Tissue expansion maps (TEMs) derived from nonlinear registration of serial 3D MR scans as an imaging biomarker for detecting brain tumor invasion and quantifying tumor response to therapy

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Target Audience – Neuroradiologists, neuro-oncologists, neurosurgeons, and basic scientists interested in imaging biomarkers for visualization and quantification of tumor infiltration, tumor growth rates, and response to therapy.

Introduction

Glioblastoma multiforme (GBM) is the most common and most aggressive form of malignant brain tumor. Median survival for patients with newly diagnosed GBM treated with maximal extent of resection, radiotherapy, and temozolomide is only approximately 14 months [1]. Clinical evaluation of individual patient tumor response to therapy currently consists of examining bidirectional measurement of the contrast-enhancing portion of the tumor [2,3], evaluation of potential changes in T2 or FLAIR hyperintense regions that may contain nonenhancing tumor [3], and neurological evaluation that may indicate a change in cognitive function from infiltrating tumor (e.g. Macdonald [2] or RANO criteria [3]). Similarly, clinical evaluation of individual patients often consists of serial measurement in tumor bidirectional measurements or volume; however, subtle changes in mass effect from infiltrating tumor and diffuse nonenhancing tumor are not often quantified. This poses a particular challenge, since the poor prognosis of GBM is at least partially attributed to undetected infiltrating tumor with a minimal imaging signature. We hypothesized that nonlinear (elastic) registration of serial high-resolution 3D post-contrast T1-weighted images in GBM patients could be used to quantify local tissue distortion from growing tumor. In the current study we explored the use of "Tissue Expansion Maps", TEMs, as a tool for quantifying tumor growth and infiltration.

Methods

All patients participating in this study signed institutional review board-approved informed consent to have their information in our neuro-oncology database. All patients examined for this study were evaluated serially on a 3T MR scanner (Siemens 3T Trio or Skyra; Erlangen, Germany). All patients had a 1mm isotropic post-contrast T1 weighted volumetric scan at various time points during various treatments. 3D T1 post-contrast images were acquired with echo time (TE) = 2-5ms; repetition time (TR) = 2100ms; inversion time (TI) = 1100ms; matrix size = 256x256; a field of view (FOV) = 256mm; and a slice thickness of 1mm. For comparison with resulting TEMs, many patients also received dynamic susceptibility contrast (DSC), diffusion tensor imaging (DTI), dynamic contrast enhancement (DCE), and ^{18}F-FDG positron emission tomographic (PET) scans. All images for each patient were first registered to a baseline T1 volumetric image using a mutual information algorithm and a 12-degree of freedom transformation using FSL (FMRIB, Oxford, UK; http://www.fmrib.ox.ac.uk/fsl/). Fine registration (1-2 degrees and 1-2 voxels) was then performed using a Fourier transform-based, 6 degree of freedom, rigid body registration algorithm. Nonlinear (elastic) registration was then performed on the serial 3D post-contrast T1-weighted images using the FMRIB nonlinear registration tool (FNIRT), a free-form deformation algorithm using a B-spline basis function. FNIRT uses a Levenberg-Marquardt modification of the Gauss-Newton method for optimizing the minimum of a sum-of-squares cost function to perform the nonlinear registration. The voxel-wise nonlinear displacement fields (***D***) and Jacobian matrices (***J***) were then extracted after registration. Tissue Expansion Maps (TEMs) were calculated by measuring the Euclidean displacement distance, $\|\mathbf{D}\| = \sqrt{D_x^2 + D_y^2 + D_z^2}$ and dividing it by the time between subsequent scans, $\frac{d\|\mathbf{D}\|}{dt}$, resulting in maps depicting the rate of tissue expansion in um/day. Additionally, the voxel-wise determinant of the Jacobian matrix, **det**(***J***), and vector representations of the nonlinear displacement field (***D***) were quantified and used for visualization.

Results

Figure 1 illustrates a typical patient with growing and/or recurrent GBM. In regions with new contrast enhancement (*Fig. 1A-Ba*), elevated rCBV (*Fig.1Ca*), and elevated ^{18}F-FDG uptake (*Fig. 1Ha*), the rate of tissue expansion was elevated on TEMs. Specifically, TEMs, reflecting the rate of deformation estimated via nonlinear registration per unit time (*Fig. 1Db*), identified a locus of rapid tumor growth near an existing blood vessel on Day 0. Vector representation of the nonlinear displacement field shows the direction of tissue expansion appearing to cross the corpus callosum to the right frontal lobe (*Fig. 1Ia*). Similar to the medial contrast-enhancing nodule, a lateral region of contrast enhancing tumor also grew in this particular patient (*Fig. 1Bc*). TEMs also identified a locus of rapid tumor growth rate at the leading edge of this lesion (*Fig. 1Dc*). Interestingly, TEMs also identified a locus of rapid tissue expansion within deep gray matter (*Fig. 1Dd*), suggesting tumor infiltration through these regions. Subtle tumor infiltration into these deep gray matter structures is slightly more apparent on FLAIR images (*Fig. 1E-F*), where the internal capsule appears hyperintense and the left anterior lateral ventricle is slightly collapsed from mass effect.

Discussion

Tissue expansion maps (TEMs) and other deformation information extracted from serial nonlinear image registration of high-resolution 3D post-contrast T1-weighted images are useful biomarkers for spatially visualizing and quantifying brain tumor growth and response to therapy.

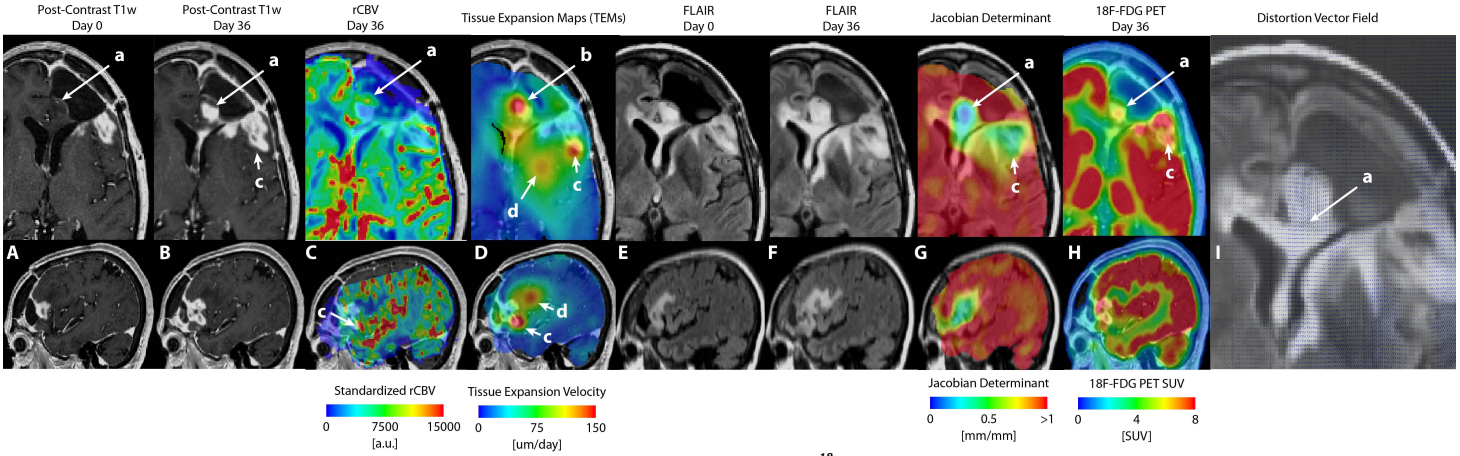

Figure 1: Tissue Expansion Maps (TEMs), Jacobian Determinant, Distortion Vector Fields, ^{18}F-FDG PET, and MRI Images of a Patient with Recurrent GBM

References: 1) Stupp, *N Eng J Med*, 2005. 2) Macdonald, *JCO*, 1990. 3) Wen, *JCO*, 2010.