REVIEW

For reprint orders, please contact: reprints@futuremedicine.com

Diffusion-weighted MRI in neuro-oncology

Joachim M Baehring^{*1} & Robert K Fulbright²

Practice Points

- The basic goal of diffusion-weighted MRI (DW-MRI) is to provide insight into microscopic tissue structure by noninvasively measuring diffusion of water molecules.
- In the diagnosis of brain tumors, DW-MRI may be used to assess cellularity; distinguish tumor from perifocal vasogenic edema, or viable tumor from necrosis; or predict tumor response to treatment. Most reproducible data are obtained in cellular neoplasms (lymphoma, medulloblastoma and germinoma).
- DW-MRI helps identify epidermoid cysts and metastases or primary brain tumors with mucinous degeneration.
- A peculiar subset of toxic leukoencephalopathies after exposure to methotrexate, capecitabine, 5-fluorouracil and other chemotherapeutic agents is defined by DW-MRI.
- DW-MRI supplements conventional MRI sequences in the diagnosis of neurologic complications of cancer, such as polioencephalopathies associated with status epilepticus, ischemic or hemorrhagic stroke as a result of disease-related or iatrogenic hypercoagulable state, vascular occlusion or hemorrhagic diathesis, and opportunistic infection.
- Diffusion tensor imaging and fiber tractography provide preoperative visualization of white matter tracts and their relationship to structural lesions such as brain tumors. Its impact on outcome has yet to be measured.

SUMMARY Diffusion-weighted MRI (DW-MRI) provides image contrast dependent on the molecular movement of water. It has been most widely used in the diagnosis of cytotoxic edema secondary to acute cerebral ischemia, but has also proven useful in assessing tumor cellularity and grade, abscess formation, cysts and various forms of white matter disorders. Furthermore, DW-MRI is used to generate maps of subcortical white matter tracts and their relationship to structural brain lesions that may serve for preoperative planning and intraoperative guidance. We provide a comprehensive review of current practical applications of DW-MRI in the diagnosis and treatment of primary brain tumors, metastases and nonmetastatic neurologic complications of cancer. A detailed

¹Department of Neurology, Medicine and Neurosurgery, Yale University School of Medicine, 15 York St, LLC1 920 E, New Haven, CT 06510, USA

²Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, CT, USA

^{*}Author for correspondence: Tel.: +1 203 785 7284; Fax: +1 203 737 2591; joachim.baehring@yale.edu

description of diffusion tensor imaging is beyond the scope of this review. We performed a comprehensive search of the PubMed database of the USA National Library of Medicine with use of various combinations of the following search terms: diffusion-weighted imaging, apparent diffusion coefficient, diffusion tensor imaging, diffusion tensor, brain, tumor, glioblastoma, lymphoma, primary CNS lymphoma, stroke, cancer, abscess, leukoencephalopathy, methotrexate, fluorouracil, capecitabine. We identified original articles and well-documented case reports of DW-MRI applications in patients with primary brain neoplasms, metastases and nonmetastatic neurologic complications that we judged to be of high impact on the field. We largely selected publications from the past 10 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles are cited to provide readers with more details and more references than can be covered here.

Diffusion-weighted MRI: a technical introduction

Diffusion is a result of Brownian motion, which is the random, irregular and continuous movement of water molecules due to thermal energy. The water molecules collide and move, resulting in a net displacement. Over time, a molecule's displacement follows a Gaussian probability distribution. Einstein formalized the diffusion process, stating that the mean squared displacement, $\langle x^2 \rangle$, of a particle starting from an initial position is:

$$\langle x^2 \rangle = 6 \times D \times \Delta t \quad (\text{Equation 1})$$

where D is the diffusion coefficient that depends on molecular size, temperature and solvent properties, and Δt represents the time elapsed from the starting position [1]. If the probability of a molecule being at a certain distance in each direction is measured, a point could be chosen in each direction that represents the root mean squared displacement [2]. The apparent diffusion coefficient (ADC) is the diffusion constant measured in clinical MRI, reflecting the fact that *in vivo* diffusion cannot be differentiated from other sources of water mobility, such as active transport, changes in membrane permeability and flow due to concentration gradients [3].

The basic goal of diffusion-weighted MRI (DW-MRI) is to provide insight into microscopic tissue structure by noninvasively measuring diffusion of water molecules. To accomplish this goal, DW-MRI uses modifications of an MRI pulse sequence to enhance the sensitivity of the MRI signal to the diffusion of water molecules. These modifications consist of two symmetrical gradient pulses to introduce variance in magnetic strength [4]. In the presence of the first

magnetic gradient, the precession rate of water protons (spins) is changed and leads to phase dispersion of their transverse magnetization (T_2 relaxation). A second, re-phasing gradient, identical in direction but opposite in magnitude to the first diffusion gradient, is applied to refocus the phase dispersion that occurred between the gradient pulses. Water protons that have moved along the gradient axis in the interval between the application of the first and second gradient pulses will not be reset to their initial state, but will acquire a phase shift relative to the protons of immobile water molecules. This phase shift results in signal loss because the overall vector sum of the proton phases in a dispersed state is less than if they were all precessing synchronously. The magnetic resonance (MR) signal decreases as the mean displacement of water molecules within the image voxel increases, or equivalently, faster diffusion results in a larger decrease in MR signal.

The signal loss resulting from the diffusion gradients is characterized by the following equation, originally described by Stejskal and Tanner:

$$S_i = S_0 \times e^{-\gamma^2 G^2 \delta^2 (\Delta - \frac{\delta}{3}) D} = S_0 \times e^{-bADC} \quad (\text{Equation 2})$$

where S_i is the signal intensity after application of the diffusion gradients; S_0 is the signal intensity prior to gradient application; γ is the gyromagnetic ratio, which is a constant representing the ratio of a proton nuclear magnetic dipole moment to its angular momentum, and when multiplied by the magnetic field strength in Tesla (T), it represents the rate of proton nuclear precession known as the Larmor frequency; G is the amplitude of the gradient; δ is the duration

of the gradient; Δ is time between application of two pulses; ADC is the apparent diffusion coefficient; and the b-value incorporates the above factors to summarize the strength of diffusion weighting [4].

In tissue that appears randomly organized on the scale of the voxel (1.5–2.5 mm), the reduction in the MR signal caused by diffusion will be independent of the direction in which it is measured, meaning the ADC value is identical for all directions (isotropy) [5]. In white matter, microstructures such as cell membranes, myelin and macromolecules restrict the movement of water molecules, which means the loss in MR signal intensity depends on the orientation of the gradients (anisotropy). The underlying structure of white matter results in larger ADC parallel to the white matter tracts, and smaller ADC values perpendicular to the tracts [6].

There are different approaches to obtain DW-MR images, but the two most commonly used are the echo-planar-based methods of diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI or DT-MRI). In DWI, the signal intensity measured at each voxel with diffusion gradients applied in three directions is compared with the signal intensity measured at each voxel without a diffusion gradient. The images obtained from DWI have contributions from T2 relaxation and diffusion, as seen in [Equation 3](#):

$$S_i = k \times e^{-TE/T_2} \times e^{-bADC} \quad (\text{Equation 3})$$

where k is a proportionality constant, T_2 is the transverse relaxation time, TE is the time to echo, ADC is the apparent diffusion coefficient, $\ln$ is the natural logarithm and S_i is the signal intensity measured in a given voxel with the diffusion gradient applied along direction i , which is the x , y or z planes. The signal intensity from all three gradient directions is then averaged at each voxel and displayed as a DWI map.

To obtain images based only on diffusion properties, ADC maps can be obtained by calculating ADC using [Equation 4](#):

$$ADC = -\ln \left(\frac{S_i/S_0}{b} \right) \quad (\text{Equation 4})$$

where ADC is the apparent diffusion coefficient, $\ln$ is the natural logarithm, S_i is the signal intensity measured in a given voxel with the diffusion gradient applied along direction i , S_0 is the signal intensity measured without a diffusion

gradient and b summarizes the diffusion gradient properties. The ADC from all three gradient directions is then averaged at each voxel and displayed as an ADC map. The ADC maps remove any T2 component to help determine whether a lesion or brain region has abnormal diffusion. ADC maps are important since lesions on DWI maps that appear to have altered diffusion could be a result of the signal intensity being driven more by T2 relaxation than by diffusion ('T2 shine-through').

DTI can reveal additional information about underlying brain structure since it employs diffusion gradients in at least six or more non-collinear directions, compared with the gradients in three directions used in DWI [7]. DTI makes it possible to quantitatively characterize the anisotropic nature of white matter and to generate anatomic maps of white matter pathways. A tensor is a mathematical abstraction that provides a way to characterize how something with length and direction transforms into something else with length and direction [101]. A tensor can imply a 3×3 symmetric matrix. More generally, a tensor is a linear transformation from vectors to vectors, or is an ordered set of numbers that change or transform when there is a change in basis (coordinate axis). The tensor plays a role in vector analysis similar to the role that slope plays in algebra [101].

The diffusion tensor models the displacements of water molecules assuming there is a single water compartment, the signal decay is mono-exponential, there is a single fiber type and orientation in each voxel, and the diffusion distribution is Gaussian [7,8]. In this formulation, the tensor is a 3×3 symmetric, positive-definite matrix, meaning that it is a matrix with three orthogonal or mutually perpendicular eigenvectors, and three positive eigenvalues. The eigenvectors and eigenvalues define an ellipsoid representing a level set of diffusion probability. The three orthogonal eigenvectors can be considered a local fiber coordinate system. The axes of the ellipsoid are aligned with the eigenvectors and the three eigenvalues, λ_1 , λ_2 and λ_3 , provide information about the length of the eigenvectors. The major eigenvector of the diffusion tensor points in the principal diffusion direction, which is the direction of the fastest diffusion.

In DTI, the ADC in [Equation 2](#) represents a 3×3 symmetric matrix of diffusivities (D) or ADC values. To calculate the six independent numbers in matrix D , at least seven images are

needed. Six (or more) images are the diffusion-weighted images from the six gradient directions, and one is the baseline image acquired without a diffusion gradient. The symmetric property of the matrix means the elements of the tensor above the diagonal are equal to those below the diagonal, which is the reason that the minimum number of independent numbers (and gradient applications) is six. The system of equations can then be solved for diffusion values using the least squares method at each voxel. In clinical practice, the number of different gradient directions is often in the range of 20–30 to increase the signal to noise ratio.

Various metrics have been derived from the diffusion tensor in order to characterize the dimensions and shape of the diffusion ellipsoid associated with the microstructure of a particular voxel [9]. These metrics can be displayed as scalar quantities or as eigenvectors mapped to colors to provide tract orientation, or can be utilized to derive a method like tractography, which is an estimate of a pathway of white matter tracts. To obtain these metrics, the three principal axes of the diffusion tensor can be calculated using basic linear algebra to diagonalize the diffusion tensor matrix D :

$$\Lambda = E \cdot D \cdot E^T \quad (\text{Equation 5})$$

where D is the diffusion tensor matrix consisting of the diffusivities in each of the six (or more) directions, as described above. From D , eigenvectors and eigenvalues are computed from the characteristic equation of D . These eigenvectors form the columns of E . E^T is the transpose of E . Matrix D is diagonalized by EDE^T , producing matrix Λ that has the eigenvalues λ_1 , λ_2 and λ_3 along the matrix diagonal. The three eigenvectors and rotationally invariant eigenvalues describe the directions and lengths of the three diffusion ellipsoid axes.

The metrics commonly derived from the eigenvalues are mean diffusivity (MD) maps, trace-weighted maps, fractional anisotropy (FA) maps and color-coded FA maps. The MD is the mean of the three eigenvalues. It is analogous to ADC maps and describes the directionally averaged diffusivity of water within a voxel. The trace is the sum of the three eigenvalues and is an additional measure of average diffusion. Trace weighted images can be generated by calculating the geometric mean of the eigenvalues. The FA measures the degree to which diffusion is

directional (anisotropic) and is determined as follows:

$$FA = \left(\frac{3}{2}\right)^{1/2} \times \frac{((\lambda_1 - MD)^2 + (\lambda_2 - MD)^2 + (\lambda_3 - MD)^2)^{1/2}}{(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)^{1/2}} \quad (\text{Equation 6})$$

where MD and λ_1 , λ_2 and λ_3 are the three eigenvalues [10]. The FA ranges from 0 to 1, with 0 indicating the diffusion is mainly isotropic and 1 meaning the diffusion is strongly directional. In color-coded FA maps, the fiber orientation characterized by the primary eigenvector can be visualized on 2D images by assigning a color to each of three orthogonal axes, with red for white matter tracts oriented right to left, green for fibers running anterior to posterior, and blue for pathways oriented primarily superior to inferior.

Tractography is another way to utilize the information provided by DTI [5,11–13]. The main goal of tractography is to map white matter pathways using various algorithms. The DTI algorithms typically fall into two categories: deterministic and probabilistic. In deterministic algorithms, there is one estimate of fiber orientation at each voxel, which is based on the principal eigenvector. A pathway is reconstructed by moving from voxel to voxel following the principal eigenvector. A probabilistic approach estimates a distribution of possible fiber orientation at each voxel. Pathways are propagated by repeatedly taking random samples from the distribution of orientations. This process leads to a distribution of possible pathways between two points.

There are many issues with DTI in general and with tractography in particular that contribute to error in DTI measurements, limiting clinical utility [5,14]. There are partial volume effects as the resolution is not on the scale of some pathways of interest. Local magnetic fields, eddy currents and susceptibility effects, among other factors, contribute to the uncertainty inherent in DTI. Diffusion is not necessarily best modeled as being Gaussian and mono-exponential, and simple linear models are not always robust. Finally, there is usually not a single fiber direction within a voxel and DTI cannot accurately differentiate complex tissue architecture, especially white matter with fibers that cross, kiss, splay, twist and fan. To attempt to address these issues, additional techniques in the acquisition and analysis of diffusion MR data include

q-ball imaging [15], diffusion spectrum imaging [16], persistent angular structure MRI [17] and spherical harmonic deconvolution [18].

Clinical applications of DW-MRI in neuro-oncology

From a formal pathogenetic point of view, DW-MRI is most useful in conditions associated with increased cellularity, ischemia, viscous or mucinous degeneration, and intramyelinic sheath edema, as these are associated with relative restriction of water diffusion. Conversely, the recognition of disorders causing cell breakdown or vasogenic edema is facilitated by demonstrating an increase in water diffusivity on DW-MRI. Interpretation is only possible by integrating DW-MRI information with signal characteristics on conventional MR sequences, other neuroimaging modalities and clinical data.

The following section is organized by clinical categories in which we have found DW-MRI most helpful.

■ Tumor diagnosis & assessment of treatment response

The utility of DW-MRI in the preoperative diagnosis of brain tumors has been studied with respect to assessing cellularity or grade; distinguishing enhancing from nonenhancing areas, tumor from perifocal vasogenic edema, or viable tumor from necrosis; or predicting tumor response to treatment.

Initial diagnosis

DW-MRI, when interpreted in the context of a comprehensive MRI protocol, computed tomography, and clinical data, has proven to be a useful addition to preoperative tumor diagnosis and grading. An inverse relationship between cellularity and diffusivity has been observed in various tumors including lymphoma, high-grade glioma, germinoma, meningioma and medulloblastoma (Figure 1A) [19–25]. Multiple factors likely contribute to this phenomenon: relative increase of intracellular versus extracellular compartment; increased tortuosity of extracellular space; the high nuclear:cytoplasmic ratio of some cancer cells; and the overall increased cellularity of high-grade lesions [26–28].

In the diagnosis of malignant gliomas, DW-MRI appears to be most useful at the early stage of tumor development or malignant transformation when there is rapid growth of a cellular mass prior to evolution of central necrosis

(Figure 2) [29]. Patients diagnosed at this stage typically have superficial tumors giving rise to early seizures. They come to medical attention before their masses show rim enhancement and central necrosis; 4% lack contrast enhancement altogether [30–32].

ADC values in high-grade gliomas have been found to be significantly lower than in low-grade gliomas [19,22]. Areas of contrast enhancement display lower signal compared with nonenhancing tumor and peritumoral edema [33]. Others have reported ADC maps to be helpful in distinguishing tumor from normal white matter and grading of malignant neoplasms, but not differentiating between benign and malignant tumors [34]. In contrast, several investigators have reported large overlap of ADC values of normal white matter, low-grade and high-grade neoplasms, and thus questioned its usefulness in individual patients [22,24,25]. No significant difference between the ADC values of enhanced tumor versus nonenhanced tumors and between nonenhanced tumors versus edema was found in

Figure 1. Patterns of diffusion-weighted MRI abnormalities. (A–C) Diffusion-weighted imaging; (D–F) apparent diffusion coefficient map. (A & D) Increased cellularity. Diencephalic germinoma (left), meningioma (right). The tumors are indicated by arrow heads on the apparent diffusion coefficient map. (B & E) Intramyelinic sheath edema. Delayed leukoencephalopathy with stroke-like presentation after intrathecal methotrexate injection in a 14-year-old boy with pre- β -cell acute lymphoblastic leukemia. (C & F) Polioencephalopathy. Cytotoxic edema involving gray matter in complex partial status epilepticus (arrow heads). Patient with cerebral parenchymal and suspected leptomeningeal metastases from non-small-cell lung cancer. A metastatic lesion adjacent to the area of cortical cytotoxic edema had been successfully treated with Gamma Knife® radiosurgery.

Figure 2. A 27-year-old gentleman was found to have a left temporal brain tumor after he had a seizure. (C) Diffusion-weighted imaging and (D) apparent diffusion coefficient map revealed an area of decreased water diffusivity within the tumor (arrowheads). A subtotal resection was performed. (A) Large tumor portions were inconspicuous, consistent with an infiltrative oligoastrocytoma, WHO grade II, (hematoxylin and eosin stain), while other areas were characterized by markedly increased cellularity and pleomorphism. (B) Immunohistochemistry for Ki-67 showed areas of low (left) and markedly increased proliferative activity (Ki-67 index up to 40%; right) corresponding to the findings on hematoxylin and eosin stain. (E) Endothelial proliferation or necrosis were not identified, either on histopathology or on T1-weighted MRI after gadolinium administration. (A & B) Scale bars: 50 μ m. Images courtesy of Alexander Vortmeyer.

one study [35]. Others reported failure to distinguish between enhancing tumor areas and peritumoral vasogenic edema based on ADC maps and lack of correlation with tumor grade [36]. In a small series of pediatric glioblastoma patients, no significant difference was found between ADC values of solid tumor portions and normal white matter [37]. In another study, ADC failed to distinguish mixed tumor and necrosis from pure tumor [38].

The conflicting data reported for high-grade gliomas reflect the heterogeneity of these tumors and variable study design. Spatial and temporal heterogeneity in ADC signal is based upon destruction of normal anatomy by tumor, vasogenic edema, tumor cellularity, degenerative changes (hemorrhage, cystic or mucinous degeneration), and compression of normal structures. Signal changes may be additive or cancel each

other out [39]. Only a few studies are available in which histopathological findings were correlated with preoperative MRI findings. Quantification has to take into account the signal heterogeneity of malignant gliomas and dynamic signal changes over time. Qualitative approaches are subject to interobserver variability. Primary CNS lymphoma (PCNSL) in immunocompetent patients appears as single or multifocal enhancing masses on conventional T1-weighted MRI with gadolinium. Relative restriction of water diffusion in PCNSL has been observed in 66–90% of tumors by us and others [BAEHRING JM, FULBRIGHT RK, UNPUBLISHED DATA] [21,40,41]. Few quantitative data are available. Overall, measured ADC values in solidly enhancing masses or in the periphery of rim-enhancing lesions have ranged widely from 0.167×10^{-3} to 1.067×10^{-3} mm^2/s , reflecting mostly methodological variations between investigators (measurement of minimum ADC, mean ADC, ADC at 25th percentile; measurement within solid portion of tumor vs average of various representative sections) [21,40–51]. ADC values are inversely correlated with cell density [21,42]. Based on twelve PCNSL cases, we found the ADC_{mean} within the peritumoral region to be significantly different from ADC_{mean} of the lesion and ADC_{mean} of contralateral normal-appearing white matter. Differences between ADC_{mean} (lesion) and ADC_{mean} (normal) are not statistically significant [BAEHRING JM, FULBRIGHT RK, UNPUBLISHED DATA].

Differential diagnosis

Restricted water diffusion within cerebral mass lesions or cysts based on increased cellularity has to be distinguished from other etiologies. Epidermoid cysts are filled with keratin in concentric lamellae, water and cholesterol from cell membrane degradation, giving rise to their characteristic slow diffusivity [52]. Metastases or primary brain tumors may appear hypointense on ADC maps due to mucinous degeneration.

Treatment response

Quantitative analysis of functional diffusion maps based on DW-MRI obtained prior to and 3 weeks after initiation of therapy was shown to predict treatment response in a variety of brain tumors. The ‘partial response’ group in this study was mostly composed of cellular tumors (anaplastic oligodendroglioma, germinoma) lacking necrosis – that is, neoplasms with less heterogeneity than the most common primary brain

tumors [53,54]. For that reason, caution should be used when predicting tumor response based on functional diffusion maps as spontaneous ADC alterations occur, especially in the early stages of malignant gliomas. In Zacharia's series, the range of ADC values increased on post-treatment scans in seven patients [40]. In the study by Barajas *et al.* patients with relatively high pretreatment ADC values within enhancing tumor (ADC at 25th percentile $>0.692 \times 10^{-3} \text{ mm}^2/\text{s}$) tended to exhibit a net decrease in ADC values on post-therapeutic MRI, while the low ADC group (ADC at 25th percentile $\leq 0.692 \times 10^{-3} \text{ mm}^2/\text{s}$) exhibited a net increase. Pretherapeutic ADC values were found to be predictive of treatment outcome. Low ADC values were associated with decreased progression-free and overall survival [42]. Post-therapeutic alterations in ADC values reflect reduction in cell density due to cell killing and tissue reorganization (increased diffusivity), as well as cell swelling, reduction of vasogenic edema and reduction in extracellular space (decreased diffusivity).

A wide spectrum of alterations in DW-MRI is encountered in recipients of bevacizumab for malignant glioma. Evolution of new cellular tumor nodules is detected as an area of reduced diffusivity preceding contrast enhancement on T1-weighted sequences with gadolinium due to the agent's effect on the blood–brain barrier (Figure 3A) [BECKER KP, MAYER T, LACY J, BAEHRING JM, UNPUBLISHED DATA] [55]. Not uncommonly, diffusion abnormalities reflect dystrophic calcification or coagulative necrosis (Figure 3B & C) [BECKER KP, MAYER T, LACY J, BAEHRING JM, UNPUBLISHED DATA]. Intratumoral hemorrhage may obscure interpretation of DW-MRI data in bevacizumab recipients. ADC histogram analysis has been shown to predict response to bevacizumab, although the minimal survival difference between 'responders' and 'nonresponders' puts in question its practical usefulness [56]. Interpretation of DW-MRI findings remains hampered by lack of correlation with histopathologic findings. Gerstner *et al.* reported a case in whom biopsy of a nonenhancing area displaying restricted diffusion revealed cellular tumor [57].

■ Toxic leukoencephalopathies

Structural alterations resulting in restricted water diffusion within cerebral white matter infrequently complicate chemotherapy with cytotoxic agents. Clinical syndromes associated with these leukoencephalopathies are variable

and can be acute or delayed acute. Reversibility is dependent upon the type of drug, its dose and mode of administration, timely recognition of the syndrome and appropriate treatment (usually, discontinuation of exposure). A delayed acute leukoencephalopathy (DLEPS) resembles cerebrovascular accident, in that it is frequently characterized by the acute onset of focal signs and symptoms starting within days to a couple of weeks after chemotherapy. Complete neurological recovery is the rule, although chronic radiographic sequelae occur. The pathophysiology of the syndrome and its time course in chemotherapy recipients has not been elucidated. In the absence of histopathological data, current knowledge is based upon neuroimaging techniques and spinal fluid analysis [58–64]. DWI and ADC maps reveal reduced water diffusion

Figure 3. Diffusion-weighted MRI abnormalities in bevacizumab recipients.

(A) Increased cellularity: in spite of bevacizumab therapy, areas of increased cellularity are noted within the faintly rim-enhancing glioblastoma lesion in the left frontal lobe. Apparent diffusion coefficient map demonstrates decreased water diffusion. Magnetic resonance spectroscopy reveals an increased choline to creatine ratio and a decreased *N*-acetylaspartate peak (for voxel selection, see thumbnail image inserts and arrowhead). (B) Coagulative necrosis: the center of the right frontal lesion likewise shows restricted water diffusion. However, magnetic resonance spectroscopy mainly shows a large lipid/lactate peak. Findings are consistent with coagulative necrosis. Imaging findings in (A) and (B) were confirmed by biopsy (for voxel selection, see thumbnail image inserts and arrowhead). (C & D) Intratumoral calcification. Glioblastoma multiforme after completion of bevacizumab salvage therapy. (C) Heavy calcification is seen at the tumor site giving rise to hyperdense signal on computed tomography (arrowhead) and (D) low signal on the apparent diffusion coefficient map (arrowhead).

Figure 4. Cerebral ischemia in neuro-oncology patients. (A–D) Small left basal ganglionic acute infarct in a woman with critical left-middle cerebral artery stenosis, likely as a result of extensive radiation necrosis. (A) Diffusion-weighted imaging (DWI), (B) apparent diffusion coefficient (ADC), (C) heterogeneous enhancement indicative of radiation necrosis in the left temporal lobe (T1 with gadolinium) and (D) magnetic resonance angiogram. The patient had received involved field radiotherapy for a left temporal glioblastoma at initial diagnosis and stereotactic radiosurgery for suspected relapse. (E & F) Right posterior cerebral artery infarct after resection of a large glioblastoma multiforme of the right temporal lobe. The artery was not visualized at surgery but likely injured by tumor adherence or infiltration in the ambient cistern and surgical trauma. (E) Preoperative computed tomography head demonstrating tumor herniation over the tentorium giving rise to obliteration of the ambient cistern (arrowhead). (F) Postoperative ADC map (area of ischemia indicated by arrowheads). (G & H) Multiple large vessel occlusions in a patient with acute lymphoblastic leukemia after treatment with pegylated L-asparaginase. The entire left hemisphere displays restricted water diffusion. (I) Intravascular non-Hodgkin lymphoma. DWI obtained at two different time points (upper and lower rows of images) and ADC (not shown) demonstrate dissemination in space and time of ischemic lesions (hyperintense lesions on DWI).

rates involving the white matter of the cerebral hemispheres spanning vascular territories (Figure 1B). Gray matter is rarely affected. While initially presenting as a hemisindrome, MRI abnormalities are commonly bilateral [65].

DLEPS is estimated to occur in less than 2% of recipients of methotrexate [66]. It has been associated with intrathecal as well as intermediate-to-high dose intravenous administration. Almost all patients with DLEPS after methotrexate are children or adolescents with acute leukemia or lymphoblastic lymphoma. Median age is 14 years (range 6–20 years). Female to male ratio is 1:1. DLEPS occurs between 6 h and 11 days after chemotherapy administration. DLEPS has to be distinguished from hyperacute and chronic methotrexate-related neurotoxicity. Diffusion MRI abnormalities similar to DLEPS have not been described in these situations. Most patients recover spontaneously within 36 h to 1 week [65,67].

DLEPS also occurs during infusion of 5-fluorouracil (5-FU) and its derivative carmofur. Recovery occurs within days of cessation of 5-FU therapy [65]. Carmofur toxicity stands out as it is the only one in which DWI abnormalities may persist for at least 3 months [68].

DLEPS complicates capecitabine chemotherapy between 3 and 7 days after treatment initiation (age range 40–74 years). All thus far reported patients were female, suffered from breast or pancreatic cancer, and recovered within days of discontinuation of capecitabine [65,69].

Other causes of leukoencephalopathies with intramyelinic sheath edema

DLEPS involving the periventricular white matter is not limited to recipients of chemotherapy. A variety of metabolic derangements and drug exposures have been described to result in a similar clinical syndrome and radiographic findings (hypoglycemia, hypoxemia, antiepileptic drug therapy). Based on its appearance on DW-MRI, DLEPS can be distinguished from other acute neurological complications of cancer and chemotherapy. Reversible posterior leukoencephalopathy syndrome is characterized by increased water diffusion (hyperintense appearance on ADC maps).

Histopathological correlates of MRI findings

Case reports of DLEPS correlating DWI/ADC data with autopsy findings are unavailable and, thus, the morphological basis of the

syndrome is currently unknown. Data from animal experiments suggest that vacuolation and intramyelinic sheath edema give rise to a relative decrease in water diffusion. Prolonged daily oral or intraventricular administration of 5-FU, 5-FU metabolites, tegafur and carmofur results in vacuolation secondary to splitting of the myelin intraperiod line or separation between the axon and the innermost layer of myelin [70–72]. Tissue culture experiments have demonstrated segmental splitting of the myelinic intraperiod line with subsequent vacuolation and myelin swelling at the early stage of α -fluoro- β -alanine/fluoroacetic acid toxicity; later stages were characterized by fragmentation, granularity and myelin loss [73].

■ Polioencephalopathy in status epilepticus

Regional DW-MRI abnormalities are encountered after seizures. In a prospective series of 54 patients with status epilepticus, cortical restricted water diffusion was seen in more than half of patients with complex-partial and generalized status epilepticus [74]. In neuro-oncology patients this phenomenon is most commonly found in patients with structural brain lesions and is an important differential diagnostic consideration (Figure 1C). Depending on seizure duration these findings may be entirely reversible or result in cortical injury (laminar necrosis).

■ Cerebral ischemia

Cancer patients suffer ischemic strokes as a result of atherosclerosis giving rise to thrombosis or vessel-to-vessel embolization, or cardiac emboli (infectious endocarditis, nonbacterial thrombotic endocarditis). Cancer patients are considered hypercoagulable, although serologic markers for this condition are scarce except for disseminated intravascular coagulopathy [75]. An iatrogenic hypercoagulable state leading to venous and arterial thromboses is seen in recipients of L-asparaginase (Figure 4C). Cerebral leukostasis can result in ischemic strokes in patients with leukemic blast crisis. Meningeal dissemination of neoplastic cells or opportunistic pathogens may result in strokes in the territory of small penetrating arteries.

Vascular occlusion by tumor cell aggregates is a rare cause of stroke in patients with intravascular non-Hodgkin lymphoma. Usually days to weeks into the clinical syndrome, DWI-hyperintense lesions of variable size appear scattered throughout the brain, affecting both gray and white matter, suggestive of ischemia (Figure 4D). These

lesions either vanish or follow the typical pattern of an ischemic stroke with evolution of abnormal FLAIR signal followed by enhancement with gadolinium in the subacute, and tissue loss as well as laminar necrosis in the chronic stage [76].

Ischemic strokes also occur in the perioperative period or when aggressive primary neoplasms, for example glioblastoma multiforme located in the insula or the opercula, infiltrate large vessels at the base of the brain (Figure 4B).

Radiation exposure in patients with head, neck and brain cancer is complicated by stenoses or occlusions of carotid and vertebral arteries, as well as branches of the circle of Willis leading to large territory infarctions (Figure 4A) [77].

Figure 5. Diffusion-weighted MRI in CNS infections. (A–C) Diffusion-weighted imaging and (D–F) apparent diffusion coefficient map. (A & D) Right subinsular streptococcus milleri abscess with extension into the Sylvian fissure in a 72-year-old man in stable remission after completion of rituximab therapy for a low-grade non-Hodgkin lymphoma (arrowhead). (B & E) Progressive multifocal leukoencephalopathy in a 68-year-old woman with chronic lymphatic leukemia and treatment-induced pancytopenia (rituximab, fludarabine). Diffusion-weighted MRI reveals restricted water diffusion at the margin of a large white matter lesion (arrowheads) involving the centrum semiovale of both hemispheres as well as the splenium of the corpus callosum. The core of the lesion is characterized by increased diffusivity indicative of necrosis. (C & F) Herpes simplex encephalitis in a patient shortly after completion of external beam radiotherapy administered to the whole brain for cerebral metastases from non-small-cell lung cancer. Diffusion-weighted MRI demonstrates cortical cytotoxic edema within the right temporal lobe (arrowheads).

Figure 6. Fiber tractography based on diffusion tensor imaging in a patient with an infiltrative glioma of the right temporal lobe. The relationship of (1) cortical hand area, (2) corticospinal tract, (3) arcuate fasciculus and (4) tumor is depicted. Images courtesy of Joseph Piepmeyer.

■ Cerebral abscess & other infectious disorders

DW-MRI can differentiate brain abscesses from other intracranial cystic lesions such as tumor-associated cysts with high sensitivity and specificity (96%) (Figure 5A & D) [78]. False-positive DW-MRI results (i.e., restricted diffusion in cystic lesions other than abscesses) are occasionally encountered in metastases (e.g., from mucinous adenocarcinomas), the few glioblastomas with mucinous degeneration and those treated with antiangiogenic compounds [79]. False-negative results are seen in partially treated abscesses and in immunocompromised hosts [80,81].

In progressive multifocal leukoencephalopathy, DW-MRI characteristics depend on disease stage. New lesions and the advancing edges of large lesions display normal to low ADC values, whereas diffusivity is increased in older lesions and the center of large lesions. This observation may be explained by cell swelling in the area of active infection (Figure 5B & E) [82].

Herpes simplex encephalitis affects the gray matter of the mesial temporal, inferomedial frontal lobes, and insular cortex. The cortical ribbon in these areas displays restricted water diffusion in the early stage of infection (Figure 5C & F). This pattern may disappear when cell destruction ensues.

■ Clinical applications of DTI & fiber tractography

DTI and fiber tractography have proven useful for the preoperative depiction of white matter tracts (pyramidal tract, language and visual pathways) and their relationship to structural

lesions such as brain tumors (Figure 6) [83]. While this technique is commonly used for preoperative planning, it has not replaced traditional methods of white matter tract localization (intraoperative stimulation, electrophysiologic monitoring), and its impact on outcome has yet to be measured.

Conclusion

DW-MRI is an extremely useful adjunct to clinical assessment and a comprehensive neuroimaging protocol in patients with cerebral neoplasms or neurologic complications of cancer. Few conditions exist in which DW-MRI appearance is pathognomonic (DLEPS, cerebral abscess, epidermoid cyst). For other indications (assessment of cellularity), DW-MRI as an isolated test does not provide sufficient sensitivity or specificity, but when integrated with other MR sequences, imaging modalities and clinical data, facilitates noninvasive diagnosis and management of neuro-oncologic problems.

Future perspective

DW-MRI has become an integral part of non-invasive diagnosis of various neurologic disorders including acute cerebral ischemia, neoplasms, abscesses, cysts and various forms of white matter disorders. The complexities of abnormal water diffusion are not completely understood and validation through correlation of imaging findings with stereotactic biopsies has not been accomplished for all observed scenarios. Further refinement of the technique and methods for quantitative assessment of regions or volumes of interest may establish DW-MRI as a valuable prognostic marker for response of brain tumors to adjuvant therapies and lead to its incorporation into formal treatment response criteria in neuro-oncology. Routine use of DT-MRI may result in improved outcomes from neurosurgical procedures.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

- of interest
 - of considerable interest
- 1 Einstein A. *Investigations on the Theory of the Brownian Movement*. Courier Dover Publications, New York, NY, USA (1956).
 - 2 Kingsley PB. Introduction to diffusion tensor imaging mathematics: part I. Tensors, rotations and eigenvectors. *Concept. Magn. Reson. A* 28A(2), 101–122 (2006).
 - 3 Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. *Radiology* 161(2), 401–407 (1986).
 - 4 Stejskal EO, Tanner JE. Spin diffusion measurements: spin-echo in the presence of a time dependent field gradient. *J. Chem. Phys.* 42, 288–292 (1965).
 - 5 Jones DK. Challenges and limitations of quantifying brain connectivity *in vivo* with diffusion MRI. *Imaging Med.* 2(3), 341–355 (2010).
 - 6 Moseley ME, Cohen Y, Kucharczyk J *et al.* Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. *Radiology* 176(2), 439–445 (1990).
 - 7 Basser PJ, Mattiello J, LeBihan D. Estimation of the effective self-diffusion tensor from the NMR spin echo. *J. Magn. Reson. B* 103(3), 247–254 (1994).
 - 8 Basser PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. *Biophys. J.* 66(1), 259–267 (1994).
 - 9 Mukherjee P, Berman JI, Chung SW, Hess CP, Henry RG. Diffusion tensor MR imaging and fiber tractography: theoretic underpinnings. *AJNR* 29(4), 632–641 (2008).
 - 10 Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *J. Magn. Reson. B* 111(3), 209–219 (1996).
 - 11 Conturo TE, Lori NF, Cull TS *et al.* Tracking neuronal fiber pathways in the living human brain. *Proc. Natl Acad. Sci. USA* 96(18), 10422–10427 (1999).
 - **Original description of fiber bundle tracking in human subjects with optimized diffusion tensor-encoded MRI.**
 - 12 Mori S, Crain BJ, Chacko VP, van Zijl PC. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Ann. Neurol.* 45(2), 265–269 (1999).
 - 13 Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. *In vivo* fiber tractography using DT-MRI data. *Magn. Reson. Med.* 44(4), 625–632 (2000).
 - 14 Jones DK, Cercignani M. Twenty-five pitfalls in the analysis of diffusion MRI data. *NMR Biomed.* 23(7), 803–820 (2010).
 - 15 Tuch DS. Q-ball imaging. *Magn. Reson. Med.* 52(6), 1358–1372 (2004).
 - 16 Wedeen VJ, Hagmann P, Tseng WY, Reese TG, Weisskoff RM. Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging. *Magn. Reson. Med.* 54(6), 1377–1386 (2005).
 - 17 Alexander DC. Multiple-fiber reconstruction algorithms for diffusion MRI. *Ann. NY Acad. Sci.* 1064, 113–133 (2005).
 - 18 Tournier JD, Calamante F, Gadian DG, Connelly A. Direct estimation of the fiber orientation density function from diffusion-weighted MRI data using spherical deconvolution. *Neuroimage* 23(3), 1176–1185 (2004).
 - 19 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* 9(1), 53–60 (1999).
 - 20 Gupta RK, Cloughesy TF, Sinha U *et al.* Relationships between choline magnetic resonance spectroscopy, apparent diffusion coefficient and quantitative histopathology in human glioma. *J. Neurooncol.* 50(3), 215–226 (2000).
 - 21 Guo AC, Cummings TJ, Dash RC, Provenzale JM. Lymphomas and high-grade astrocytomas: comparison of water diffusibility and histologic characteristics. *Radiology* 224(1), 177–183 (2002).
 - 22 Kono K, Inoue Y, Nakayama K *et al.* The role of diffusion-weighted imaging in patients with brain tumors. *AJNR* 22(6), 1081–1088 (2001).
 - **Examines apparent diffusion coefficient values in patients with gliomas, brain metastases and meningiomas. Concluding that apparent diffusion coefficient may predict the degree of malignancy of astrocytic tumors, although considerable overlap between tumor categories was noted.**
 - 23 Wilke M, Eidschink A, Muller-Wehrich S, Auer DP. MR diffusion imaging and 1H spectroscopy in a child with medulloblastoma. A case report. *Acta Radiol.* 42(1), 39–42 (2001).
 - 24 Pauleit D, Langen KJ, Floeth F *et al.* Can the apparent diffusion coefficient be used as a noninvasive parameter to distinguish tumor tissue from peritumoral tissue in cerebral gliomas? *J. Magn. Reson. Imaging* 20(5), 758–764 (2004).
 - 25 Castillo M, Smith JK, Kwok L, Wilber K. Apparent diffusion coefficients in the evaluation of high-grade cerebral gliomas. *AJNR* 22(1), 60–64 (2001).
 - 26 Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G. Diffusion tensor MR imaging of the human brain. *Radiology* 201(3), 637–648 (1996).
 - 27 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* 9(1), 53–60 (1999).
 - 28 Cha S. Update on brain tumor imaging: from anatomy to physiology. *AJNR* 27(3), 475–487 (2006).
 - 29 Baehring JM, Bi WL, Bannykh S, Piepmeyer JM, Fulbright RK. Diffusion MRI in the early diagnosis of malignant glioma. *J. Neurooncol.* 82(2), 221–225 (2007).
 - 30 Mittal S, Farmer P, Kalina P, Kingsley PB, Halperin J. Correlation of diffusion-weighted magnetic resonance imaging with neuropathology in Creutzfeldt–Jakob disease. *Arch Neurol.* 59(1), 128–134 (2002).
 - 31 Hammoud MA, Sawaya R, Shi W, Thall PF, Leeds NE. Prognostic significance of preoperative MRI scans in glioblastoma multiforme. *J. Neurooncol.* 27(1), 65–73 (1996).
 - 32 Ginsberg LE, Fuller GN, Hashmi M, Leeds NE, Schomer DF. The significance of lack of MR contrast enhancement of supratentorial brain tumors in adults: histopathological evaluation of a series. *Surg. Neurol.* 49(4), 436–440 (1998).
 - 33 Tien RD, Felsberg GJ, Friedman H, Brown M, MacFall J. MR imaging of high-grade cerebral gliomas: value of diffusion-weighted echoplanar pulse sequences. *AJR* 162(3), 671–677 (1994).
 - 34 Bulakbasi N, Kocaoglu M, Ors F, Tayfun C, Ucoz T. Combination of single-voxel proton MR spectroscopy and apparent diffusion coefficient calculation in the evaluation of common brain tumors. *AJNR* 24(2), 225–233 (2003).
 - 35 Lam WW, Poon WS, Metreweli C. Diffusion MR imaging in glioma: does it have any role in the pre-operation determination of grading of glioma? *Clin. Radiol.* 57(3), 219–225 (2002).

- 36 Brunberg JA, Chenevert TL, McKeever PE *et al.* *In vivo* MR determination of water diffusion coefficients and diffusion anisotropy: correlation with structural alteration in gliomas of the cerebral hemispheres. *AJNR* 16(2), 361–371 (1995).
- 37 Chang YW, Yoon HK, Shin HJ, Roh HG, Cho JM. MR imaging of glioblastoma in children: usefulness of diffusion/perfusion-weighted MRI and MR spectroscopy. *Pediatr. Radiol.* 33(12), 836–842 (2003).
- 38 Rock JP, Scarpace L, Hearshen DM *et al.* Associations among magnetic resonance spectroscopy, apparent diffusion coefficients, and image-guided histopathology with special attention to radiation necrosis. *Neurosurgery* 54(5), 1111–1117 (2004).
- 39 Batra A, Tripathi RP. Atypical diffusion-weighted magnetic resonance findings in glioblastoma multiforme. *Australas. Radiol.* 48(3), 388–391 (2004).
- 40 Zacharia TT, Law M, Naidich TP, Leeds NE. Central nervous system lymphoma characterization by diffusion-weighted imaging and MR spectroscopy. *J. Neuroimaging* 18(4), 411–417 (2008).
- 41 Akter M, Hirai T, Makino K *et al.* Diffusion-weighted imaging of primary brain lymphomas: effect of ADC value and signal intensity of T2-weighted imaging. *Comput. Med. Imaging Graph* 32(7), 539–543 (2008).
- 42 Barajas RF Jr, Rubenstein JL, Chang JS, Hwang J, Cha S. Diffusion-weighted MR imaging derived apparent diffusion coefficient is predictive of clinical outcome in primary central nervous system lymphoma. *AJNR* 31(1), 60–66 (2010).
- 43 Calli C, Kitis O, Yuntun N, Yurtseven T, Islekel S, Akalin T. Perfusion and diffusion MR imaging in enhancing malignant cerebral tumors. *Eur. J. Radiol.* 58(3), 394–403 (2006).
- 44 Quadery FA, Okamoto K. Diffusion-weighted MRI of haemangioblastomas and other cerebellar tumours. *Neuroradiology* 45(4), 212–219 (2003).
- 45 Stadnik TW, Chaskis C, Michotte A *et al.* Diffusion-weighted MR imaging of intracerebral masses: comparison with conventional MR imaging and histologic findings. *AJNR* 22(5), 969–976 (2001).
- 46 Yamasaki F, Kurisu K, Satoh K *et al.* Apparent diffusion coefficient of human brain tumors at MR imaging. *Radiology* 235(3), 985–991 (2005).
- 47 Ducreux D, Wu RH, Mikulis DJ, terBrugge K. Diffusion-weighted imaging and single-voxel MR spectroscopy in a case of malignant cerebral lymphoma. *Neuroradiology* 45(12), 865–868 (2003).
- 48 Kitis O, Altay H, Calli C, Yuntun N, Akalin T, Yurtseven T. Minimum apparent diffusion coefficients in the evaluation of brain tumors. *Eur. J. Radiol.* 55(3), 393–400 (2005).
- 49 Reiche W, Hagen T, Schuchardt V, Billmann P. Diffusion-weighted MR imaging improves diagnosis of CNS lymphomas. A report of four cases with common and uncommon imaging features. *Clin. Neurol. Neurosurg.* 109(1), 92–101 (2007).
- 50 Server A, Kulle B, Maehlen J *et al.* Quantitative apparent diffusion coefficients in the characterization of brain tumors and associated peritumoral edema. *Acta. Radiol.* 50(6), 682–689 (2009).
- 51 Toh CH, Castillo M, Wong AM *et al.* Primary cerebral lymphoma and glioblastoma multiforme: differences in diffusion characteristics evaluated with diffusion tensor imaging. *AJNR* 29(3), 471–475 (2008).
- 52 Nagasawa D, Yew A, Safae M *et al.* Clinical characteristics and diagnostic imaging of epidermoid tumors. *J. Clin. Neurosci.* 18(9), 1158–1162 (2011).
- 53 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. USA* 102(46), 16759–16764 (2005).
- **Functional diffusion maps were found to correlate with radiographic response, time-to-progression, and overall survival in patients with malignant glioma (see also [54]).**
- 54 Moffat BA, Chenevert TL, Lawrence TS *et al.* Functional diffusion map: a noninvasive MRI biomarker for early stratification of clinical brain tumor response. *Proc. Natl Acad. Sci. USA* 102(15), 5524–5529 (2005).
- **Describes a method measuring changes in water diffusivity within a tumor during the early stages of treatment. These ‘functional diffusion maps’ proved to be predictive of outcome.**
- 55 Gupta A, Young RJ, Karimi S *et al.* Isolated diffusion restriction precedes the development of enhancing tumor in a subset of patients with glioblastoma. *AJNR* 32(7), 1301–1306 (2011).
- 56 Pope WB, Lai A, Mehta R *et al.* Apparent diffusion coefficient histogram analysis stratifies progression-free survival in newly diagnosed bevacizumab-treated glioblastoma. *AJNR* 32(5), 882–889 (2011).
- 57 Gerstner ER, Frosch MP, Batchelor TT. Diffusion magnetic resonance imaging detects pathologically confirmed, nonenhancing tumor progression in a patient with recurrent glioblastoma receiving bevacizumab. *J. Clin. Oncol.* 28(6), e91–e93 (2010).
- 58 Paakko E, Vainionpaa L, Pyhtinen J, Lanning M. Minor changes on cranial MRI during treatment in children with acute lymphoblastic leukaemia. *Neuroradiology* 38(3), 264–268 (1996).
- 59 Paakko E, Harila-Saari A, Vanionpaa L, Himanen S, Pyhtinen J, Lanning M. White matter changes on MRI during treatment in children with acute lymphoblastic leukemia: correlation with neuropsychological findings. *Med. Pediatr. Oncol.* 35(5), 456–461 (2000).
- 60 Asato R, Akiyama Y, Ito M *et al.* Nuclear magnetic resonance abnormalities of the cerebral white matter in children with acute lymphoblastic leukemia and malignant lymphoma during and after central nervous system prophylactic treatment with intrathecal methotrexate. *Cancer* 70(7), 1997–2004 (1992).
- 61 Wilks MJ, Tie ML, Pozza CH. CT and MRI appearances of methotrexate leucoencephalopathy. *Australas. Radiol.* 46(1), 80–83 (2002).
- 62 Lovblad K, Kelkar P, Ozdoba C, Ramelli G, Remonda L, Schroth G. Pure methotrexate encephalopathy presenting with seizures: CT and MRI features. *Pediatr. Radiol.* 28(2), 86–91 (1998).
- 63 Genvresse I, Dietzmann A, Massenkeil G, Spath-Schwalbe E, Possinger K. Subacute encephalopathy after combination chemotherapy including moderate-dose methotrexate in a patient with gastric cancer. *Anticancer Drugs* 10(3), 293–294 (1999).
- 64 Oka M, Terae S, Kobayashi R *et al.* MRI in methotrexate-related leucoencephalopathy: disseminated necrotising leucoencephalopathy in comparison with mild leucoencephalopathy. *Neuroradiology* 45(7), 493–497 (2003).
- 65 Baehring JM, Fulbright RK. Delayed leucoencephalopathy with stroke-like presentation in chemotherapy recipients. *J. Neurol. Neurosurg. Psychiatry* 79(5), 535–539 (2008).
- **Describes a peculiar type of white matter damage in recipients of various chemotherapeutic agents.**

- 66 Mahoney DH Jr, Shuster JJ, Nitschke R *et al.* Acute neurotoxicity in children with B-precursor acute lymphoid leukemia: an association with intermediate-dose intravenous methotrexate and intrathecal triple therapy – a Pediatric Oncology Group study. *J. Clin. Oncol.* 16(5), 1712–1722 (1998).
- 67 Haykin ME, Gorman M, van Hoff J, Fulbright RK, Baehring JM. Diffusion-weighted MRI correlates of subacute methotrexate-related neurotoxicity. *J. Neurooncol.* 76(2), 153–157 (2006).
- 68 Fujikawa A, Tsuchiya K, Katase S, Kurosaki Y, Hachiya J. Diffusion-weighted MR imaging of carmofer-induced leukoencephalopathy. *Eur. Radiol.* 11(12), 2602–2606 (2001).
- 69 Videnovic A, Semenov I, Chua-Adajar R *et al.* Capecitabine-induced multifocal leukoencephalopathy: a report of five cases. *Neurology* 65(11), 1792–1794 (2005).
- 70 Okeda R, Karakama T, Kimura S, Toizumi S, Mitsushima T, Yokoyama Y. Neuropathologic study on chronic neurotoxicity of 5-fluorouracil and its masked compounds in dogs. *Acta Neuropathol.* 63(4), 334–343 (1984).
- 71 Okeda R, Shibutani M, Matsuo T, Kuroiwa T. Subacute neurotoxicity of 5-fluorouracil and its derivative, carmofer, in cats. *Acta Pathol. Jpn* 38(10), 1255–1266 (1988).
- 72 Okeda R, Shibutani M, Matsuo T, Kuroiwa T, Shimokawa R, Tajima T. Experimental neurotoxicity of 5-fluorouracil and its derivatives is due to poisoning by the monofluorinated organic metabolites, monofluoroacetic acid and alpha-fluoro-beta-alanine. *Acta Neuropathol.* 81(1), 66–73 (1990).
- 73 Akiba T, Okeda R, Tajima T. Metabolites of 5-fluorouracil, alpha-fluoro-beta-alanine and fluoroacetic acid, directly injure myelinated fibers in tissue culture. *Acta Neuropathol.* 92(1), 8–13 (1996).
- 74 Chatzikonstantinou A, Gass A, Forster A, Hennerici MG, Szabo K. Features of acute DWI abnormalities related to status epilepticus. *Epilepsy Res.* 97(1–2), 45–51 (2011).
- 75 Cestari DM, Weine DM, Panageas KS, Segal AZ, DeAngelis LM. Stroke in patients with cancer: incidence and etiology. *Neurology* 62(11), 2025–2030 (2004).
- Provides data on the incidence and type of strokes in patients with cancer at a major referral center.
- 76 Baehring JM, Henchcliffe C, Ledezma CJ, Fulbright R, Hochberg FH. Intravascular lymphoma: magnetic resonance imaging correlates of disease dynamics within the central nervous system. *J. Neurol. Neurosurg. Psychiatry* 76(4), 540–544 (2005).
- 77 Plummer C, Henderson RD, O’Sullivan JD, Read SJ. Ischemic stroke and transient ischemic attack after head and neck radiotherapy: a review. *Stroke* 42(9), 2410–2418 (2011).
- 78 Reddy JS, Mishra AM, Behari SM *et al.* The role of diffusion-weighted imaging in the differential diagnosis of intracranial cystic mass lesions: a report of 147 lesions. *Surg. Neurol.* 66(3), 246–250 (2006).
- 79 Hartmann M, Jansen O, Heiland S, Sommer C, Munkel K, Sartor K. Restricted diffusion within ring enhancement is not pathognomonic for brain abscess. *AJNR* 22(9), 1738–1742 (2001).
- In patients with ring-enhancing cerebral mass lesions, restricted diffusion might be characteristic, but not pathognomonic for abscess.
- 80 Cartes-Zumelzu FW, Stavrou I, Castillo M, Eisenhuber E, Knosp E, Thurnher MM. Diffusion-weighted imaging in the assessment of brain abscesses therapy. *AJNR* 25(8), 1310–1317 (2004).
- 81 Camacho DL, Smith JK, Castillo M. Differentiation of toxoplasmosis and lymphoma in AIDS patients by using apparent diffusion coefficients. *AJNR* 24(4), 633–637 (2003).
- 82 Bergui M, Bradac GB, Oguz KK *et al.* Progressive multifocal leukoencephalopathy: diffusion-weighted imaging and pathological correlations. *Neuroradiology* 46(1), 22–25 (2004).
- 83 Inoue T, Shimizu H, Yoshimoto T. Imaging the pyramidal tract in patients with brain tumors. *Clin. Neurol. Neurosurg.* 101(1), 4–10 (1999).
- Website
- 101 Brannon RM. Functional and Structured Tensor Analysis for Engineers (2003). www.mech.utah.edu/~brannon/public/Tensors.pdf