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Table 3: imaging cohort comparisons ('Group B'), key methods & analysis

First author, year	Type of analysis	Cohort matching	Statistical methods	Effects considered	Estimation of RBE / difference between cohorts
Gunther 2015	Patient level	Proton patients were more likely to undergo gross total resection, were younger at diagnosis and treatment, had higher RT dose and were more likely to have chemotherapy after RT than photon patients.	Logistic regression to identify predictors of imaging changes.	Modality, tumour location, age at diagnosis, histology, extent of resection, sex, time to radiation, age at radiation, duration of radiation (days), dose, number of resections, and chemo-therapy status before or after radiation or both.	From multivariable analysis, proton therapy was associated with a higher risk of imaging changes (odds ratio 3.89, 95% CI 1.20-12.61, P=0.024), adjusting for time before RT, age and RT type / age interaction.
Acharya 2018	Patient level	Proton patients typically had different chemotherapy regimens, shorter median follow-up times and were treated to a lower median prescription dose.	Cox proportional hazards regression to identify predictors of clinically significant radiation necrosis. Death and recurrence included as competing risks in the model.	Modality, sex, race, age, extent of surgical resection, chemotherapy regimen, radiation dose, treatment volume, fraction size, histology, location, time to RT.	No statistically significant association between modality and clinically significant radiation necrosis (hazard ratio for protons vs photons 1.81, 95% CI 0.67-4.9; P=0.24), although some evidence of difference in 2-year cumulative incidence.
Bronk 2018	Patient level	Patients with grade III tumours more likely to be treated with photons and to receive concurrent chemotherapy than patients with grade II tumours. All other clinical variables evenly distributed across the groups.	Cox proportional hazards regression to identify predictors of pseudo-progression.	Modality, age, gender, histology, tumour grade, tumour location, radiation dose, radiation type, extent of surgical resection, chemotherapy regimen, treatment volumes, 1p/19q co-deletion status, and IDH mutation status.	Rates of pseudo-progression similar in patients treated with photons versus protons (14% vs 16% for oligodendroglioma and 13% vs 11% for astrocytoma). Time to pseudo-progression for oligodendroglioma patients was shorter for protons vs photons (48 vs 131 days, $p<0.01$).
Underwood, 2018	Voxel level analysis of changes in CT number using deformable image registration. Additional qualitative	Cohorts were matched with regard to clinical factors.	Voxel level: linear mixed-effects modelling. Qualitative: Wilcoxon signed rank test.	Principal fixed effects: radiation modality, mean lung dose and follow-up interval (without interaction terms). To consider inter-patient variations in radio-sensitivity, "subject" was considered as a random effect.	Radiation modality was a statistically significant factor, with more substantial image changes in proton patients. On RBE for asymptomatic lung fibrosis: "interpatient variation severely limits our ability to quantify RBE: Our RBE estimates from HU/Gy (RBE) and ΔHU/Gy (RBE) of 2.7 and 4.7 respectively, are associated with relative standard errors exceeding 100%."

	radiological grading				
Li, 2019	Voxel level analysis of changes in CT number using deformable image registration. Additional qualitative radiological grading	Cohorts were matched with regard to clinical factors.	Voxel level: Wilcoxon's signed rank tests to assess for statistically significant differences in the individual dose-response curves between paired patients and different time periods. Qualitative: Spearman's rank correlation for correlating the severity of response as expressed by the dose-response curves with the qualitative radiology assessment.	Modality and follow-up time	Normal lung response following SBPT significantly increased in the early time period (CTs acquired <6 months, median 3 months) post-treatment, and then did not change significantly in the later time period (CTs acquired 6–14 months, median 9 months). For SBRT, the normal lung response was similar to SBPT in the early time period, but then increased significantly from the early to the late time period ($p = 0.007$). These differences were most pronounced in sensitive (response >6 HU/Gy) patients and in the internally matched cohort. However, there was no significant difference in the maximum observed response in the entire cohort over all time periods, median 3.4 [IQR, 1.0–5.4] HU/Gy (SBPT) versus 2.5 [1.6–5.2] HU/Gy (SBRT). Qualitative radiological evaluation was highly correlated with the quantitative analysis ($p < 0.0001$).
Ludmir 2019	Patient level	Histological factors significantly different between the two cohorts. IMRT patients had higher RT dose and longer follow-up.	Cox proportional hazards regression to identify predictors of pseudo-progression; cumulative incidence curves.	RT dose (>50.4 Gy[RBE] vs ≤50.4 Gy[RBE]); RT modality and histology included in the multivariable model.	Proton patients significantly more likely to exhibit pseudo-progression; hazard ratio: 2.83, 95% CI: 1.14–7.04, P = 0.03 (from multivariable analysis).
Song 2021	Patient level	No significant differences in WHO grade, RT dose, size of CTV, performance status or comorbidities between the two groups.	Cox proportional hazards regression to identify predictors of image changes; cumulative incidence curves.	Radiation modality, brain invasion (invasion vs no invasion), brain dose (D_{max}) and CTV volume.	2-year cumulative incidence of T1-weighted contrast enhanced +T2-weighted image changes 26.8% for protons and 5.3% for photons ($p = 0.02$); hazard ratio: 5.40, 95% CI: 1.06–27.47, P= 0.042 (from bivariate analysis). No statistically significant differences for symptomatic RT injury (P=0.67) and for T2-weighted image changes alone (P=0.53).
Ritterbusch 2021	Patient level	Proton cohort had higher percentage of IDH mutated tumours	Types of pseudo-progression characterised according to post-treatment imaging changes and	Modality, sex, age, tumour grade, IDH status, 1p/19q status,	24.6% of proton patients vs 0% of photon patients exhibited distinct type of pseudo-progression ($p<0.001$).

		and MGMT methylated tumours.	compared between modalities using chi-square test.	methylation status, chemotherapy regimen.	
Zhang 2021	Structure level: temporal lobe tolerance dose volume histograms (DVHs) were calculated for the photon and proton cohorts	Between the two cohorts, no significant differences were found in patient, treatment, and tumour characteristics.	Temporal lobe tolerance dose-volume cut-off points from V10 (volume receiving 10 Gy or Gy(RBE)) to V70 (volume receiving 70 Gy or 70 Gy(RBE)) were calculated using logistic regression to compute the receiver operating characteristic (ROC) curve and the Youden index. The proton RBE for brain tissue was calculated by dividing the D1% (dose received by 1% of the volume) of the photon curve by that for the proton curve.	N/A	RBE for temporal lobe enhancement calculated to be 1.18 (based on D1%).