Identification of Early Stage Glioblastoma Multiform in Rats by Multi-parametric MR Imaging Techniques: Preliminary Results

Xu Han[1,2], Hua Guo[2], Le He[2], Xiaodong Ma[2], Tingting Ha[3], Kai Wang[4], Yanfeng Xu[5], Jianming Cai[1], and Xihai Zhao[2]

[1]*Department of Radiology, Chinese PLA general hospital, Beijing, China,* [2]*Center for Biomedical Imaging Research & Department of Biomedical Engineering, Tsinghua University, Beijing, China,* [3]*Department of Radiology, Tiantan hospital, Capital Medical University, Beijing, China,* [4]*Imaging Center of Neuroscience, Tiantan Hospital, Capital Medical University, Beijing, China,* [5]*Institute of Laboratory Animal Sciences, Chinese Academy of Medical Sciences, Beijing, China*

Introduction: Glioblastoma multiform (GBM) is the most malignant neuroepithelial tumor. The prognosis for GBM remains poor (<1year) despite significant advances in treatment [1,2]. Early detection of these lesions might decrease the mortality and improve the life quality of GBM patients. Clinically, traditional MR imaging techniques, such as T1- and T2-weighted imaging, provide important structure information but play limited role in diagnosis at early stage [3]. Even in animal studies, traditional MR imaging was also the most common imaging protocols for viewing brain tumors in vivo [4-5]. Multi-parametric MR imaging, including structure, function (DWI and DCE-MRI) and metabolism (MRS) imaging sequences, is an emerging imaging tool for diagnosing various diseases [6]. We hypothesized that multi-parametric MRI has the potential capability to identify brain tumor at early stage.

Purpose: This study sought to determine the feasibility of multi-parametric MRI in identification of early stage GBM in rats with histology validation.

Methods: Thirty-six adult female Wistar rats (200-250g) were used and randomly divided into tumor group (n=18) and control group (n=18). During preparation of animal model, 5×10^5/10μL C6 glioma cells and the same amount of saline were injected into the right caudate nucleus of rats in tumor and control group, respectively. All the rats in each group were randomly and equally divided into three subgroups based on three time points (3rd, 7th and 14th day). ***MR imaging:*** The MR imagimg was performed at a 3.0T whole body scanner (Achieva, Philips Medical System, Best, Netherlands) with custom-designed 3 channel rat coil at each time point. Traditional (T1W, T2W, and EPI-DWI) and multi-parametric imaging (Spiral DWI, VDS-DWI, DCE-MRI, CE-T1W) protocols were scanned with the parameters that are detailed in Table 1. ***Histology processing:*** After image acquisitions at each time point, the rats in corresponding subgroup were subject to histopathological analysis. Once the breathing stops after euthanasia, the rat's brain was excised and preserved in 4 % paraformaldehyde at 4°C for 48 hours for tissue fixation. Next, 10-μm-thick cryostat sections were cut and processed for hematoxylin and eosin (H&E) staining for histopathological evaluation. ***Data analysis:*** All the images we acquired were analyzed by two experienced radiologists at Philips MR workstation (MR WorkSpace 2.6.3.3, The Netherlands). Presence of abnormal signal was identified at each imaging sequence at each time point. The presence or absence of cerebral mass was also determined by traditional imaging protocol and multi-parametric protocol independently at each time point.

Table 1. MR imaging protocols

	Sequence	FOV (mm)	Matrix	TR/TE (ms)	Flip angle (°)	b (s/mm^2)
Traditional protocol						
T1W	TSE	50×50	172×170	511/20	90	-
T2W	TSE	50×50	144×142	511/20	90	-
EPI-DWI	SE	50×50	172×170	511/20	90	1000
Multi-parametric protocol						
Spiral DWI	Spiral	40×40	100×100	1700/121	90	1000
VDS-DWI	Sprial	40×40	68×68	1700/50	90	1000
DCE-MRI	FFE	40×40	68×68	4.5/2.2	8	-
CE-T1W	TSE	50×50	172×170	511/20	90	-

Results: Twelve of 36 rats (9 in tumor group and 3 in control group) who completed MRI and histology examinations were included in the final analysis. Of 9 rats in tumor group, the frequencies of abnormal signals on different sequences were listed in Table 2 along with the three time points (3rd, 7th and 14th day after surgery). Abnormal signals can be depicted by most of image sequences in multi-parametric protocol but few traditional imaging techniques at early stage (3rd day). For tumor group, by using traditional MR imaging protocol, 11.1%, 33.3% and 100% of rats can be identified to develop mass at 3rd, 7th and 14th day after surgery. Using multi-parametric MR imaging protocol, all rats in tumor group were identified to have mass at any time point. Of 3 rats in control group, patchy high signals were found on T2W images at 3rd day but disappeared at next two time points. Until now, 5 rats (2 in control group and 3 in tumor group) have been received histopathological analysis, and showed high-grade glioma in 3 rats of tumor group.

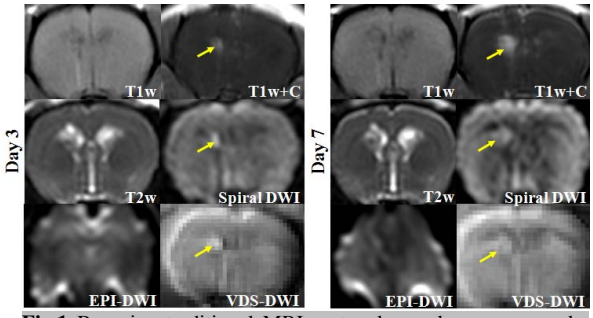

Fig.1 By using traditional MRI protocol, no clear mass can be found, whereas an increasingly enlarged mass was successfully depicted by multi-parametric MRI sequences (yellow arrows).

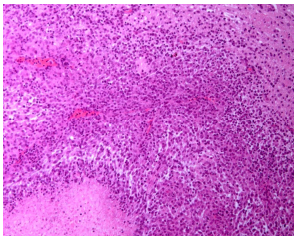

Fig.2 Histopathological analysis (HE) showed intensive tumor cells (dark areas). The tumor cells had no clear boundary with the adjacent normal brain tissue (light areas). (x100)

Table 2. Presence of abnormal signals

MR imaging	Tumor group		
	TP1 (N=9)	TP2 (N=6)	TP3 (N=3)
Traditional protocol			
T1W	33.3%	50.0%	100%
T2W	55.6%	83.3%	100%
EPI-DWI	11.1%	33.3%	100%
Multi-parametric protocol			
Regular spiral DWI	88.9%	100%	100%
VDS-DWI	100%	100%	100%
DCE-MRI	100%	100%	100%
CE-T1W	100%	100%	100%

Discussion and Conclusions:
In this ongoing study, the preliminary results indicate that the multi-parametric MR imaging technique is feasible to identify the GBM in rats at early stage (Fig.1-2). Compared to the traditional imaging sequences, each sequence of our multi-parametric imaging protocol, such as spiral DWI, VDS-DWI, DCE-MRI and CE-T1W, enables discrimination of the early stage GBM from post-injury brain edema. Previous studies have demonstrated that the VDS spiral DWI can achieve higher SNR and apply off-resonance correction algorithm to reduce image blurring in normal rat's brain [7]. For VDS-DWI, the increase of SNR and removal of distortion can be also obtained in GBM animal model in our study. The multi-parametric imaging techniques might be an alternative imaging approach to detect early lesions no matter in brain or other organs at clinically.

References:

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