Perfusion MRI Fractional Tumor Bulk Mapping: Correlation with Multiple Stereotactic Biopsies in Recurrent GBM

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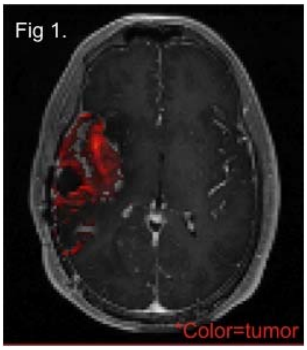
Purpose: We present methods to calculate 'Perfusion MRI (pMRI) fractional tumor bulk,' which quantifies and spatially localizes areas of tumor recurrence within non-specific contrast enhanced (CE) MRI lesions. We correlate these measures with the percentage, or fraction, of tissue samples histopathologically diagnosed as tumor, in a group of recurrent Glioblastoma Multiforme (GBM) patients undergoing multiple stereotactic biopsies.

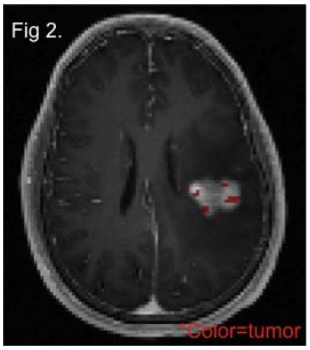
Introduction: Initial standard multi-modality therapy for Glioblastoma Multiforme (GBM) increases median survival to 14-15 months, although these tumors almost universally recur and ultimately prove fatal.[1] Many clinicians and researchers focus on developing new treatment strategies to combat recurrence and extend survival. Unfortunately, significant progress has yet to be made, due in large part to the overwhelmingly common difficulties in non-invasively diagnosing the presence and quantity of tumor recurrence, and differentiating tumor from non-tumoral inflammatory changes, such as post-treatment radiation effect (PTRE). Conventional surveillance contrast enhanced (CE)-MRI detects tumor and PTRE with high sensitivity but low specificity, as both entities often demonstrate identical imaging appearances.[2,3] Moreover, heterogeneous lesions commonly occur and contain varying admixtures of tumor and PTRE, further blurring diagnostic accuracy. Appropriate clinical management depends critically on accurate histologic diagnosis and quantification of the relative abundance, or fractional bulk, of tumor relative to PTRE, which correlates with survival.[4] Definitive diagnosis currently relies on surgical biopsy, which has disadvantages of high costs, operative risks, and patient morbidity. Recent work, however, suggests Perfusion MRI (pMRI) as an alternative, non-invasive technique to diagnose histologically distinct areas of tumor and PTRE with over 95% accuracy, using stereotactically validated relative cerebral blood volume (rCBV) thresholds.[5,6] To date, no study has applied these rCBV thresholds to non-invasively quantify tumor fractional bulk or characterize the spatial heterogeneity of CE-MRI lesions in recurrent GBM patients.

Methods: Following Institutional Review Board approval, we retrospectively analyzed a group of previously treated GBM patients, in whom pMRI was performed prior to surgical resection of new enhancing lesions on surveillance CE-MRI. Preoperative imaging consisted of pMRI (gradient-echo echo-planar imaging (EPI); TR/TE/flip angle (FA), 2000 ms/20 ms/60°; FOV, 24 x 24 cm; matrix, 128x96; 5-mm sections; no gap; 0.05mmol/kg Gadodiamide hand injection at 3-5 cc/sec via large bore i.v. catheter at the 10th time point) and pre- and post-contrast stereotactic T1W spoiled gradient-refocused-echo (SPGR) inversion recovery-prepped MRI (TI/TR/TE, 300/6.8/2.8 ms; matrix, 320x224; FOV, 26 cm; section thickness, 2 mm). We acquired pMRI following 0.1 mmol/kg preloading dose with a six-minute incubation time. The data were imported to an Osirix (v. 3.6.1) workstation using IB Neuro 1.1.430, and IB Registration 1.0.454 (Imaging Biometrics, LLC, Wisconsin) to calculate whole-brain rCBV maps coregistered to stereotactic data, as previously reported. [5-7] Using IB LDM 1.0 and IB ROI Tool 1.0, we performed 1) one-to-one subtraction of voxel values between the coregistered pre- and post-contrast SPGR, 2) created a region of interest (ROI) that included all abnormal enhancing tissue, excluding the remaining brain, and 3) adjusted signal thresholds to exclude non-enhancing brain and necrotic tissue within the ROI, forming a mask. Following coregistration to the rCBV map, all voxels within the mask were categorized as PTRE (rCBV < 1.07) or tumor (rCBV $\geq$ 1.07) based on validation of previously reported thresholds. [5,6] We defined pMRI tumor bulk for each patient as the percentage of tumor voxels out of the total number of mask voxels. Each patient underwent multiple stereotactic biopsies from spatially distinct subregions of large enhancing lesions at the time of surgical resection, without knowledge of pMRI information. The histopathologic diagnosis of each biopsy sample was categorized as either 1) pure tumor, 2) mixed tumor and PTRE, or 3) pure PTRE. We computed a Pearson correlation between pMRI tumor bulk and the percentage of biopsy samples diagnosed as 'pure tumor'. Since mixed samples also contain tumor, we computed a second Pearson correlation comparing pMRI tumor bulk and the percentage of biopsy samples that contained any amount of tumor (both 'pure' and 'mixed' categories) ($p < 0.05$).

Results: We included 11 patients (Table 1), each undergoing between five and eight separate biopsies. Six (55%) patients had at least one biopsy containing pure tumor. The pMRI tumor bulk highly correlated with the percentage of 'pure tumor' biopsies ($r=0.76$, $p=0.007$), and showed slightly diminished correlation when combining 'pure tumor' and 'mixed tumor' categories ($r=0.68$, $p=0.02$). Figures 1 (high bulk) and 2 (low bulk) demonstrate examples of pMRI color overlays depicting tumor regions (rCBV $\geq$ 1.07) in CE-MRI lesions.

Pt	Total samp	Tumor only	Mix	PTRE only	pMRI bulk (%)
A	8	3	2	3	54.5
B	6	4	0	2	71.7
C	5	0	0	5	31.5
D	5	0	0	5	20.7
E	7	2	3	2	82.0
F	8	0	7	1	40.8
G	7	0	7	0	63.5
H	6	0	6	0	47.7
I	5	4	1	0	85.1
J	7	3	3	1	73.9
K	6	1	3	2	55.1





Discussion: pMRI tumor bulk highly correlates with tumor-positive stereotactic biopsies, suggesting the utility of pMRI as an alternative to biopsy to non-invasively identify and quantify the presence of tumor recurrence and fractional bulk, and may provide a helpful marker in clinical trials. Ongoing studies will confirm results in a larger population and correlate bulk with clinical survival.

References: 1) NEJM 352(10):987-96. 2) Radiology 217(2):377-84. 3) Acta Neuropathol 111:197–212 . 4) J Neurosurg 82:436–444. 5) AJNR 30(3):552-8. 6) AJNR Sep 12. [Epub]. (in press) 7) AJNR 27(4):859-67

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