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Apparent diffusion coefficient from magnetic resonance imaging as a biomarker in oncology drug development

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Abstract Magnetic resonance imaging (MRI) can be made sensitive to diffusion of water molecules in biological tissues: this phenomenon can be quantitated to provide a biomarker, the apparent diffusion coefficient (ADC). Over the past decade, evidence has accumulated from numerous clinical and animal studies that ADC is abnormal in tumours; that elevated ADC reflects an elevated non-cellular fraction; and that acute increases in ADC following therapy can indicate that tumour cells have been killed. However there remain substantial challenges in ensuring robust and valid ADC measurements, particularly in multicentre studies in common sites of metastasis such as lung and liver. Moreover, there is uncertainty about how best to select the timing of observation post-therapy to avoid false-negatives, and how to minimise the confounding factors which could decouple drug-induced ADC increase from drug-induced cell kill. In this review we summarise the physical basis of the biomarker, the evidence that it reflects non-viable fraction, particularly in extracranial tumours, and suggest a roadmap for validation and qualification.
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1. Introduction

The quest for non-invasive imaging biomarkers for better detection and characterisation of tumours or earlier prediction of treatment response has led to the introduction of molecular and physiological imaging biomarkers to complement anatomical imaging. Magnetic resonance imaging (MRI) is able to provide image contrast sensitive to micro structural and cellular remodelling: in particular, diffusion weighted MRI (DWI) has gained interest amongst oncologists and drug developers because of its correlation with cellular density.[1] Moreover it is easily integrated into clinical care because it does not employ ionising radiation, thus

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allowing unlimited follow-up, nor does it require the use of any tracers or contrast media, avoiding the costs, risks, supply, and regulatory barriers associated with such agents. However for oncologists and drug developers, used to thinking about biomarkers as manifestations of the molecular biology of cancer, DWI with its basis in the biophysics of tumour water may initially appear non-specific and arcane. This article reviews the physical basis of DWI, its utility in providing diagnostic information and as a pharmacodynamic biomarker for drug development, the challenges in ensuring robust and valid measurements, and the evidence for using the apparent diffusion coefficient as biomarker of treatment response in preclinical and clinical studies. Finally we suggest a roadmap for validation and qualification.

2. Physical basis of DWI

Pathological processes typically lead to tissue alterations for instance changes in cell volume, membrane integrity, or modulations of the extracellular matrix. Thermally diffusing water molecules (Brownian motion), present everywhere in biological tissues, are the ideal vehicles to probe architectural changes since the effective diffusion length depends on the spatial details of the structures restricting their motion. Pure water at body temperature is known to have a self-diffusion coefficient of $D \sim 3 \times 10^{-3}$ mm^2/s and, at typical evolution time of ~50 ms the root-mean-square displacement will be approximately 30 μm. Given the dimension of cells (~1–15 μm) and the fact that the majority of water is intracellular, it is clear that water molecules will encounter many cellular and subcellular impediments over this 50 ms time interval. Thus, cell organisation, cell size and cell density influence diffusivity, characterised by the so-called apparent diffusion coefficient (ADC). Cell kill leads to a loss of cell membrane integrity, and reduction in tumour cell density, with increase in the interstitial space, and hence in the measured ADC in the tumour tissue. In principle ADC should respond to cell death whether induced through apoptosis, autophagy, ischaemia, by cytotoxic agents, radiotherapy or any other therapeutic approach. These changes are expected to be pharmacodynamic and detectible on DWI before objective response in tumour volume.

The reason for this unique capability of MRI to be sensitive to molecular processes, despite an image resolution of the order of sub-millimetre to millimetre, is rooted in the specific mechanism of MR-image formation. In proton MRI, the magnetic spin of each hydrogen atom of every water molecule within the region of interest contributes to the signal observed in the final image. Local signal strength depends on the presence or abundance of water molecules, but also on whether the direction of the individual spins (i.e. their phase) are aligned (leading to a strong signal) or randomly oriented (leading to a drop in signal). During MR data acquisition, the phase of individual spins can be altered according to the molecules' positions in space. This change in orientation of the spin (not to be confused with the spatial position of the corresponding water molecule) can be reversed after a certain waiting time. For stationary molecules, this procedure will lead to a zero change in phase and a strong signal will be recovered. Brownian motion, however, causes a characteristic mean displacement during this waiting period, leading to an imperfect reversal of the phase, and hence a loss of phase-coherence amongst spins. This process manifests itself as signal loss in the macroscopic image voxel, giving rise to an image whose contrast is determined by diffusive processes. However, although this method is sensitive to water diffusion at the μm-level, it is certainly not specific for it: microscopic motion of water molecules in biological tissue (so-called intravoxel incoherent motion (IVIM)) includes microcirculation of blood in the capillary bed (perfusion) as well as molecular diffusion. Due to the rather random orientation of the capillary network in each macroscopic image voxel, perfusion contributes to image contrast on DWI and contributes to the loss in signal on a DWI. Fortunately, the movement of water due to microcirculation has an ADC 10 times larger than true diffusion.[2] One way to separate microcapillary perfusion from the diffusion is to render the DWI sequence so sensitive to IVIM that signals originating from perfusion effects are entirely lost and consequently do not contribute to the observed relative signal loss. The DWI sequence parameter responsible for the variable sensitivity to IVIM (the so-called *b*-value) includes the strength of the created phase change and the waiting time. It has become common in the MR community to discuss solely the effect of different *b*-values on the sensitivity or specificity of DWI to pathological processes. However, different evolution times can change the correlation between ADC alterations and cellular processes.[3]

3. Standardisation and technical challenges in data acquisition

In clinical imaging, the sequence typically used is a classical spin-echo sequence with two mono-polar gradients next to the refocusing pulse. To allow for sufficient sensitivity to IVIM, a long echo-time of approximately 50–90 ms at 1.5 T is necessary due to limited gradient strength on clinical systems (~30–60 mT/m). Therefore, segmented or single-shot echo-planar-imaging readout techniques are used to accelerate data acquisition. Fat suppression methods are necessary to minimise geometrical distortions originating from the long read-out. Parallel imaging methods can further be used to reduce the read-out length and shorten acquisition time. This is

essential because DWI sequences are exquisitely sensitive to motion. For upper abdominal DWI, various acquisition methods to reduce or average out motion are used such as breath-hold, respiratory/cardiac–triggering free breathing. Interestingly, a recent study in volunteers has shown larger reproducibility of the ADC values for free-breathing methods than for breath-hold or respiratory triggered image acquisitions.[4,5] Another study demonstrated superior image sharpness of a TRacking Only Navigator echo (TRON) method over free breathing DWI.[6] Robust and reliable use of DWI in common sites of metastasis such as lung and liver which are subject to motion is essential if DWI is to reach its potential in drug development.

It is commonly accepted that ADCs calculated using b-values below $\sim$100 s/mm^2 include micro perfusion effects. The contribution to ADC from microperfusion depends on the volume fraction of flow and can lead to significant overestimations of the ADC values. Bi-exponential fitting methods may help to account for the perfusion and diffusion components.[7] To estimate the true diffusion component an optimal high b value needs to be selected which depends on the ADC of the tissue[8] and is given by $b_{opt} \times ADC \sim 1.1$. Values are usually between 500 and 800 s/mm^2 with values beyond 1000 s/mm^2 rarely of any utility due to low SNR at these values. However, although DWI has shown great promise for detection and characterisation of lesions as well as being a useful marker for early treatment response, there is need for standardisation in order to make results clinically robust and stable, reproducible and comparable.

Further methodological advances in DWI techniques are exploring time course of spin evolution during application of the diffusion gradients. A recent method called 'oscillating gradient' technique explored the dimension of evolution time down to a few milliseconds for a fixed b-value of $\sim$400 s/mm^2.[3] Short evolution times render the sequence sensitive to cellular and subcellular diffusion processes. This study demonstrated in a rat model of C6 gliosarcoma implanted in the brain that ADC values increased when lowering the allowed evolution time keeping the b-value fixed. Hence, the degree of restriction changes with scale, which is typical for a fractal structure. Interestingly, this method potentially may be sensitive to the ratio of nuclear volume to cell volume, whereas classical diffusion methods bound to long evolution times are insensitive to this parameter.[9] Because the size of the cell nucleus increases between benign and malignant lesions and with increasing tumour grade, this method potentially could aid tumour characterisation. These observations are in line with the fractal organisation of tissue[10] with measurements dependent on the time scale of the experiment. Unfortunately, the applicability of the oscillating gradient method is currently limited to small animal systems which provide the necessary gradient strength to render the DWI sequence sufficiently sensitive to IVIM given short evolution times of $\sim$3 ms. Novel approaches for DWI sequences are on the horizon based upon steady state free precession sequences.[11]

4. Characterisation of malignant versus non-malignant lesions: ADC as a diagnostic/prognostic biomarker

Typically, malignant lesions tend to have lower ADC values indicating a restriction of diffusivity. This has been mainly attributed to changes in tissue cellularity/cell density.[12–14] However, although neoplastic tissue is altered in terms of cellular organisation, a drop of the ADC also reflects the net effect of other alterations such as the ratio between free and bound water, the tortuosity of the extracellular space and extracellular matrix (ECM) changes. For example DWI is able to distinguish benign from malignant focal liver lesions,[15] because liver metastases and hepatocellular carcinomas (HCC) have low ADC values, whilst benign lesions (including cysts and hemangiomas) have high values. Although other studies have shown similar good separation between benign and malignant liver lesions, there is overlap in ADC values between metastases and benign hepatocellular lesions.[16] Within tumours ADC values have shown ability to separate histological subtypes for example in breast cancer and may be explained by structural differences within different histological types such as presence of glandular elements or focal necrosis.[17,18] In haemorrhagic tumours on the other hand ADC may be reduced due to the influence of blood products on DWI.[19] Certainly, necrosis and haemorrhage can both co-exist leading to a complex time evolution on DWI.[20,21] The presence of fat within tumours or adjacent stromas such as in bone marrow lesions and the choice of fat suppression method can also influence the ADC value; the effect is more pronounced at higher b values.[22]

In clinical diagnosis the use of DWI has been established for improved detection of malignant liver lesions[23] to aid tumour detection in prostate cancer[24] peritoneal metastases from ovarian cancer,[25] staging endometrial[26] and cervical[27] cancer and for assessing response to neoadjuvant therapy in breast[28] and rectal[29] cancer. DWI has also been applied to the assessment of diffuse diseases such as the determination of the degree of liver fibrosis with moderate success.[30,31] However, a study in rats demonstrated that decreased ADC correlated with increased liver fibrosis in living rats, but not after death.[32] This indicates that other factors such as decreased perfusion have to explain the decrease of the hepatic ADC. A recent development is in whole body imaging: the technique denoted as DWIBS (diffusion weighted whole body imaging with background body signal suppression) which uses very high b-values and hence suppresses most of the background signal[33] has been used as whole body examination for detecting

distant metastases and shows great promise although it remains to be validated.

5. DWI for monitoring early response to treatment: ADC as a response biomarker

Although the interpretation of ADC values in a diagnostic context as described above can be complex, the use of acute changes to provide a response biomarker is potentially more straightforward (Fig. 1). In conventional chemotherapy, a decrease in tumour size may serve as a biomarker of treatment response, and tends to predict an improvement in outcome. Unfortunately, this simple relationship does not necessarily hold for targeted anticancer agents. For example, metastases from gastrointestinal stromal tumours may become larger after targeted treatment because of cystic degeneration or haemorrhage.[34] Similarly, following treatment with antiangiogenic agents, tumour manifests as alterations of the vasculature and increase of the necrotic tumour fraction. In these cases conventional measurements of lesion size may be inadequate in assessing response.

Following treatment with cytotoxic as well as targeted agents there is an early alteration in tissue microstructure: cell swelling and cell death are accompanied by a loss of cell membrane integrity and changes to tumour cell density. An increase in the interstitial space leads to an increase in freedom of water molecules to move and an increase of the measured ADC in the tumour tissue. These changes are detectable with DWI before the onset of macroscopic effects such as changes in tumour volume. In a pre clinical model the influence of yCD/5FC gene therapy was studied in rat brains[35] orthotopically implanted with 9L glioma cells; ADC maps acquired over 10 days showed an increase in ADC values within the tumours by 31% after 8 days of treatment that preceded tumour growth arrest and regression. In another pre-clinical study DWI was able to discriminate between non-perfused but viable and necrotic tumour tissues in rats subcutaneously implanted with rhabdomyosarcomas in both flanks.[36] Hence, ADC has potential to become a pharmacodynamic biomarker for early detection of treatment response in tumours.[37,38]

In the clinic, an increase in ADC also is taken to indicate treatment response. This has been shown in brain tumours,[39] breast cancer,[40] liver tumours (primary and metastatic)[4] and peritoneal metastases from ovarian cancer.[25] A more complex response has been measured in a DWI study of advanced hepatocellular carcinoma

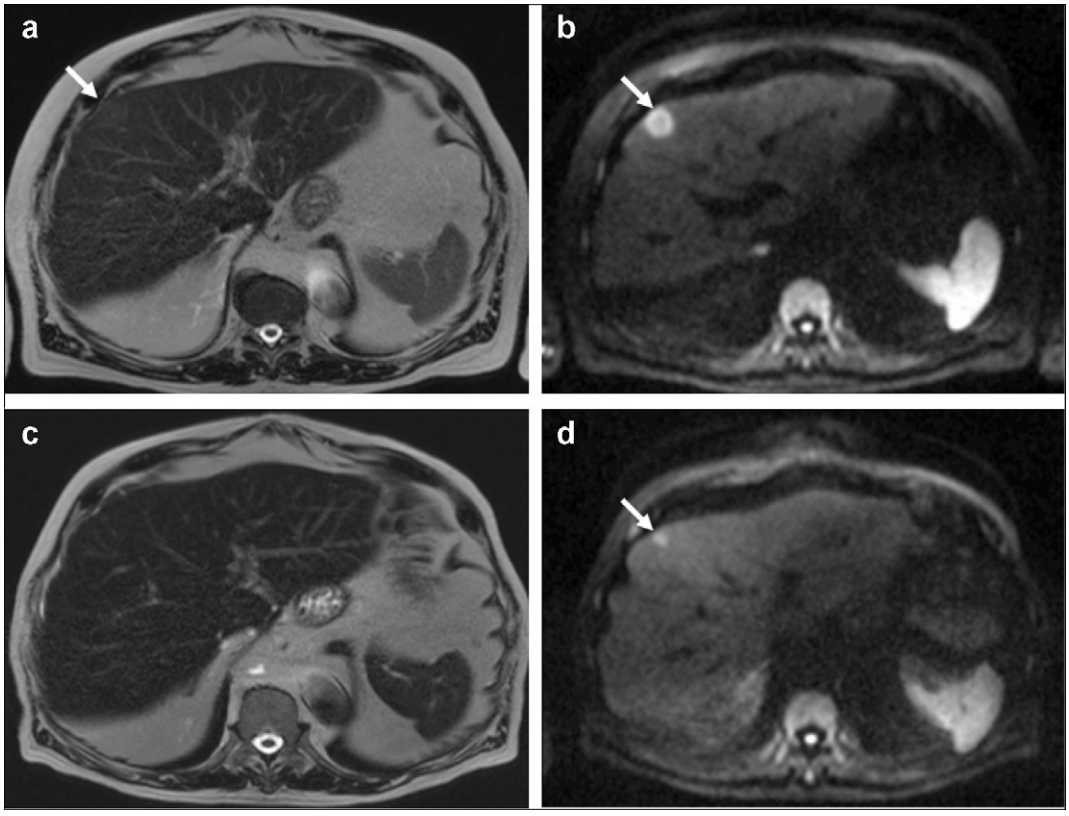

Fig. 1. T2W HASTE (TE 241ms) images with corresponding $b = 750$ images through the liver pre (a) and post (b) chemotherapy in a patient with a metastasis from colon cancer. The metastasis is barely visible on the pre-treatment T2-w images but easily seen on DWI (c). After treatment residual.

during sorafenib treatment[20]: in the early phase, a temporary decrease in ADC was most likely caused by heamorrhagic necrosis. Subsequently, the antiproliferative and antiangiogenic effects of sorafenib induced cell necrosis and destruction of cell membrane integrity which increased diffusivity. A drop of ADC indicated tumour progression in certain patients. It is interesting to note that a similar behaviour was found in an animal model using combretastatin A4 phosphate but on a time scale characteristic for rats, i.e. initial drop of the ADC due to pronounced cell swelling in the periphery of the lesion with subsequent increase due to necrosis.[36,41] These two examples for monitoring the effects of antivascular therapies underline the importance of timing to maximise the chance of detecting a significant drug effect and minimise the possibility of false-negative. It demonstrates clearly the strength of DWI being sensitive to the cellular alterations induced by cell kill and the subsequent induced increase in ADC, but also shows that wrong timing might easily lead to wrong conclusions regarding the efficacy of a certain drug. Other confounding effects might equally lead to an initial reduction of the ADC, for example cellular swelling or changes in the extracellular volume due to vascular renormalisation in case of anti-angiogenic therapies. The perfusion fraction f (present at low b-values) also potentially carries valuable diagnostic information. In a study of sorafenib treatment in advanced HCC f and not ADC or the diffusion fraction was a valuable marker.[7] Post-treatment inflammatory change may confound interpretation. In rats with intracerebral 9L gliosarcomas no significant changes were observed for ADC values due to treatment-associated inflammatory reaction,[42] despite significant changes on FDG-PET.

Tumour response is typically heterogeneous in human tumours unlike the largely homogenous response in subcutaneous or even orthotopic xenografts. To address this functional diffusion mapping (fDM) has been explored to reflect regional changes in ADC.[39,43] Consecutive ADC maps before, during and after therapy are co-registered and the tumour is segmented into areas of positive, negative and negligible ADC change. Using this technique in animal models with implanted brain tumours has demonstrated a clear correlation between ADC changes and regional differences in cell density.[44]

6. Roadmap for validation and qualification

When trying to establish ADC as biomarker in decision making for drug development, it is mandatory to correlate ADC changes to detailed histology in order to establish a profound understanding of the influence of the various pathophysiological processes on ADC. Hence, pre-clinical animal studies with well characterised models are required allowing for the temporal evolution of ADC response to be evaluated. Clinical studies with biopsies before and after treatment constitute a desirable, albeit often difficult, subsequent step. Optimal timing is of utmost importance and it is desirable to develop strategies to translate preclinical data into the clinic. Correlation of ADC with cell density, size, extracellular space and nuclear to cytoplasmic ratio done in xenografts cannot easily be translated to clinical studies because of the heterogeneity of human tumours. With PET-MRI on the horizon, correlation with FDG-PET, thymidine-PET or FLT-PET is becoming increasingly feasible and would allow for a non-invasive correlation between ADC and specific radiotracers at high temporal resolution during the same scan.

Conflict of interest statement

None declared.

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Appendix A.

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