Probabilistic Tractography in Patients with Recurrent Malignant Gliomas

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Introduction:
Malignant gliomas are the most common primary brain tumor in adults. Standard treatment consists of surgical resection with adjuvant radiotherapy and temozolomide. Even after aggressive treatment, survival remains poor at mean 14.6 months after diagnosis. Currently, standard radiotherapy involves a uniform pattern of irradiation around the tumor unless other critical neural structures lie within that margin. Developing techniques to predict progression pathways could permit increased focal radiation to high-risk areas and decreased radiation to normal brain tissue. Diffusion tensor imaging (DTI) is an MR imaging technique that measures the diffusion of water in the brain to generate maps of white matter tracts. Because tumor progression typically occurs along white matter tracts, we hypothesized that DTI could predict the location of future progression of high-grade gliomas.

Materials and Methods:
We prospectively identified 7 patients with high-grade gliomas and retrospectively identified 9 additional patients with high grade-gliomas. All patients were naïve to chemoradiation therapy. DT images were acquired on a 1.5 T (n=5) or 3.0 T (n=5) magnet (Signa HDx and Excite, GE Medical Systems, Milwaukee, WI) using a standard quadrature head coil. DTI was acquired with a single shot echo planar sequence using 15 or 25 noncollinear gradient directions, TR/TE=13,500/100 msec, matrix 128×128, in-plane resolution 1.88×1.88 mm, slice thickness 3 mm, b-value 1000 sec/mm^2, NEX 1 and maximum diffusion gradient strength 22mTm^{-1}. Probabilistic maps were generated using DTI&FiberTools (Medical Physics, Department of Diagnostic Radiology, University Hospital, Freiburg, Germany) based on an extended Monte Carlo simulation of Random Walks using the Probabilistic Index of Connectivity (PICo) method. Maps were generated based on one ROI located directly around the widest margins of the tumor in three dimensions. The connectivity maps were rated based on maximal fiber length as well as by the maximal fiber connectivity. All images were examined in consensus by a medical student (PL, 1 year experience) and a board certified radiologist who holds a certificate of added qualification in neuroradiology (RJY, 10 years of experience). Predictions of high-risk regions of progression were determined by 1) maximal fiber length and 2) maximal fiber connectivity. Patients were followed every 1-2 months for signs of progressive disease. Using modified response assessment criteria, progressive disease was defined as ≥25% increase in enhancing disease, new enhancing disease, or significant increase in nonenhancing disease (in patients receiving anti-angiogenic therapy). Sites of progression were compared to the two high-risk regions determined by the probabilistic maps.

Results: The mean progression free survival was 8.9 months (range, 3.5 -15.9 months). At least one of the two predicted progression pathways was correct in all 16 cases. The maximal fiber length method showed the strongest predictive value and was consistent with the location of progression in 14/16 cases. In 4/16 cases, the maximal local fiber connectivity was consistent with the location of tumor progression. Five of the patients in the study had tumors that grew locally in multiple directions. For our analysis, the predicted pathway was considered to be accurate if the tumor in expanded in at least one of the directions predicted by the probabilistic maps.

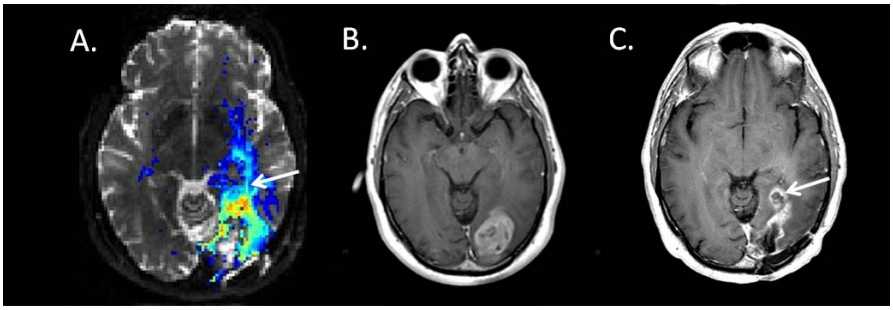

Figure 1. Maximal fiber length. (A) Connectivity map demonstrates the longest fibers (arrow) extending anteriorly in the periatrial region. Contrast T1WI (B) before surgery shows the enhancing tumor in the left occipital lobe, and (C) 10 months later reveals progressive disease in the same location (arrow).

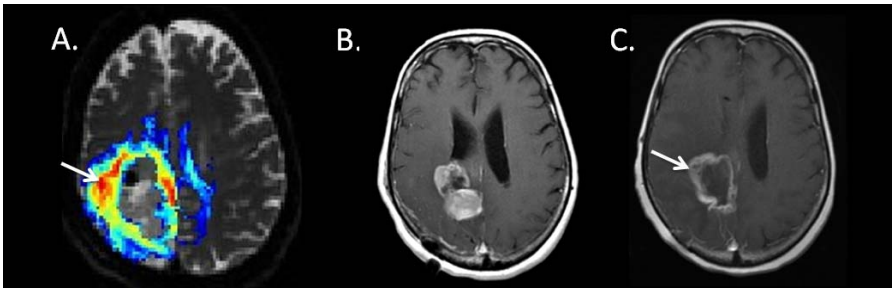

Figure 2. Maximal fiber connectivity. (A) Connectivity map shows strongest probability paths (arrow, red voxels) at the lateral margin of the tumor. Contrast T1WI (B) after subtotal resection and before radiotherapy demonstrates mild enhancement at the margins of the blood filled surgical cavity, and (C) 4 months later reveals progressive disease in the same location (arrow).

Discussion:
The majority of malignant gliomas recur locally after standard radiation therapy. The isotropic margins used in current radiotherapy may lead to unnecessary radiation toxicity to normal brain, and may insufficiently treat more malignant areas that have higher probability of developing progression. The probabilistic maps constructed from seed ROI surrounding the tumors showed a strong correlation with the actual locations of tumor progression. These preliminary data suggest that probabilistic tractography is useful in predicting the sites of progression. Further work is necessary to determine if individualized radiation therapy plans based on probabilistic tractography can improve patient outcomes.

References: Krishnan, et al. IJROBP 2008; 71: 1553-62. Mukherjee, et al. AJNR 2008; 29: 632-41. Jena, et al. Clin Oncol 2006; 17: 581-90. Choucair J Neurosurg 1986; 65: 654-8. Wen, et al. JCO 2010; 28: 1963-72.