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 (CEL_{vol}) and also of NEL (NEL_{vol}). CEL and NEL ROIs were co-registered with diffusion maps on the serial MR studies to obtain ADC values (CEL_{ADC} and NEL_{ADC}). 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: CEL_{vol} measurements showed a progressive decrease (Graph) in responders with a median % change of -73.2% at 1 year. Non-responders also showed decrease of CEL_{vol} at 6 weeks and 3 months as compared to baseline with a median % change of -33.4% at 1 year. CEL_{vol} 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. NEL_{vol} 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, NEL_{vol} 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: CEL_{ADC} 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. NEL_{ADC} 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 CEL_{ADC} as well as NEL_{ADC} 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, NEL_{ADC} 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. CEL_{ADC} and NEL_{ADC} 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 CEL_{ADC} and NEL_{ADC} suggesting increase of tumor cell density, hyper cellular infiltrative tumor growth and treatment failure.

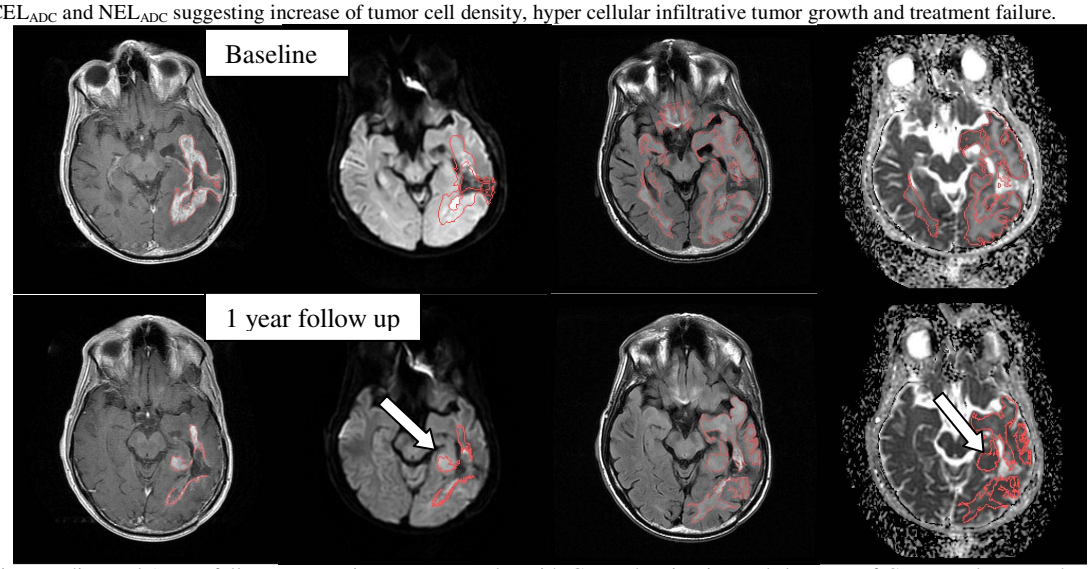

Fig. Baseline and 1 year follow up MRI in a non-responder with GBM showing interval decrease of CEL_{vol} and NEL_{vol}, however, there is infiltrative hypercellular lesion noted in the medial part of the temporal lobe (arrow) which shows reduced ADC values. CEL_{ADC} and NEL_{ADC} were both reduced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