MRI-PET guided surgical targeting and generation of parametric maps reflecting cellular proliferation and microvascular permeability in high grade gliomas

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Background:

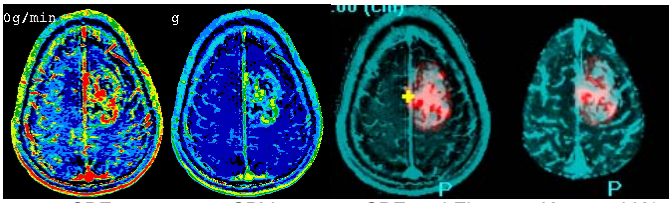
The intratumoral and intertumoral molecular heterogeneity of high-grade gliomas has posed significant challenges to the development of targeted therapies. This has been further complicated by tumors harboring cell populations that survive initial surgical management and radiotherapy, and which become increasingly resistant to further treatments, leading to tumor recurrence. The implementation of non-invasive imaging approaches that can identify growth-regulating molecular events associated with highly aggressive cell populations, as well as detect changes associated with disease recurrence, may facilitate tumor classification and development of targeted therapeutics. Although anatomic MRI is a routine diagnostic tool for characterizing tumors and monitoring tumor recurrence, many imaging features lack biologic or molecular correlates. Signal changes and contrast enhancement associated with intracerebral masses often reflect a combination of multiple superimposed physiologic processes. In addition, such signal changes, are non-specific in appearance and often incompletely characterized. As a result, much of the molecular information encoded within these studies cannot be extracted and remains unknown. The use of specific functional and metabolic imaging methods, such as ^{18}F-FLT PET[1] and DCE-MRI, may yield improved sensitive read-outs of particular histologic and molecular events. In this study, we co-registered dynamic ^{18}F-FLT PET[1] and DCE-MRI to identify potential imaging biomarkers on the basis of voxel-wise multimodal parameter estimates across the entire tumor, with histologic correlation. In conjunction with precise stereotactic tumor targeting, links between observed differences in proliferative activity or microvascular permeability and the results of histologic/molecular assays may potentially be achieved.

Methods:

This IRB-approved study investigated a cohort of 8 untreated high grade glioma patients using dedicated pre-operative anatomic/functional MRI, which included high-resolution contrast-enhanced and DCE-MRI on a 1.5T GE scanner, as well as dynamic ^{18}F-FLT PET-CT scans on GE Discovery STE scanner. ^{18}F-FLT PET-CT images were initially acquired after intravenous (i.v.) injection of ^{18}F-FLT (6 frames of 30 sec, 7 frames of 1-minute, 10 frames of 5-minutes) of the whole brain over 1-hr (47 slices, 3.27 mm slice thickness, FOV 70 cm) and reconstructed using standard protocols with attenuation correction. T1-weighted DCE-MR images were initially acquired with TR/TE=4.7ms/2.15ms, flip angle=25º, field of view (FOV) =240 x 192, slice thickness= 5mm, matrix size=256 x 256 following i.v. GdDTPA (0.1 mmol/kg body weight) at a rate of 2-3 ml/sec. Intraoperative MR guidance and neuronavigation system was used for obtaining targeted surgical biopsy specimens within a short time interval following imaging evaluation. In two cases, motion artifact precluded evaluation using compartmental analysis methods. Initially, voxel-wise pharmacokinetic modeling of dynamic ^{18}F-FLT PET data, using BioGuide™, and DCE-MRI data was performed using non-invasively derived curves as inputs to the model. Alll data was subsequently post-processed employing algorithms developed in-house[2]. For ^{18}F-FLT, a two-tissue compartment, four-rate constant model[3] defining tracer exchange between the blood and tumor tissue compartments was used. In this model, the four rate constants are defined as follows: K_1, transport rate constant from blood to tissue (describes both bulk tracer delivery and transport across cell membrane); k_2, transport from the exchangeable tissue compartment back to blood; k_3, the rate limiting step describing tracer transport between exchangeable and bound (trapped) tissue compartments; k_4, tracer efflux rate out of the imaging region due to nucleoside transport or dephosphorylation; and metabolic flux (K_i), a composite parameter (K_1*k_3/(k_2+k_3)) describing the rate at which the tracer leaves the blood and moves through the biochemical pathways to become trapped. For DCE-MRI-based data sets, the following parametric maps reflecting first pass and equilibrium phases of the bolus injection were generated: cerebral blood volume (CBV); cerebral blood flow (CBF); volume transfer constant (K_{trans}), defined as the exchange of contrast agent between blood plasma and the extravascular extracellular space (EES); volume fraction of EES (V_e), and the rate constant transfer between the EES and plasma (K_{ep}) sets. These were subjected to statistical evaluation to investigate relationships among voxel-based determinations of PET- and MRI-based kinetic parameters during the first-pass and equilibrium phases of the study.

Results and discussion: Clusters of voxels were averaged for each kinetic parameter to generate ROI-based measurements. Statistical evaluations among select parameter values, averaged over all patients, were then performed using Pearson correlative coefficients including K_{trans} *vs* K_i and K_{trans} *vs* K_1. For all patient, the following mean and standard deviation values for derived: K_i: 0.025±0.003 ml/g/min; K_1=0.020±0.006 ml/g/min, k_2: 0.683±0.539 min^{-1}, k_3: 0.076±0.03 min^{-1}, k_4: 0.072±0.05 min^{-1}, CBV: 4.11±1.46 mL/100g, CBF: 60.3± 22.2 mL/100g/min, K_{trans}: 0.562± 0.18 min^{-1}, V_e: 0.2 ± 0.02, K_{ep}: 0.70 ± 0.9 min^{-1}. Figures left to right: CBF, CBV, superimposed CBF- K_i, and superimposed K_{trans}-K_1. These preliminary findings demonstrate the feasibility of deriving voxel-wise parameter estimates following precise co-registration of multimodal parametric (MRI-PET) images in high grade glial tumors, as well as reveal statistical significance among PET- and MRI-based kinetic parameters during the first-pass and equilibrium phases of the study.

Figure: Representative Parametric maps co-registered on MRI-PET



CBF CBV CBF and Flux K_{trans} and K1

References: 1. Bradbury MS, Hambardzumyan D, Zanzonico PB, et al. *J Nucl Med*. 2008;49:422–429. 2. Pauliah M, Vipin S, et al; MRI, 2007: 25(9):1292-1299. 3**.** Bartlett R, Heiko, Steven Larson and John Humm; J Nucl Med. 2010; 51 (Sup 2):339.