Characterization of brain tumor infiltration into adjacent brain tissue in experimental models with diffusion tensor imaging (DTI)

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Introduction: The primary neurosurgical planning goal in the treatment of malignant gliomas is maximum tumor resection and minimum damage to surrounding brain tissue to preserve neuronal structure[1]. Therefore, it is essential to assess the local extent of the tumor and its infiltration to important structures such as adjacent white matter. The aim of this study is to characterize growth patterns of glioma in the brain, including peritumoral edema and adjacent normal-appearing white matter (NAWM) using DTI.

Materials and methods: Three tumor cell lines were used in this study, including 9L gliosarcoma (*n=8*, 25,000 tumor cells), F98 tumor (*n=5*, 25,000 tumor cells), and glioblastoma 22 cell line (GBM22, *n=6*, 100,000 tumor cells). The rats underwent MRI at day 11 ~13 (9L), day 10~11 (F98), and day 26~28 (GBM22) post-tumor implantation, with a tumor diameter of 3-4 mm. DTI were acquired on a 4.7T animal MR system, using a multiple-slice, multiple-spin echo diffusion-weighted (DW) sequence (TR = 2s, four echoes with TEs of 26.3/36.7/47.1/57.5 ms, resolution = 0.33 mm × 0.33 mm, NA = 4). Seven DW images with different b values were acquired (b value = 50 or 1000 s/mm^2). The ROIs were manually drawn in several anatomical regions, including peritumoral edema, and ipsilateral and contralateral NAWM (external capsule). Peritumoral edema was further subdivided into immediate peritumoral region (IPR, ~1 mm width) and distant peritumoral region (DPR, other regions of edema)[2]. "Peritumoral index" was defined as a DTI index ratio of IPR/DPR. Histological specimens were analyzed within the regions corresponding to the quantitative MRI measurements (H&E staining).

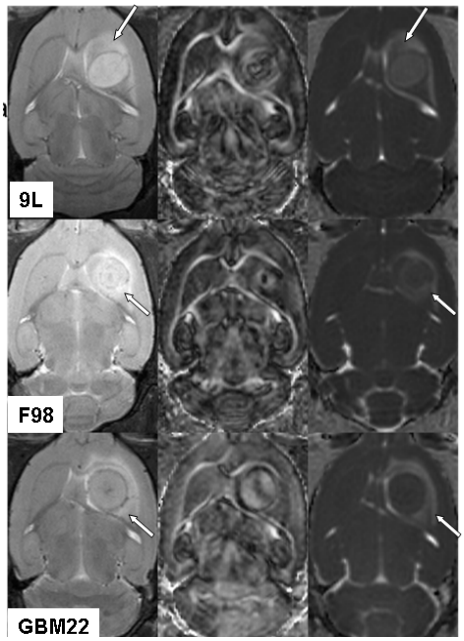

Figure 1: T2WI and DTI features of rat glioma models. Peritumoral edema (arrow) with an increased MRI signal is clearly seeable on T2WI and the trace maps.

Results:

Peritumoral edema: For all three tumors, peritumoral edema with an increased MRI signal was clearly visible on T2WI and the trace maps (Figure 1). The ANOVA test indicated that the peritumoral indices of 9L gliosarcoma and F98 tumor were significantly higher than that of GBM22 tumors (increase of 15% and 17% respectively, all $p<0.01$). The invasion of individual 9L gliosarcoma or F98 tumor cells into contiguous brain parenchyma in IPR was clearly observed. DPR seemed normal. In contrast, GBM22 tumor cells invaded to adjacent brain parenchyma with islands of tumor cells at varying distances in both IPR and DPR.

NAWM adjacent to glioma: There were no differences between NAWM DTI indices for both hemispheres in 9L gliosarcoma and F98 tumors. However, in the case of GBM22, significantly decreased FA (-33%, $p<0.001$) with increased trace (28%, $p = 0.03$) was found in ipsilateral NAWM, compared with contralateral NAWM. In addition, significantly increased $\lambda_{\perp}$ (40%, $p = 0.006$) with similar $\lambda_{//}$ was found in ipsilateral NAWM, compared to contralateral NAWM. Histology showed that GBM22 tumor cells invaded and damaged ipsilateral white matter. In 9L and F98 tumor models, adjacent white matter seemed integrity (Figure 2).

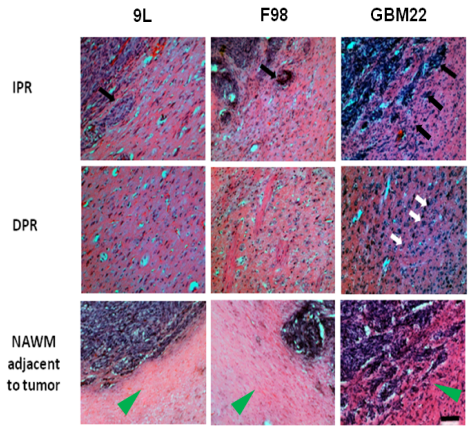

Figure 2: IPR: Isolated tumor cells were observed for 9L and F98, but lots of invading tumor cells observed for GBM22 (black arrow). **DPR:** Randomly distributed tumor cells are observed for GBM22 (white arrow). **NAWM:** Ipsilateral WM is integrated for 9L and F98, but disrupted for GBM22 (green arrow head).

Discussion: Malignant brain tumors consist of a core mass and surrounding individual cells that infiltrate into adjacent brain tissue. Significantly higher diffusion anisotropy in the IPR regions of glioma reflected tumor compression, whereas tumor cell infiltration disrupted neurofibers and decreased diffusion anisotropy. Significantly decreased FA and increased $\lambda_{\perp}$ (with similar $\lambda_{//}$) may be regarded as useful imaging patterns to determine damaged NAWM adjacent to glioma. Quantitative analysis of the DTI indices provides useful information to assess tumor cell organization and identifies tumor cell invasion of peritumoral edema and adjacent white matter.

1. Stupp et al., N Engl J Med 2005;352:987-996. 2. Wang et al., NeuroImage 2009;44:653-60. 3. Zhang et al., MRM 2007;58:454-462.