Diffusion MRI: A Biomarker for Cancer Treatment Response

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Anatomical imaging in clinical oncology practice traditionally has relied upon comparison of patient images following completion of therapeutic intervention with pre-treatment images. Therapeutic success is quantitatied in terms of gross changes in tumor size from the anatomical images 6-12 weeks following completion of treatment. The hope is that new approaches such as "molecular imaging" could provide opportunities for obtaining additional insights into the effects of treatment which reflect tissue changes at the cellular or physiologic level. Thus, the identification of a noninvasive imaging-based biomarker sensitive to early, therapeutic-induced changes in tumor tussue would provide for an early indicator of treatment response/outcome in individual patients. This capability could yield tremendous changes in the clinical care of oncology patients as patients would be no longer have to be treated based soley upon statistical data of percent treatment response for a particular therapy as treatments could be modified prior to current anatomical endpoints thus allowing for individualization of care. Furthermore, delineation of therapeutic-induced spatial heterogeneity within a tumor mass may also be used to provide additional information related to specific regions that are resistant or responsive to treatment. This educational contribution will overview the use of diffusion MRI in pre-clinical and clinical oncology studies and will address how this approach may be applied in the future for the management of patients with solid tumors.

INTRODUCTION

Conventional oncologic MRI provides an invaluable opportunity to noninvasively follow gross tumor morphology and how it evolves following therapeutic intervention. Conventional MRI exploits a variety of endogenous tissue properties that allow the neuro-oncologist/neuro-radiologist to assess gross tumor extent on the resultant MRI contrasts, such as "T2-weighted" and "gadolium-enhanced T1-weighted" images. The typical radiologic assessment is somewhat interpretive and based on the spatial extent and location of anomalous contrast. The actual image contrast values are rarely quantified as these are usually arbitrarily scaled and do not have a simple relationship to tissue properties. It is thought that there is significant untapped potential for MRI techniques designed to provide additional functional, structural, or molecular information related to tumor biology and physiology. Such information may be derived from quantitation of tissue properties which reflect, for example, perfusion dynamics, oxygenation

levels, biochemistry/metabolism, cellularity and levels of gene expression. Since the spatial information is retained, regional heterogeniety in these tissue properties and their change with therapy are also measurable.

While tissue function, perfusion, oxygenation, and metabolism are actively being studied in relation to brain tumors, the specific interest in this overview is the application of MRI to provide information related to the microscopic cellular environment in solid tumors. The use of water "apparent diffusion coefficient" (ADC) as a biomarker to probe tissue cellularity is compelling since this parameter is strongly affected by molecular viscosity and membrane permeability between intra- and extra-cellular compartments, active transport and flow, and directionality of tissue/cellular structures that impede water mobility. Thus, diffusion MRI can be applied for a variety of tumor characterization purposes including distinguishing cystic regions from solid, highly cellular regions as well as detection of treatment response which is manifest as a change in cellularity within the tumor. In brief, diffusion MRI sequences incorporate an additional pair of magnetic field gradient pulses to render an MR signal intensity that is dependent on the mobility of the signal source, i.e. water molecules[1]. Conceptually, the first of these two gradient pulses imparts a phase shift to each water molecule proportional to its initial location. The second gradient pulse removes the phase shift if the water molecule remains at its original location. Any molecular movement between first and second pulses, however, leads to incomplete rephasing. The large number of water molecules and their respective random trajectories produce a net dephasing or signal loss. The amount of signal loss is a direct reflection on water mobility - that is, the greater signal loss implies greater molecular mobility. If the time interval between gradient pulses is sufficient to allow water molecules to migrate distances comparable to the size of and spacing between cells, then the apparent mobility will be reduced by the impediments of cellular membranes and tortuosity of the extracelluar space. In addition, the directionality of cellular structures such as in highly-ordered white matter fiber tracts can be probed by controlling the direction of the applied diffusion pulses. The study of diffusion directionality or "anisotropy" is itself a significant area of investigation, however, tumor diffusion measures are typically directionally-independent via careful combination of data from several diffusion gradient directions[2, 3].

Often in clinical practice the raw "diffusion-weighted" image is utilized as a sensitive, albeit qualitative, diagnostic screen for acute ischemia in brain tissue[4-6]. The clinical interpretation is that regions of conspicously bright signal on diffusion-weighted MR images suggests restricted diffusion in and amongst cells swollen by cytotoxic edema secondary to ischemic insult. Acquisition of images at multiple diffusion sensitivities, however, allows the calculation of an apparent diffusion coefficient (ADC) at each point in the image. Water mobility is reduced in the restricted environment of cellular-dense tissues relative cellular-sparse tissues that exhibit high diffusion properties. While it is an over simplification of the biophysics involved, we will consider the ADC value to be inversely related to the cellularity of brain tumors. The relative tissue contrast on an ADC image shows high diffusion/mobility areas as bright in acellular/cystic tissues is actually reversed from the contrast of diffusion-weighted MRI. While this can be a source of confusion, the key feature of the ADC representation is that it is quantitative. As such, ADC may be used for the diagnostic assessment of tumors, for comparison across individuals, or serially within an individual undergoing treatment and is independent of the equipment brand and magnet field strength.

The central hypothesis in utilization of diffusion to assess the impact of therapy is that successful treatment of a tumor with cytotoxic agents results in significant damage and/or killing of cells thus altering cell membrane integrity and the degree of cellularity prior to tumor volume regression. This has a net effect of increasing the fractional volume of the interstitial space due

to cell loss resulting in an increase in the mobility (diffusion) of water within the damaged tumor tissue. The sensitivity of diffusion MRI for detection of therapeutic-induced changes depends upon the possible overall dynamic range which can be observed by ADC measurements. For example, tissue such as normal adult brain has an ADC value of 0.6-0.8 x $10^{-3}mm^2/sec$ while CSF is about 3.0 x $10^{-3}mm^2/sec$. This represents the range of ADC values typically observed in the CNS. Enthusiasm for the use of diffusion MRI for therapy assessment stems from animal studies which have reported that this approach can be used to monitor early events in tumor treatment in a variety of tumors models [7-11] along with application to patients with primary CNS tumors[20-22].

Potential Clinical Impact

Presently, a comparison of sequential MRI scans is the method of choice for monitoring the response of CNS tumors to therapy which compares the change in maximal diameter, cross sectional area of the tumor via the product of the maximal perpendicular tumor diameters, or full volume determination[12]. Gadolinium-enhanced T1-weighted images are often used, but T2-weighted or other MR contrast strategies may be employed. Comparisons of tumor burden are usually made between pre-treatment scans and those obtained weeks to months following the conclusion of a therapeutic protocol[13]. Methods of assessing treatment response that are not dependent on relatively slow changes in tumor volume may be capable of providing earlier indications of therapeutic outcome since molecular and cellular changes typically precede observable macroscopic changes in gross tumor size. Therefore, the use of a quantitative MRI bio-marker scheme (i.e. water diffusion) to determine therapeutic-induced changes in the tumor cellular matrix as recently reported is an area of active research investigation.

Cellular Density

Diffusion-weighted MRI (DWI) has proven to be a sensitive technique for identifying regions of ischemic tissue damage in animal models of stroke and in human patients [4-6]. Monte Carlo simulations suggest that changes in tissue water diffusion following tissue damage are predominantly attributable to alterations in the volume and tortuosity of the extracellular space [14-16]. These properties of the extracellular space are primarily a function of cell density, and recent work has shown that tumor water diffusion is associated with tumor cellularity[17-19]. Comparison of ADC values from individual tumors with biopsy-derived histological sections provides important validation of this approach for noninvasively assessing cellularity of tumor tissue. This ability can be exploited in the clinical setting where classification of a CNS lesion as a cyst or a tumor may be difficult based only upon the information obtained from anatomical images. In these examples, an arachnoid cyst and epidermoid tumor both presented as hyperintense lesions on T2-weighted MRI in two different patients. However, diffusion MRI revealed the cyst as a lesion with an extremely high ADC value (3.0 x 10^{-3} mm^2/s) while the tumor had a low ADC value (0.9 x 10^{-3} mm^2/s). These examples reveal that diffusion MRI can provide valuable information reflecting the cellularity of a lesion within the CNS which can aid in clinical diagnosis.

Treatment Assessment

The temporal gradation of increasing diffusion values from pre-treatment viable tumor to treatment-induced acellular tumors was first reported using a rat glioma model[7]. Since this initial report, there have appeared numerous studies verifying and expanding upon the ability of diffusion MRI for following treatment response[8-11]. Evaluation of the clinical potential of diffusion MRI for detection of early therapeutic-induced changes in tissue structure are ongoing

but recent results have been very promising[20-22]. In these recent studies diffusion MRI has been used to provide early evidence of cancer treatment efficacy in individual patients prior to the completion of the therapeutic regimen[21,22].

Tumor Hetergeneity

Tumors are known to be highly heterogeneous in terms of cell viability, perfusion and oxygenation level. Since these biophysical properties are factors that can modulate efficacy of chemo and radio therapies, one could reasonable expect that therapy-induced changes may heterogeneous within a given tumor. Since ADC images are quantitative they can be used to regionally map therapy response. Such information has the potential to be valuable to guide spatially-directed therapies such as gamma knife radiosurgery or intra-tumoral injection of agents. Since tissue "change" is of key interest, temporal shifts in diffusion coefficients are measurable by select region-of-interests defined on ADC images. Alternatively, an "ADC difference" map provides an efficient means to survey regional tissue alterations.

The histogram-based analysis of tumor diffusion data sets provides the opportunity to quantify mean tumor ADC values. However, alternative methods of analyzing diffusion data are required for analysis of clinical data which have large regions of spatially-varying heterogeneity in ADC values. A recent approch termed functional diffusion mapping (fDM) appears very promising wherein ADC maps are acquired pre-treatment and early on during treatment with chemo- and/or radio-therapy[21,22]. Images are digitally co-registered to the pretreatment scan, and tumor diffusion values calculated and correlated with subsequent response defined by change in tumor size on MRI by standard radiographic criteria. Results obtained using fDM have revealed early changes in tumor diffusion values occur which could be used to predict patient response with high sensitivity and specificity[21,22]. Thus, diffusion MRI appears to provide an early biomarker for predicting treatment response in patients with brain tumors and should be considered a very important avenue for future research investigations.

REFERENCES

1. Stejskal EO ,Tanner J. Spin diffusion measurements: spin-echoes in the presence of a time-dependent field gradient. *J Chem Phys*. 1965;42:288-292.
2. Chenevert TL, Brunberg JA, Pipe JG. Anisotropic diffusion in human white matter: demonstration with MR techniques in vivo. *Radiology*. 1990;177:401-405.
3. Chenevert TL, McKeever PE, Ross BD. Monitoring early response of experimental brain tumors to therapy using diffusion magnetic resonance imaging. *Clin Cancer Res*. 1997;3:1457-1466.
4. Moseley ME, Cohen Y, Kucharczyk J, *et al.* Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. *Radiology*. 1990;176:439-445.
5. Warach S, Gaa J, Siewert B, Wielopolski P, Edelman RR. Acute human stroke studied by whole brain echo planar diffusion-weighted magnetic resonance imaging. *Ann Neurol*. 1995;37:231-241.
6. Sorensen AG, Buonanno FS, Gonzalez RG, *et al.* Hyperacute stroke: evaluation with combined multisection diffusion-weighted and hemodynamically weighted echo-planar MR imaging. *Radiology*. 1996;199:391-401.
7. Ross BD, Chenevert TL, Kim B, Ben-Yoseph O. Magnetic resonance imaging and spectroscopy: Application to experimental neuro-oncology. *Q Magn Reson Biol Med*. 1994;1:89-106.

8. Chinnaiyan AM, Prasad U, Shankar S, *et al.* Combined effect of tumor necrosis factor-related apoptosis-inducing ligand and ionizing radiation in breast cancer therapy. *Proc Natl Acad Sci U S A*. 2000;97:1754-1759.
9. Stegman LD, Rehemtulla A, Hamstra DA, *et al.* Diffusion MRI detects early events in the response of a glioma model to the yeast cytosine deaminase gene therapy strategy. *Gene Ther*. 2000;7:1005-1010.
10. Galons JP, Altbach MI, Paine-Murrieta GD, Taylor CW, Gillies RJ. Early increases in breast tumor xenograft water mobility in response to paclitaxel therapy detected by non-invasive diffusion magnetic resonance imaging. *Neoplasia*. 1999;1:113-117.
11. Zhao M, Pipe JG, Bonnett J ,Evelhoch JL. Early detection of treatment response by diffusion-weighted 1H-NMR spectroscopy in a murine tumour in vivo. *Br J Cancer*. 1996;73:61-64.
12. Sorensen AG, Patel S, Harmath C, *et al.* Comparison of diameter and perimeter methods for tumor volume calculation. *J Clin Oncol*. 2001;19:551-557.
13. Therasse P, Arbuck SG, Eisenhauer EA, *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92:205-216.
14. Norris DG, Niendorf T, Leibfritz D. Health and infarcted brain tissues studied at short diffusion times: the origins of apparent restriction and the reduction in apparent diffusion coefficient. *NMR Biomed*. 1994;7:304-310.
15. Sykova E, Svoboda J, Polak J, Chvatal A. Extracellular volume fraction and diffusion characteristics during progressive ischemia and terminal anoxia in the spinal cord of the rat. *J Cereb Blood Flow Metab*. 1994;14:301-311.
16. Szafer A, Zhong J, Gore JC. Theoretical model for water diffusion in tissues. *Magn Reson Med*. 1995;33:697-712.
17. Sugahara T, Korogi Y, Kochi M, *et al.* Usefulness of diffusion-weighted MRI with echo-planar technique in the evaluation of cellularity in gliomas. *J Magn Reson Imaging*. 1999;9:53-60.
18. Lyng H, Haraldseth O, Rofstad EK. Measurement of cell density and necrotic fraction in human melanoma xenografts by diffusion weighted magnetic resonance imaging. *Magn Reson Med*. 2000;43:828-836.
19. Gupta RK, Sinha U, Cloughesy TF, Alger JR. Inverse correlation between choline magnetic resonance spectroscopy signal intensity and the apparent diffusion coefficient in human glioma. *Magn Reson Med*. 1999;41:2-7.
20. Chenevert TL, Stegman LD, Taylor JM, *et al.* Diffusion magnetic resonance imaging: an early surrogate marker of therapeutic efficacy in brain tumors. *J Natl Cancer Inst*. 2000;92:2029-2036.
21. Moffat, BA, Chenevert TL, Lawrence TS *et al*. Functional diffusion map: A noninvasive MRI biomarker for early stratification of clinical brain tumor response. roc. Natl. Acad. Sci. 2005;102:5524-5529.
22. Hamstra DA, Chenevert TL, Moffat, BA, *et al*. Evaluation of the functional diffusion map as an early biomarker of time-to-progression and overall survival in high-grade glioma. Proc. Natl. Acad. Sci. 2005;102:16759-16764.