

Probabilistic functional diffusion maps (fDMs) in human glioblastoma

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Introduction

Functional diffusion mapping (fDM) uses the voxel-wise changes in apparent diffusion coefficient (ADC) measured in the same patient over time as a biomarker for cancer response to therapy¹⁻⁹. This technique is advantageous for quantification of treatment related changes in spatially heterogeneous tumors and has shown to be predictive of response in glioblastoma under a variety of treatment paradigms¹⁻⁹. Despite these promising findings, quantification of fDM response is still highly dependent on the quality of image co-registration between ADC maps. A recent study has demonstrated increased clinical sensitivity of fDMs when nonlinear (elastic) registration techniques are employed², which exemplifies the need for more robust and accurate fDM quantification techniques. In the current study we introduce a *probabilistic* approach to fDM quantification, where finite translational and rotational perturbations are performed after linear registration of ADC maps. These probabilistic fDMs (prob-fDMs) were then applied to a large cohort of newly diagnosed glioblastoma (GBM) patients treated with standard radiochemotherapy ($n = 143$).

Methods

All patients participating in this study signed institutional review board-approved informed consent to have their information in our neuro-oncology database. A total of $n = 143$ histologically-confirmed, newly diagnosed GBM patients with high quality diffusion-weighted images before and after initiation of radiochemotherapy (external beam radiation therapy + temozolomide) were included in the current study. Baseline (post-surgical, pre-treatment) scans were obtained approximately 1 week before therapy and post-treatment scans were obtained 4-6 weeks after completion of radiochemotherapy. All data was collected on clinical 1.5T MR systems using pulse sequences supplied by the manufacturer. Diffusion weighted images (DWIs) were collected with $b = 0$ and $b = 1000$ s/mm², slice thickness of 5mm (1mm gap), using a twice-refocused, spin echo echoplanar (SE-EPI) acquisition. ADC maps were calculated from acquired DWIs. All image for each patient were registered and interpolated to pre-treatment, pre-contrast, T1-weighted images using a mutual information algorithm and a 12-degree of freedom transformation using FSL (FMRIB, Oxford, UK). After linear registration, finite perturbation of both baseline (pre-treatment) ADC maps and post-treatment ADC maps were performed along 6 degrees of freedom (x, y, and z translation and θ , ϕ , and ψ rotation) using a uniform probability density. Maximum translation was 5mm and maximum rotation was ± 15 degrees. After application of finite perturbations, voxel-wise subtraction was performed between ADC maps acquired post-treatment and baseline (pre-treatment) ADC maps. Individual voxels were stratified based on the change in ADC relative to the baseline ADC map. Voxels having an ADC increase [ADC(+)] or decrease [ADC(-)] beyond a Δ ADC threshold of $0.4 \mu\text{m}^2/\text{ms}$ ⁴, were labeled for each perturbation for a total of 1000 finite, random perturbations. The fraction of all perturbations resulting in significant increases or decreases in Δ ADC were retained for further analysis, resulting in probabilistic maps $p(\text{ADC}(+))$ and $p(\text{ADC}(-))$. The total hypercellular [ADC(-)] and hypocellular [ADC(+)] burden was quantified as the sum of all probabilities within post-surgical, pre-treatment FLAIR hyperintense regions of interest (ROI) divided by the volume of FLAIR abnormal regions:

$$\text{Prob-fDM \%ADC}(+) = \frac{\iiint_{\text{ROI volume}} p(\text{ADC}(+)) dx dy dz}{\text{ROI volume}}$$

$$\text{Prob-fDM \%ADC}(-) = \frac{\iiint_{\text{ROI volume}} p(\text{ADC}(-)) dx dy dz}{\text{ROI volume}}$$

Probabilistic fDMs were stratified by the median volume fraction for all patients ($>20\%$ and $<20\%$ of pre-treatment FLAIR ROI). Log-rank statistical analysis was used to test the hypothesis that a large probabilistic fDM-classified volume fraction of decreasing ADC [%ADC(-) $> 20\%$] is indicative of a non-responsive, growing hypercellular tumor and will result in a significantly shorter progression-free survival (PFS). Log-rank analysis was also performed to test the hypothesis that a large probabilistic fDM-classified volume fraction of increasing ADC [%ADC(+) $> 20\%$] is indicative of destruction of tumor cells, a favorable response to radiotherapy, resulting in a significantly longer PFS. PFS was defined from the time of diagnosis to radiographic or neurological progression as indicated by a board certified radiologist according to a modified RANO criterion¹⁰ and clinical assessment by a board certified neuro-oncologist, respectively.

Results

Probabilistic fDMs illustrating the probability of obtaining fDM-classification per voxel during random, finite perturbations, clearly showed regions of increasing and decreasing ADC with the tumor of newly diagnosed and recurrent GBM (Fig. 1A). The regions of highest probability of increasing and decreasing ADC corresponded well spatially with traditional fDMs; however, probabilistic fDMs did identify regions suspect of subtle tumor growth not identified by traditional fDMs (arrows). Log-rank analysis applied to Kaplan-Meier data suggested patients with probabilistic fDM-classified volume fraction of decreasing ADC in more than 20% of pre-treatment FLAIR abnormal regions [%ADC(-) $> 20\%$] had a significantly shorter PFS compared with patients having a lower volume fraction (Log-rank, $P < 0.0001$; HR=3.3). Median PFS for patients with probabilistic fDM-classified %ADC(-) $> 20\%$ was 239 days compared with 602 days for patients having %ADC(-) $< 20\%$. Log-rank analysis suggested patients with probabilistic fDM-classified volume fraction of increasing ADC in more than 20% of pre-treatment FLAIR abnormal regions [%ADC(+) $> 20\%$] had a significantly longer PFS compared with patients having a lower volume fraction (Log-rank, $P < 0.0001$; HR = 0.39).

Discussion

Probabilistic fDMs provide a robust alternative to the use of traditional fDMs with respect both to visualization and quantification of patient response to treatment. Probabilistic fDMs allow for a relatively registration-independent estimate of fDM parameters by utilizing the sum of all probabilities of fDM-classification as a new biomarker. Our results demonstrate better clinical sensitivity of probabilistic fDMs when compared to traditional fDMs in newly diagnosed glioblastoma patients treated with standard radiochemotherapy. Probabilistic fDMs represent the state-of-the-art in voxel-wise parametric response mapping in human glioblastoma.

References

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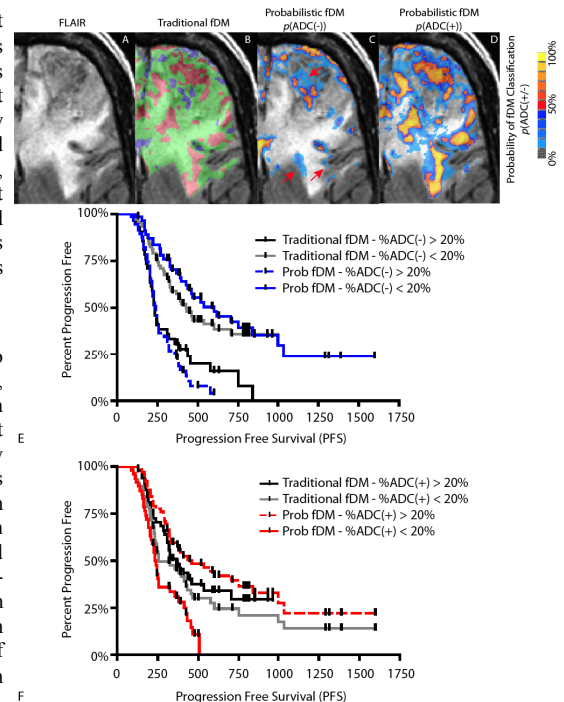


Figure 1: Probabilistic Functional Diffusion Maps in Glioblastoma A) FLAIR, B) traditional fDM (red=increased ADC, blue=decreased ADC), C) probabilistic fDMs - %ADC(-), and D) probabilistic fDMs - %ADC(+). E) Volume fraction of decreasing ADC for traditional and probabilistic fDMs both stratify short and long-term PFS. F) Volume fraction of increasing ADC for traditional fDMs does not separate short and long-term PFS; however, probabilistic fDMs separate short and long-term PFS.