Tumor Heterogeneity Imaging (THI): Initial Experience in the Evaluation of Brain Gliomas

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Abstract:

Brain tumors are typically heterogeneous, and may contain different grades of tumor cells, different types of tumor cells, edema and/or abnormal vascular structures. Anatomical imaging alone can be limited in the evaluation of tumor heterogeneity, especially in those tumors that demonstrate little to no enhancement. While there are physiologic MR tools available in daily clinical practice such as perfusion or diffusion, we wanted to develop a more powerful, sensitive sequence for the characterization of tumor heterogeneity. We propose that Tumor Heterogeneity Imaging (THI)1 can provide quantitative distributions of different grades of tumor cells and capillary blood perfusion within the tumor in a single clinical imaging scan with more accuracy than previously reported with traditional diffusion techniques.2

Introduction:

Primary brain tumors encompass a spectrum of diseases that, in the landscape of cancer, are less common but unfortunately often carry a grim prognosis. The most common malignant primary brain tumor is glioblastoma (GBM) and despite aggressive treatment with surgery, radiation, and chemotherapy, patient survival is typically <2 years and <10% of patients survive >5 years. Magnetic Resonance Imaging (MRI) plays an important role in understanding GBM tumor biology and response to treatment since MRI is already part of routine clinical practice and recent advances in imaging can now capture a variety of anatomical and physiological processes.

GBMs are well visualized on MRI because they profoundly disrupt normal tissue architecture. These tumors are densely cellular and widely infiltrate into normal brain. The pathological hallmark of GBM is increased expression of proangiogenic cyotkines (ex. vascular endothelial growth factor, VEGF) leading to the formation of highly abnormal tumor vasculature characterized by hyperpermeable vessels (Figure 1a), increased vessel diameter, and heterogeneous tumor blood flow. Some areas of tumor receive too much blood flow and other areas do not receive enough blood flow resulting in areas of hypoxia. The hyperpermeable blood vessels allow fluid to leak from the intravascular space to the extravascular space producing significant peri-tumoral edema. All of these pathological processes – tumor cell density, abnormal tumor vasculature, and peritumoral edema - can be studied, and more importantly quantitated, using MRI.

Materials and Methods:

11 adult patients with known or suspected brain gliomas that were non- enhancing or had substantial non-enhancing regions (>50%) underwent simultaneous 3,4-dihydroxy-6-[18F]fluoro-L- phenylalanine (18F- FDOPA)3 PET/MRI prior to planned standard-of-care surgical resection and/or stereotactic biopsy. Of these, 7 patients also underwent THI, a new diffusion MRI protocol, microstructure modeling, and inverse computation technique. The THI maps were then compared to the 18F- DOPA and coordinate-guided biopsy or surgical resection results.

Perfusion maps extracted from THI were calculated.4 ADC cut-offs for tumor grade based on the THI data were then determined and tumor grade maps created. (See Figure 1).

Results:

Grade 4 tumor ADC cutoff was 0.3-0.5 10−3 mm2/s. Grade 3 was

0.5-0.8 10−3 mm2/s. Grade 1 and 2 was 0.8-1.5 10−3 mm2/s. Table 1 summarizes the subject's demographic characteristics and well as the correlation between 18F-FDOPA and THI maps. We found that in 7/7 patients (100%) THI maps correlated with tumor grade on pathological evaluation. Interestingly, 18F-FDOPA was negative on subject S7, whereas THI correctly identified not only the tumor, but the tumor grade at the region of stereotactic biopsy sample.

Figure1. A 66-year-old women (S3) with recurrent oligodendroglioma, WHO grade II was imaged using FLAIR, FDOPA PET, perfusion and THI imaging. Region of interest was label in magenta.

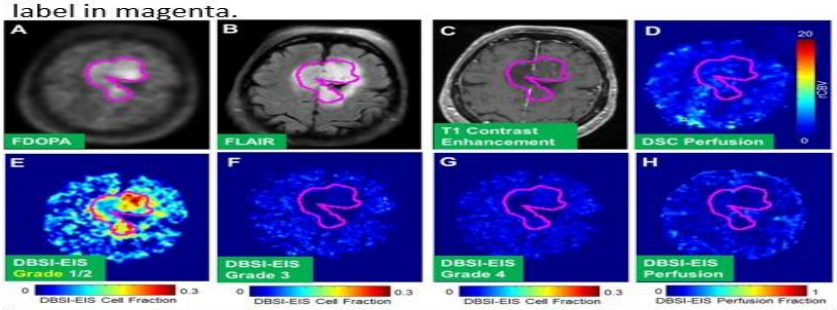


Table 1. Characteristics of patients and the tumor grades detected by biopsy and THI

Patient #	Age	Gender	FDOPA uptake	Tumor pathology	DBSI-EIS tumor grade
S3	66	Female	Yes	Oligoastrocytoma WHO grade II	Grade 1/2
S5	36	Female	Yes	Oligodendroglioma WHO grade II	Grade 1/2
S6	38	Male	Yes	Oligoastrocytoma WHO grade II	Grade 1/2
S7	30	Male	**No**	Diffuse astrocytoma WHO grade II	Grade 1/2
S8	33	Female	Yes	Oligodendroglioma WHO grade II	Grade 1/2
S9	48	Male	Yes	Oligodendroglioma WHO grade III	Grade 3
S11	62	Male	Yes	Glioblastoma WHO grade IV	Grade 4

Conclusion:

This preliminary study demonstrated the capability of a new diffusion MRI method, THI, to noninvasively characterize the structural heterogeneity in brain tumors, including various grades

of tumor cells and capillary blood perfusion within the tumors, consistent with pathology assessment on biopsy tissues. Although our preliminary data suggest THI is a promising multi-parametric imaging technique to accurately measure cellularity and tumor grade, larger studies will be needed before definitive conclusions can be made about the role of this technique. This preliminary study also suggested the unmet need to develop new generation of MRI technique that is capable to provide direct pathophysiological measures for tumor characterization.

References:

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