Motexafin Gadolinium (MGd)-Enhanced Molecular MR and Optical Imaging of Rat Gliomas for Potential Intraoperative Determination of Tumor Margins

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Purpose: Malignant glioma is an extremely aggressive neoplasm known for its highly infiltrative growth and dissemination (1). Identification of the real tumor margin during surgery plays a pivotal role in ensuring the complete eradication of tumors (2). The aim of this study was to investigate the possibility of using motexafin gadolinium (MGd)-enhanced molecular MR imaging and optical imaging to identify the genuine margins of rat gliomas.

Method and Materials: Rat glioma model was created by inoculating C6 glioma cells in right caudate nucleuses of male Sprague-Dawley rats (200g). Twenty four rats with tumors were randomized into six groups (n=4/group). Five animal groups were euthanized at different time points of 15 and 30 mins, as well as 1, 2 and 4 hours after intravenous administration of 6-mg/kg MGd (Pharmacyclics, Inc.), while one animal group received saline as a control. After a craniotomy, ex vivo optical imaging was performed to identify the tumors featuring as MGd-emitting red fluorescence. Then, the whole brains were harvested for ex-vivo T1-weighted MRI (T1WI) and T2-weighted MRI (T2WI). Optical photon intensities and MRI signal intensities were quantified for plotting the times to photon/signal intensity curves. Tumor margins were demarcated on both optical and MR imaging. Subsequently, confocal microscopy of brain tissues was performed to confirm the intracellular uptake of MGd by tumor cells and correlate the tumor margins determined on both optical and MR images.

Results: Fluorescent optical imaging could sensitively detect the deep-seated tumors with red fluorescence in rat brains and clearly outlined the tumor margins. The photon intensity reached the peak at 15 mins after MGd administration. T1WI showed the tumors heterogeneous enhancement, and the maximal enhancement on T1WI was measured at 15 mins after MGd administration. Confocal microscopy confirmed the intracellular localization of MGd in the regions between tumors and normal brain tissue, which was well correlated with imaging findings (Figure).

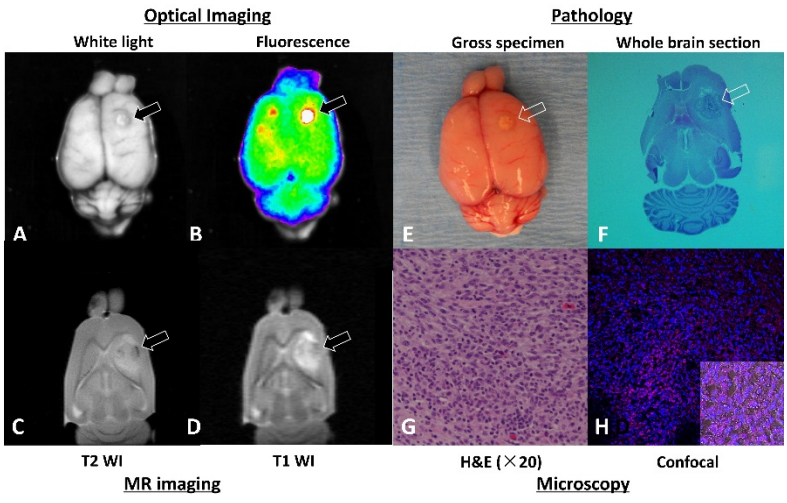

Figure: (A&B) Optical imaging of a rat brain at (A) white light and (B) overlay of Fluorescent image on white light, showing the fluorescent signal on the tumor inoculated area (arrows). (C&D) MRI showed abnormal signal region on T2WI (C) and contrast-enhanced tumor on T1WI (D). Pathology with (E) gross specimen and (F) whole brain section demonstrated the existence of the tumor in the right brain (arrows), while microscopy with H&E staining (G) confirmed the xenograft as glioma tumor and fluorescent confocal microscopy (H) demonstrated the high accumulation of MGd-positive glioma tumor cells along the tumor margins. Lower right corner image on H showed the intracellular localization of MGd.

Conclusion: Both MGd-enhanced optical imaging and molecular MR imaging can sensitively determine rat glioma tumor margin within the optimal time window of 15 mins post-MGd administration, which pose the potential clinical application for aiding the complete removal of gliomas at a hybrid surgical setting with intraoperative optical and MR imaging capabilities.

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