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PHYSICS CONTRIBUTION

EVIDENCE THAT MR DIFFUSION TENSOR IMAGING (TRACTOGRAPHY) PREDICTS THE NATURAL HISTORY OF REGIONAL PROGRESSION IN PATIENTS IRRADIATED CONFORMALLY FOR PRIMARY BRAIN TUMORS

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Purpose: Stereotactic radiotherapy (SRT) is fast becoming the method of choice for treatment of nonsuperficial brain lesions. SRT treatment plans of malignant brain tumors typically incorporate a 20-mm isotropic margin to account for microscopic tumor spread; however, distant or progressive tumors occur outside this margin. Our hypothesis is that paths of elevated water diffusion may provide a preferred route for transport or migration of cancer cells. If our hypothesis is correct, then future SRT treatment volumes could be modified to provide elongated treatment margins along the paths of elevated water diffusion, thereby creating a biologically better treatment plan that may reduce the incidence of progression.

Methods and Materials: Magnetic resonance diffusion tensor imaging (DTI) datasets were acquired on patient subjects before the appearance of >5 mm diameter progressive lesions or secondary tumors. DTI was performed using an echo-planar imaging sequence on a 1.5T clinical General Electric scanner with voxel dimensions of 0.98 × 0.98 × 6 mm. After SRT, patients were given repeated magnetic resonance imaging follow-ups at regular intervals to identify early tumor progression. When progressive disease was detected, DTIstudio and FMRIB Software Library software was used to compute paths of preferred water diffusion through the primary tumor site and the site of progression.

Results: Our preliminary results on 14 patient datasets suggest a strong relationship between routes of elevated water diffusion from the primary tumor and the location of tumor progression.

Conclusions: Further investigation is therefore warranted. Future work will employ more sophisticated fiber analysis in a prospective study. © 2008 Elsevier Inc.

Diffusion tensor imaging, Tractography, Stereotactic radiotherapy, Treatment margins, Brain tumor.

INTRODUCTION

Approximately 17,000 new cases of primary brain cancer are diagnosed in the United States annually (1). Several common types of primary brain cancer have a historical and physiologic basis for aggressive tumor spread in the brain that thwarts our most sophisticated technology and all existing pharmacologic agents. These include oligodendrogliomas, low-grade astrocytomas, anaplastic astrocytomas, and glioblastomas. With current chemotherapy and radiation techniques, the 5-year survival rate for patients older than age 45 ranges from 16% for those with anaplastic astrocytomas to 2% or less for those with glioblastomas (2). High-dose stereotactic radiotherapy (SRT) is a relatively new treatment technology that can be used to deliver a lethal dose of radiation to a small target site with rapid dose falloff into the surrounding normal tissue to minimize the side effects of harmful radiation to normal tissue (3–6). High dose conformal RT, including SRT, is fast becoming the method of choice for treatment of nonsuperficial brain lesions.

A typical SRT treatment plan for a high-grade astrocytoma includes a uniform margin of up to 25 mm surrounding the lesion to account for any unobserved microscopic spread of tumor cells. This margin size is based on histologic analysis of maximal tumor spread at autopsy dating from the 1980s (7). Because there are no means to directly observe microscopic tumor spread *in vivo*, the same margin size is used in all directions (isotropic) unless there is a need to avoid critical structures in the brain. Unfortunately, the use of large

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isotropic margins leads to unnecessary ablation of healthy brain tissue, resulting in cognitive dysfunction, whereas the margins are too small in some regions, leading to tumor progression, often with catastrophic results. The goal of this study is to use magnetic resonance (MR) diffusion tensor imaging (DTI) to predict the microscopic spread of aggressive brain tumors and to help us better understand the mechanisms of tumor spread. These enhancements could then lead to improved anisotropic margins for radiation treatment of malignant brain tumors that would achieve greater local cancer control and increased patient survival while potentially decreasing harmful side effects associated with radiation therapy by reduction of margins in low-risk regions.

Our scientific hypothesis is that migrating brain cancer cells follow the paths of least resistance as determined from MR DTI. This hypothesis is supported by the following observations. First, in areas of white matter, the direction of greatest diffusion usually parallels the predominant underlying fiber orientation and it is known from postmortem studies in humans that glioma cancer cells that migrate the greatest distance from primary tumor sites are located predominantly along white matter tracts (8–11). Second, Jacobsen *et al*. (12) observed that, during embryogenesis, neonatal astrocytes show a preferential movement along developing axon tracts.

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If cell migration were to occur in an isotropic medium, then there would be an equal probability of spread in all directions; however, it is known that diffusion of water in the brain is highly anisotropic. The local anisotropic diffusion of water molecules in the brain can be measured noninvasively *in vivo* using MR DTI (13–21). The local diffusion coefficient along any predefined direction can be quantified using a standard MR imaging sequence augmented with a pair of diffusion encoding gradients. The local three-dimensional diffusion environment is expressed by the diffusion tensor and the process of computing the diffusion tensor at each voxel in the image is DTI. DTI tractography is the process by which the voxel-wise values of the diffusion tensor are used to estimate the paths that water will travel from one voxel to the next. In the brain, the paths of greatest diffusion are found to parallel the neuronal fiber tracts. Thus when applied in regions of white matter, DTI tractography can be used to reconstruct the local nerve fiber architecture (13, 16–18).

Tractography is commonly realized using either streamline or probabilistic approaches. The streamline approach is also commonly referred to as deterministic tractography. In the streamline approach, the reconstructed tract through each voxel runs parallel to the voxel's principal diffusion direction defined as the eigen vector corresponding to the largest eigen value of the 3×3 diffusion tensor (15, 19–21). Knowledge of the direction from the previous step and of the diffusion directions in adjacent voxels is often incorporated into the algorithm to achieve a more reasonable and reproducible solution. Streamlined methods typically assume one dominant fiber direction per voxel and hence fail in instances of fiber crossing. Probabilistic tractography incorporates the uncertainty associated with the diffusion parameters into an estimate of the probability of connection between two points (14). The advantage of such probabilistic methods is that they can be more robust to noise when the difference between the magnitude of the diffusion tensor eigen values is small (*i.e*., when the fractional anisotropy value is small) and can therefore track fibers within gray matter and where multiple nonparallel fiber bundles are present within a single voxel.

METHODS AND MATERIALS

Patient selection

Data were collected for patients who were treated for aggressive gliomas with SRT at the University of Rochester Medical Center and who had documented tumor progression and where the progression was entirely or mainly outside of the original planning target volume. On identification of a potential subject, the patient's medical image database was examined for the presence of a DTI dataset that was acquired before the diagnosis of progressive disease. The DTI datasets used for analysis were typically acquired around the time of SRT planning. The protocol inclusion criteria required there to be DTI data acquired before the presence of extensive progressive disease that could potentially alter the diffusion environment that was present at the time when the first wave of migratory cancer cells was active (22). No other factors were taken into account when selecting patient datasets for analysis. The protocol was approved by the institutional Internal Review Board according to federal and institutional guidelines. Three categories of patients were defined. Category 1 (Distant Secondary Tumor Group) included Patients 1–5 who had secondary tumors located greater than 2 cm beyond the SRT treatment volume. Category 2 (local secondary tumor group) included patients 3 and 6–11 who had secondary tumors within 2 cm or on the boundary of the treatment plan and had no sign of progression in the DTI dataset. Category 3 (progression group) included patients 12–14 who had surgical resection followed by SRT and progression on or near the margin of the primary tumor.

Image acquisition

The datasets were acquired using a clinical whole-body 1.5 Tesla (1.5T) scanner (General Electric SIGNA EXCITE, Milwaukee, WI) as part of the standard of care imaging protocol in place at the authors' institution. After an initial acquisition of axial and coronal T1 and T2 weighted anatomic images with voxel dimensions $0.98 \times 0.98 \times 3$ mm, DTI was performed using one of the following echo-planar imaging sequences using the following parameters: *(1)* TR 10 s; echo time 89.4 ms; 20 serial axial slices; 25 diffusion gradient directions and three reference scans ($b = 0$) scans; and voxel dimensions of $0.98 \times 0.98 \times 6$ mm; or *(2)* repetition time 10.8 s; echo time 101.3 ms; 38 axial slices; 21 diffusion gradient directions and two reference scans and voxel dimensions of $0.94 \times 0.94 \times 3$ mm. As per standard of care, after SRT, patients were given repeated MR image follow-ups at regular intervals to identify early progressive disease. When progressive disease was detected, DTI data acquired before SRT were processed using DTIStudio and FMRIB Software Library (FSL) software to compute all paths of preferred water diffusion through the primary tumor site. In the analyses shown, all fiber pathways from the area of tumor are depicted, although the complete three-dimensional fiber architecture is often not fully appreciated when viewing is limited to two-dimensional projections.