Differentiation of radiation necrosis from glioma in rat models using diffusion tensor MR imaging

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Introduction: Radiation therapy for brain cancer can cause necrosis within months to years post-radiation[1]. Patients with tumor recurrence need alternative therapies, whereas patients with radiation necrosis (treatment response) require continuation of current therapy. Therefore, non-invasive differentiation of tumor recurrence versus treatment response has immediately clinical implications. However, conventional MRI and clinical features of these two pathologies are very similar. This study specifically addresses the issue of radiation necrosis versus glioma, by comparing their DTI features with histology in animal models.

Materials and methods: GBM22 (n=6, 100,000 tumor cells) and 9L gliosarcoma (n=8, 25,000 tumor cells) cell lines were used in this study. Thirteen adult rats (Fischer 344; 250–300 g) were irradiated at left hemisphere with a single, well-collimated x-ray beam (40 Gy, 10×10 mm^2)[2]. The rats underwent MRI scanning at day 11~13 (9L) and day 26~28 (GBM22) post-implantation (tumor diameter 3-4mm). For the radiation model, the rats were monitored with anatomical MR images monthly until radiation necrosis was found. DTI was acquired on a 4.7T animal MR system, using a multiple-slice, multiple-spin echo diffusion-weighted sequence (TR = 2s, TE = 26.3/36.7/47.1/57.5 ms, resolution = 0.33 mm×0.33 mm, NA = 2). Seven DW images with different b values were acquired (one image with b value = 50 s/mm^2 and the rest with b value = 1000 s/mm^2). ROIs were drawn in the rims and central zones of radiation necrosis and tumors. Histological specimens were analyzed within the regions corresponding to the quantitative MRI measurements.

Results: ***Radiation necrosis and glioma have similar conventional MRI features:*** Radiation necrosis started to appear at around 22–24 weeks post-radiation. The necrotic lesion was heterogeneous on T2WI and showed gadolinium-enhancement on post-contrast T1WI (not shown), as seen in the clinic, which cannot be reliably differentiated from GBM22 and 9L tumors. ***Distinct DTI features between radiation necrosis and glioma:*** In the case of radiation necrosis, the FA map demonstrated a dark lesion with low FA, compared to the contralateral brain tissue, and there was a clear trace pattern (hyperintense rim v.s. hypointense core) in the lesion. On the contrary, a clear FA pattern (high-FA rim v.s. low-FA central zone) can be seen inside both the GBM22 and 9L tumors (Fig. 1). Both two tumor xenografts were hyperintense and relatively homogeneous on the trace maps. ***Differentiation of radiation necrosis from glioma:*** **FA:** Radiation necrosis had lower FA than the tumors in the rim (Fig. 2), which was significant for 9L (p=0.023) and no for GBM22 due to a small sample size. No difference was found in the central zone. **Trace:** Radiation necrosis was significantly lower than the GBM22 or 9L tumor in the central zone (both p<0.01). **$\lambda_{//}$ and $\lambda_{\perp}$:** $\lambda_{//}$ of radiation necrosis was significantly lower than that of 9L in the central zone and the rim (both p<0.01). $\lambda_{\perp}$ of radiation necrosis was significantly lower than those of 9L and GBM22 tumors in the central zone (both p<0.05), but they were similar in the rims. Receiver operating characteristic (ROC) analysis showed that $\lambda_{\perp}$ in the center was the best parameter for differentiating between radiation necrosis and glioma, corresponding to an area under the ROC curve (AUC) of 0.98, followed by the trace (AUC = 0.96) and $\lambda_{//}$ (AUC = 0.91) in the center (all p<0.001). ***Histology:*** There was coagulative necrosis in the radiation necrosis central zone and reactive astrogliosis and thickness of vessel wall in the radiation necrosis rim (Fig. 3).

Conclusions: Our study has indicated that radiation-induced necrosis and viable glioma in rat models exhibit different DTI features. There is decreased directionality and magnitude of water diffusion in the lesion of radiation necrosis, particularly in its central zone. DTI indices provide useful diagnostic information to distinguish between these two pathologies.

1. Valk et al., AJNR 1991; 12:45-62. 2. Wong et al., Int J Radiat Oncol Biol Phys 2008;71:1591-99.

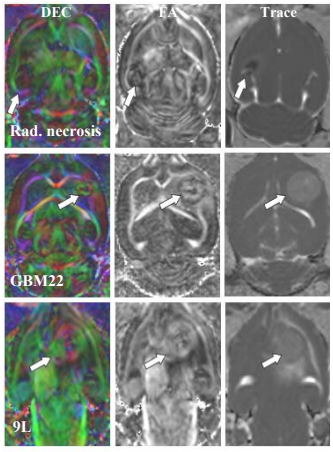

Fig. 1. DTI features of radiation necrosis, GBM22 and 9L tumors. Radiation necrosis shows low FA and no meaningful DEC pattern in the lesion. However, there is a clear pattern, hypointense in the central region and hyperintense in the rim (arrow), on the trace map. **GBM22** exhibits a radial tumor cell orientation and **9L** a circular orientation (arrow) in the tumor rims on the DEC maps. Both tumors have high FA in the rims and low FA in the center; they are relatively homogeneous, hyperintense on the trace maps.

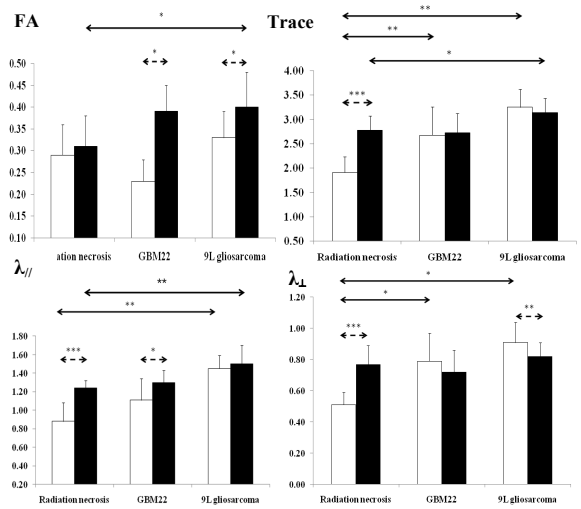

Fig. 2. DTI indices of the central zones and the rims of radiation necrosis (n=13), GBM22 (n=6) and 9L gliosarcoma (n=8). White bar = central zone; black bra = rim. Solid line = comparison between radiation necrosis and tumor; dash line = comparison between the lesion center and the rim. *<0.05, **<0.01, ***<0.001.

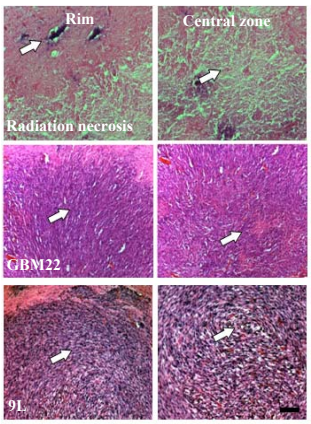

Fig. 3. Histological features of radiation necrosis, GBM22 and 9L tumors. Radiation necrosis shows parenchymal coagulative necrosis in the center and reactive astrogliosis and thickness of vessels in the rim (arrow). **GBM22** tumor consists of a radial pattern of growth and a necrotic core. **9L** gliosarcoma shows a homogeneous mass from the tumor central zone to the boundary (arrow), with a circular growth pattern of tumor cells in the rim. Scale bar =10 μm.