Diffusion in Brain Tumors

Danielle van Westen, MD PhD

Technique

Diffusion weighted imaging (DWI) probes the random motion of water molecules over distances corresponding to the size of human cells and less [1]. Thus water mobility strongly reflects tissue microstructure and its changes with physiological and pathological states. Gradient parameters determine the sensitivity of the DWI sequence, summarized in the 'b-value' with measurement at two b-values enabling calculation of an apparent diffusion coefficient (ADC). Directional, i e anisotropic, water displacement is estimated from diffusion measurements in six non colinear directions or more (diffusion tensor imaging, DTI) and allows for calculation of the fractional anisotropy (FA), which is the degree to which molecular displacements vary in space [2]. Following reconstruction of three-dimensional vector field maps representing fiber orientation in each voxel, an algorithm may connect subsequent voxels on the basis of their fiber orientation. Inference of continuity in the fibers renders maps of 'virtual' fiber bundles across the brain (Diffusion Tensor Tractography, DTT). Non Gaussian water diffusion can be modeled as the diffusional kurtosis with the kurtosis representing the extent to which diffusion deviates from a Gaussian curve [3].

Tumor characterisation and grading

The sensitivity of DWI to cellular density and the directional organisation of tissues is demonstrated in neuro-oncology by the relationship between ADC and tissue cellularity, with low ADC being associated with cellular dense areas on histology [4-7]. Considerable overlap between tumor-specific ranges of diffusion values precludes the use of ADC for a definitive diagnosis of tumor type and grade [8]. Instead the ADC may support a diagnosis suspected from morphological and other functional images. While ADC generally is increased in tumor as compared to normal brain tissue, it may be decreased in lesions with very high cell density, such as the contrast enhancing part of glioblastomas [6, 7], in contrast enhancing lymphomas [5], in some meningiomas [6] and metastases [6, 9] as well as in medulloblastomas [10], although to a lesser extent than in acute ischemic infarctions [8]. Low ADC and restricted diffusion commonly differentiate epidermoids from arachnoid cysts that complete lack structures restricting water mobility [11], and abscesses in the early phase from cystic tumors, due to the abundance of granulocytes in pus [12]. Occasionally central necrosis of a tumor or metastasis can show the same DWI signal characteristics as pus [13]. Use of the ADC for differentiation of noncontrast enhancing tumor and peritumoral edema has been hampered by overlap between tumor types. The FA is generally reduced in tumors suggesting structural disorder, which may not add information for tissue classification. Kurtosis reportedly differs between grade II, III and IV gliomas [14].

Preoperative mapping of white matter tracts

Delineating fiber pathways using DTI/DTT improves preoperative evaluation, planning and surgical targeting by neuronavigation. Pathways of primary relevance in the clinic are the pyramidal tract, the arcuate fascicle and the optic radiation. In addition to displacing, infiltrating or destructing tracts, lesions can alter the diffusion signal: low FA due to perilesional edema may cause failing to reconstruct fiber tracts that are invaded by tumor but still functional when electrically stimulated.

Treatment monitoring

DWI is potentially sensitive to effects from cellular necrosis, apoptosis and membrane lysis present before mass shrinkage of the tumor [15]. Converging evidence suggests that an

increase in tumor ADC is correlated with positive clinical response to treatment comprising chemotherapy, chemoradiation or stereotactic radiotherapy [16-18]. Greater increases in ADC in response to therapy over time have been observed in those patients alive at 1 year compared with those who died as a result of disease [19]. Moreover, the strongest predictor of 1-year survival is reportedly the volume of tumor with increased ADC after 3 weeks of treatment compared to baseline, with a larger difference in ADC predicting longer median survival. Also, pretreatment minimum ADC values are correlated with longer survival in patients with malignant supratentorial astrocytomas [20]. Tumor recurrence has been associated with an increase as well as a reduction of the ADC and is not reliably differentiated from radiation injury with DWI. In general, radiation necrosis is heterogeneous on DWI with areas of necrosis containing abundant leukocytes possibly decreasing the ADC. Normal appearing white matter adjacent to perilesional edema exhibits an increased FA ratio, relative to the contralateral side, in radiation necrosis compared to recurrent tumor [21]. During treatment with bevacizumab (Avastin®), a monoclonal antibody decreasing microvascular density and vascular permeability, ADC in contrast enhancing and non contrast enhancing tumor areas showed a stable to slightly progressive increase in non-progressors and a progressive decrease in progressors, especially early on.

This presentation will focus on the clinical application of DWI in neuro-oncology and its value for tumor characterisation and treatment monitoring.

References:

1. Le Bihan D. Looking into the functional architecture of the brain with diffusion MRI. Nat Rev Neurosci. 2003 Jun;4(6):469-80.
2. Basser PJ, Jones DK. Diffusion-tensor MRI: theory, experimental design and data analysis - a technical review. NMR Biomed. 2002 Nov-Dec;15(7-8):456-67.
3. Jensen JH, Helpern JA, Ramani A, Lu H, Kaczynski K. Diffusional kurtosis imaging: the quantification of non-gaussian water diffusion by means of magnetic resonance imaging. Magn Reson Med. 2005 Jun;53(6):1432-40.
4. Gauvain KM, McKinstry RC, Mukherjee P, et al. Evaluating pediatric brain tumor cellularity with diffusiontensor imaging. AJR Am J Roentgenol 2001;177(2): 449–54.
5. Guo AC, Cummings TJ, Dash RC, et al. Lymphomas and high-grade astrocytomas: comparison of water diffusibility and histologic characteristics. Radiology 2002;224(1):177–83.
6. Kono K, Inoue Y, Nakayama K, et al. The role of diffusion-weighted imaging in patients with brain tumors. AJNR Am J Neuroradiol 2001;22(6):1081–8.
7. Sugahara T, Karogi 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(1):53–60.
8. Yamasaki F, Kurisu K, Satoh K, Arita K, Sugiyama K, Ohtaki M, Takaba J, Tominaga A, Hanaya R, Yoshioka H, Hama S, I t o Y, Kajiwara Y, Yahara K, Saito T, Thohar MA. Apparent diffusion coefficient of human brain tumors at MR imaging. R adiology, 2005; 235: 985–991.
9. Gauvain KM, McKinstry RC, Mukherjee P, Perry A, Neil JJ, Kaufman BA, Hayashi RJ. Evaluating pediatric brain tumor cellularity with diffusion-tensor imaging. AJR Am J Roentgenol. 2001 Aug;177(2):449-54.
10. Rumboldt Z, Camacho DL, Lake D, et al. Apparent diffusion coefficients for differentiation of cerebellar tumors in children. AJNR Am J Neuroradiol 2006; 27: 1362–1369
11. Tsuruda JS, Chew WM, Moseley ME, et al. Diffusion-weighted MR imaging of the brain: value of differentiating between extraaxial cysts and epidermoid tumors. AJNR Am J Neuroradiol 1990; 11: 925–931
12. Ebisu T, Tanaka C, Umeda M, Kitamura M, Naruse S, Higuchi T, Ueda S, Sato H.Discrimination of brain abscess from necrotic or cystic tumors by diffusion-weighted echo planar imaging. Magn Reson Imaging. 1996;14(9):1113-6.
13. Mortimer A, O'Leary S, Bradley M, Renowden SA.Pitfalls in the discrimination of cerebral abscess from tumour using diffusion-weighted MRI. Clin Radiol. 2010 Jun;65(6):488-92. Epub 2010 Apr 3.
14. Raab P, Hattingen E, Franz K, Zanella FE, Lanfermann H.Cerebral gliomas: diffusional kurtosis imaging analysis of microstructural differences. Radiology. 2010 Mar;254(3):876-81. Epub 2010 Jan 20.
15. 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(24):2029–36.
16. Schubert MI, Wilke M, Muller-Weihrich S, et al. Diffusion-weighted magnetic resonance imaging of treatment-associated changes in recurrent and residual medulloblastoma: preliminary observations in three children. Acta Radiol 2006;47(10):1100–4.
17. Mardor Y, Pfeffer R, Spiegelmann R, et al. Early detection of response to radiation therapy in patients with brain malignancies using conventional and high b-value diffusion-weighted magnetic resonance imaging. J Clin Oncol 2003;21(6):1094–100.
18. Tomura N, Narita K, Izumi J, et al. Diffusion changes in a tumor and peritumoral tissue after stereotactic irradiation for brain tumors: possible prediction of treatment response. J Comput Assist Tomogr 2006; 30(3):496–500.
19. Hamstra DA, Galbán CJ, Meyer CR, Johnson TD, Sundgren PC, Tsien C, Lawrence TS, Junck L, Ross DJ, Rehemtulla A, Ross BD, Chenevert TL. Functional diffusion map as an early imaging biomarker for high-grade glioma: correlation with conventional radiologic response and overall survival. J Clin Oncol. 2008 Jul 10;26(20):3387-94. Epub 2008 Jun 9.
20. Murakami R, Sugahara T, Nakamura H, et al. Malignant supratentorial astrocytoma treated with postoperative radiation therapy: prognostic value of pretreatment quantitive diffusion-weighted MR imaging. Radiology 2007;243: 493–99.
21. Sundgren PC, Fan X, Weybright P, Welsh RC, Carlos RC, Petrou M, McKeever PE, Chenevert TL. Differentiation of recurrent brain tumor versus radiation injury using diffusion tensor imaging in patients with new contrast-enhancing lesions. Magn Reson Imaging. 2006 Nov;24(9):1131-42. Epub 2006 Sep 18.
22. Jain R, Scarpace LM, Ellika S, Torcuator R, Schultz LR, Hearshen D, Mikkelsen T. Imaging response criteria for recurrent gliomas treated with bevacizumab: role of diffusion weighted imaging as an imaging biomarker. J Neurooncol. 2010 Feb;96(3):423-31. Epub 2009 Oct 27.