls. Protons: initial n=9/57 (IMPT)	Rectal bleeding (Common Terminology Criteria for Adverse Events grade $\geq$2). Details on the bleeding time course are not provided.	Maybe: "Our results demonstrated the importance of rectal "hot spots" in both high LET and high dose in inducing rectal bleeding."
Group B: image change comparisons between proton and photon cohorts, with regard to proton RBE				
Gunther, 2015	Paediatric Ependymoma	Patients diagnosed within a specific window at two institutions: 37 treated with protons, 35 treated with photons. In total, 22 developed image changes. Protons: n = 16/37 (delivery method not specified) Photons: n = 6/35 (IMRT)	Image changes scored according to a published scale using T1-weighted images post contrast and T2-weighted images. For the proton patients the median time to image change onset was 3.8 months (range 1.1-7.5), compared a median of 5.3 months (range 1-9.2) for the photon patients.	Maybe: "It is possible that higher rates of imaging changes seen with PBRT [proton beam radiotherapy, compared to photon IMRT] are due to effective doses higher than those prescribed".
Acharya, 2018	Glioma (Grade II or III)	Patients diagnosed within a specific window were evaluated: 37 treated with protons, 123 treated with photons. 18 developed clinically significant radiation necrosis.	Clinically significant radiation necrosis (cRN), diagnosed according to: review of the clinical course, radiologic (MRI) findings and available pathologic data. The overall median time to cRN was 11 months (range 2.8-34.2 months).	No: "There is insufficient evidence at this time to conclude a significant difference in the incidence of cRN [clinically significant radiation necrosis] between proton and photon therapy."

		Protons: n = 6/37 (PS) Photons: n = 12/123 (IMRT)		
Bronk, 2018	Glioma (Grade II or III)	Patients treated within a specific window were evaluated: 34 treated with protons, 65 with photons. 14 developed pseudo-progression. Protons: n=5/34 (n=29 PS, n=5 BS) Photons: n = 9/65 (IMRT, 6 MV)	Pseudo-progression, defined as new areas of MRI contrast enhancement that developed within 6 months of completion of radiotherapy and were concerning for possible tumour progression. For proton patients the median time to pseudo-progression was 32 days (range 18-77) whereas for photo patients the median was 116 days (range 18-158).	Maybe: "Overall rates of PsP [pseudo-progression] were similar in patients treated with photons versus protons. Patients with oligodendroglioma who developed PsP did so at a shorter interval after proton therapy than photon therapy. These differences were not observed in astrocytoma, suggesting a differential biological effect of proton therapy in oligodendroglioma."
Underwood, 2018	Breast cancer	10 proton cases treated within a specific window were evaluated, alongside 10 matched photon cases. Protons: n=10 (PS) Photons: n=10 (3D CRT)	Asymptomatic density changes in normal lung determined from post-treatment CT scans. Changes were present in all follow-up scans, which were collected from 3 months to approximately 3.5 years after treatment.	Yes: "Our data support the hypothesis that the proton RBE for lung-density changes exceeds 1.1. This RBE elevation could be attributable to (*1*) the late, normal tissue endpoint that we consider or (*2*) end-of-range proton linear energy transfer elevation—or a combination of the two."
Li, 2019	Early-stage non-small cell lung carcinoma	23 patients who received (hypo fractionated) stereotactic body proton therapy (SBPT) within a specific window were evaluated. 18 of these were matched to patients who received photon stereotactic body radiotherapy (SBRT). Protons: n=23 (PS) Photons n=18 (3D CRT, IMRT or volumetric modulated arc therapy).	Density changes in normal lung determined from post-treatment CT scans. Changes were present in all follow-up scans. Scans were grouped into an early time period (< 6 months post-treatment, median 3 months) and a later time period (CTs acquired 6-14 months, median 9 months).	Maybe: "While there was no significant difference in maximum response after SBPT versus SBRT, dose-defined lung inflammation occurred earlier after proton irradiation… This warrants further investigation into the mechanisms of inflammation after proton and photon irradiation in lung. The large inter-patient variability presents the main barrier to further study."
Ludmir, 2019	Paediatric glioma (Grade I and II)	Patients treated within a specific window across two institutions were evaluated: 51 treated with protons and 32 treated with photons. 31 developed pseudo-progression. Protons: n = 23/51 (n = 49 PS, 2 PBS) Photons: n = 8/32 (IMRT)	Pseudo-progression, identified from T1-weighted images pre-and post-contrast. Most reported pseudo-progression arose within the first six months following treatment (all incidents reported arose within 12 months, median follow-up was 5.6 years).	Maybe: "Multivariable analysis confirmed the independent effects of RT [radiotherapy] modality (P = 0.03) and RT dose (P = 0.01) on PsP [pseudo-progression] incidence."
Song, 2020	Meningioma (grade I-III)	Patients treated within specific windows across two institutions were evaluated: 38 treated with protons, 39 treated with photons. 7 developed image changes.	Image changes were categorised into: abnormal T2-weighted fluid-attenuated inversion recovery (FLAIR) changes (suggestive of white matter lesions), or T1	Maybe: "Proton therapy was associated with significantly higher rates of T1c+T2 [T1-weighted post-contrast and T2-weighted MR] changes compared with photon therapy, but severe adverse

		Proton: n=4/38 (n=23 PBS, n=15 Uniform Scanning) Photon: n=3/39 (n=32 VMAT, n=7 Tomotherapy)	post-contrast sequence changes (suggestive of radiation necrosis). The median time to T2 changes from the end of radiotherapy was 169 days and the median time to T1c+T2 changes was 368 days.	events were uncommon in both groups and survival outcomes were comparable between the two groups".
Ritterbusch, 2021	Glioma (grade II / III)	Proton patients treated within a specific window were evaluated (n=57), alongside photon patients treated over the same period (n=43). 14 developed pseudo-progression. Protons: n=14/57 (PBS or uniform scanning) Photons: n=0/43	Pseudo-progression, identified from T1-weighted images pre-and post-contrast. The earliest change appearing on a follow-up MRI was 7 months following radiotherapy and the latest manifesting 27 months after therapy. For patients whose enhancements resolved, the mean time was 8.7 months from the first MRI with the imaging change seen to its disappearance.	Maybe: "Proton radiation therapy can induce a pattern of Ps [pseudo-progression] which manifests differently than Ps following photon therapy." "The specificity to proton radiation and the locality of ProPs [proton therapy pseudo-progression] can possibly be explained by the increased RBE of protons at the end range and beam angle selection".
Zhang, 2021	Nasopharyngeal Carcinoma	60 consecutive patients treated using proton therapy were studied and 506 photon (IMRT) patients treated within a specific timeframe. 29 developed temporal lobe enhancement. Protons: n=9/60 (PS) Photons: n=20/506 (IMRT)	Temporal lobe enhancement was defined as development of an enhancement in the temporal lobe on T1-weighted MRI, with or without accompanying clinical symptoms. The median latency for this was 34 months.	Yes: "our data suggest that the RBE for radiographic changes in the temporal lobe is 1.18. The end-of-range RBE is likely to be higher… Given the retrospective nature and the relatively small number of TLE [Temporal lobe enhancement] cases, a prospective study with a large cohort would be necessary to confirm our findings."