Role of functional diffusion maps as an imaging biomarker for treatment response assessment in recurrent/progressive malignant gliomas treated with bevacizumab

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Aims and objectives
Anti-angiogenic agents inhibit angiogenesis and seem to control tumor enhancement initially, however, infiltrative non-enhancing tumor may continue to grow, and measuring only tumor area/volume might overestimate the response. The purpose of this study was to assess the usefulness of functional diffusion maps as an additional imaging biomarker for treatment response in recurrent/progressive malignant gliomas treated with bevacizumab alone or in combination with other chemotherapeutic agents.

Materials and methods
Twenty patients with recurrent/progressive malignant gliomas (WHO grade IV=16, grade III=3, grade II=1) treated with bevacizumab alone or concurrent chemotherapy were included in this study (16 males and 4 females) age ranging from 32-67 years. These patients were followed up for a period ranging from 146-396 days (mean 288.3 days) with serial MR imaging (baseline, 6 weeks, 3 months, one year) on a 3.0 T scanner. Regions of interest (ROI) were drawn by a combination of thresholding and manual tracing using an interactive software package (Eigentool, http://www.radiologyresearch.org/eigentool.htm) for the contrast enhancing lesion (CEL) on post-contrast T1-weighted images and non-contrast enhancing lesion (NEL) seen on FLAIR images to obtain volume of CEL (CELvol) and also of NEL (NELvol). CEL and NEL ROIs were co-registered with diffusion maps on the serial MR studies to obtain ADC values (CELADC and NELADC). Patients were divided into two groups based on imaging and clinical criteria of responders/stable disease and non-responders/progressive disease at one year.

Results
Tumor volumetric analysis: CELvol measurements showed a progressive decrease (Graph) in responders with a median % change of -73.2% at 1 year. Non-responders also showed decrease of CELvol at 6 weeks and 3 months as compared to baseline with a median % change of -33.4% at 1 year. CELvol decrease for both responders and non-responders suggests that assessment of only CEL can not be used as criteria for imaging response in patients with anti-angiogenic therapy as most of the tumors will show reduction of CEL due to normalization of blood vessels particularly in the initial period. NELvol measurements also showed a decrease in responders on follow up imaging. This could also be partially explained by decreasing edema in these patients. In non-responders, NELvol measurements showed initial decrease followed by slight increase by 1 year follow up suggesting that non-enhancing infiltrative tumor shows progressive growth despite a control over CEL.

Functional diffusion map analysis: CELADC measurements in responders showed a serial progressive increase and a positive % change as compared to baseline suggesting increasing water diffusivity which could be attributed to treatment response leading to increasing interstitial edema, decreasing tumor cell density and microcystic changes. NELADC measurements in responders did not show any significant change suggesting probably not much change in the non-enhancing infiltrative component of the tumor. Non-responders showed a progressive negative % change of CELADC as well as NELADC measurements (Graph) suggesting restricted water diffusivity in both CEL and NEL which could be attributed to increasing tumor cell density and treatment failure. In non-responders, NELADC measurements at 6 weeks, 3 months and 1 year follow up showed significant reduction as compared to baseline study with p-values (signed rank test) of 0.054, 0.023 and 0.078 respectively.

Conclusions
Imaging criteria of measuring tumor area/volume especially of CEL only, to assess treatment response may not be sufficient in patients on anti-angiogenic therapy and other functional imaging biomarkers such as ADC values can be helpful in treatment response assessment of these patients. CELADC and NELADC showed a progressive increase in responders suggesting treatment response, probable tumor cell death and decreasing tumor cell density. Non-responders showed a progressive decrease of CELADC and NELADC suggesting increase of tumor cell density, hyper cellular infiltrative tumor growth and treatment failure.

Fig. Baseline and 1 year follow up MRI in a non-responder with GBM showing interval decrease of CELvol and NELvol however, there is infiltrative hypercellular lesion noted in the medial part of the temporal lobe (arrow) which shows reduced ADC values. CELADC and NELADC were both reduced at 1 year follow up as compared to baseline study.