Diffusion-Weighted MR Imaging in Oncology

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Published online: 22 March 2014
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Abstract In this article, we review recent updates in the deployment of diffusion weighted magnetic resonance imaging (DW-MRI) in oncology for disease detection and characterization. We appraise the use of DW-MRI for the evaluation of treatment response, including its emerging role as a predictive and/or prognostic biomarker. We discuss the use of more sophisticated data analysis to derive quantitative parameters, particular those that account for non-mono-exponential signal attenuation behavior of DW-MRI in tissues. Last but not least, we survey the unfulfilled challenges and potential future applications of DW-MRI. Knowledge of the fundamentals of DW-MRI is assumed and will not be discussed.

Keywords Diffusion weighted magnetic resonance imaging · DW-MRI · Diagnosis · Oncology

Introduction

Diffusion weighted magnetic resonance imaging (DW-MRI) is widely used in the body, particularly in the setting of oncologic patients, from the initial detection of malignancy through to the assessment of tumor response to treatment. There is now a better appreciation of its strengths and weaknesses. The benefits are clear; it is a non-ionizing modality, which obviates the need for

potentially nephrotoxic intravenous contrast agents, and can be acquired quickly in a clinical setting. Not surprisingly, the technique is now commonplace in the imaging of many tumors.

Technical Developments

The technical knowledge of body DW-MRI continues to grow, as major MR vendors implement techniques to improve image quality. The use of surface receiver coils is now standard in clinical practice on most MR systems, both at 1.5 and 3.0 T. At the time of writing, DW-MRI appears to be more robust at 1.5 T, especially over large field-of-view. However, high quality 3.0 T DW-MRI images using reduced field-of-view technique can now be routinely acquired on high performance MR systems. Whole body DW-MRI is a technique that is also increasingly utilized in oncology for disease detection, cancer staging and the assessment of treatment response [1–3]. Recent work to better understand the performance of different MR systems for measuring the apparent diffusion coefficient (ADC) has revealed inter-scanner differences [4], which can help vendors make improvements to ensure that high quality quantitative DW-MRI can be consistently attained.

Disease Detection

The use of DW-MRI for disease detection in the abdomen and pelvis is well established, especially for the evaluation of hepatic, peritoneal and prostatic diseases. Whilst diffusion-weighted imaging sequences are quick to perform, whole-body DW-MRI can still take 30–60 min. Nonetheless, DW-MRI provides excellent contrast between cellular disease

This article is part of the Topical Collection on *Essentials in Oncologic Imaging*.

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Fig. 1 Liver metastases. **a** FDG PET–CT demonstrates a metabolically active lesion in segment V (*black arrow*). **b–d** The MRI performed within 2 days of the PET–CT shows a further 6 mm lesion more medially on the T2 (**b**, *blue arrow*), but is best appreciated on the high b value image (**c**, *blue arrow*). The lesion is less well visualized on the ADC map (**d**). However, the ADC map should be used in conjunction with the high b value to avoid misinterpreting areas of T2 shine through, in this case from the gall-bladder (*arrow head*), as disease

and the signal suppressed background. Literature emerging in the last few years reaffirms previous findings, but also establishes the technique at other sites of malignancy. Evidence for the use DW-MRI for evaluating bone metastases and bone marrow diseases (e.g. multiple myeloma) is growing, especially in the setting of whole body DW-MRI.

Lung

MR imaging of the lung has remained challenging. However, the published literature suggests that there is value in using DW-MRI to assess lung cancer. A previous study showed DW-MRI could distinguish tumor from adjacent lung collapse [5]. A recent study by Yang et al. [6] reaffirmed this finding. On contrast enhanced computed tomography (CT), it can be difficult to differentiate central lung tumors from the surrounding lung atelectasis. Positron emission tomography (PET)–CT can be used to improve tumor localization and for targeting biopsy. However, PET–CT utilizes ionizing radiation and in their cohort of 38 patients, Yang et al. [6] demonstrated that DW-MRI signal intensity of tumors were always higher than the surrounding atelectasis. Using whole body DW-MRI, Sommer et al. [7] found the technique to have similar staging accuracy compared with fluorodeoxyglucose (FDG) PET–CT in patients with non-small cell lung cancer, in line with previous observations [8, 9].

Liver

DW-MRI aids focal lesion detection in the liver (Fig. 1). In the evaluation of colorectal liver metastases, even with the use

of liver selective contrast agent (Gd-EOB-DTPA), the highest diagnostic accuracy is achieved by a combined reading of the hepatocellular phase Gd-EOB-DTPA enhanced T1-weighted images together with DW-MRI images [10]. The combination of Gd-EOB-DTPA enhanced imaging and DW-MRI also show higher diagnostic sensitivity and accuracy for detecting metastases less than 1.5 cm in size [11].

Whilst the sensitivity of DW-MRI for lesion detection may be diminished in the presence of liver cirrhosis, DW-MRI is still helpful for the detection of hepatocellular carcinoma (HCC) [12–14]. Small (2 cm) [13, 14] and hypovascular [12] HCCs may be recognized by their high signal impeded diffusion on DW-MRI. Well-differentiated HCC has also been described as being hypointense on the hepatocellular phase Gd-EOB-DTPA enhanced imaging, and hyperintense on DW-MRI [15].

Urinary Bladder

In newly diagnosed carcinoma of the urinary bladder, DW-MRI has been shown to improve local T-staging, and the quantitative ADC value may also predict tumor grade [16]. A recent exploratory study evaluated the potential role of DW-MRI in the follow-up of superficial bladder tumours post-transurethral resection, and found that there was no significant difference in the sensitivity of detecting macroscopic recurrence using either DW-MRI or cystoscopy [17]. Clearly, when further validated, the technique could prove useful as a non-invasive tool for disease surveillance.

Once a bladder malignancy has been diagnosed, DW-MRI has been used to detect synchronous urothelial tumors

elsewhere along the urinary tract [18]. However, only about 50 % of areas of impeded diffusion along the urinary tract in one study were proven to be synchronous tumors, with a high false-positive rate [18]. Furthermore, flat tumors and carcinoma-in situ are readily missed on DW-MRI. Thus, the readers should be aware of the potential gains and limitations of the DW-MRI when applied to the urinary tract [19].

Bone

The diagnosis of metastatic bone disease has often been made using radionuclide bone scintigraphy. However, bone metastases confined to the marrow may result in false negative results. CT imaging also has lower sensitivity in detecting early metastases and marrow infiltration without significant disruption to the bony trabeculae. A number of studies have now shown the enhanced diagnostic sensitivity of DW-MRI, including whole body DW-MRI compared with skeletal scintigraphy, for the diagnosis of metastatic bone disease [20, 21]. A study by Nakanishi et al. [22] demonstrated that the sensitivity and positive predictive value for bone metastatic deposits are increased by using DW-MRI in addition to standard short-tau inversion recovery (STIR) and T1W body imaging. Pearce et al. [23] compared STIR with a DW-MRI sequence (*b* value of 900), and demonstrated that prostate and myeloma metastases were more conspicuous on DW-MRI than on STIR. Their results did not, however, prove to be statistically significant in breast cancer bone metastases. This suggests that in certain groups of patients, DW-MRI could replace the STIR sequence with more sensitive results.

Whole body (WB)-DW-MRI has the potential to replace bone scintigraphy and CT for the diagnosis of bone metastases in high-risk prostate cancer patients (Fig. 2) [24]. A meta-analysis showed similar diagnostic performance of WB-DW-MRI versus FDG PET-CT for the detection of primary and metastatic malignancies [1•]. In patients with multiple myeloma, areas of marrow infiltration show impeded diffusion, which can be detected with increased conspicuity [23, 25, 26]. Not surprisingly, DW-MRI has been shown to detect more skeletal lesions compared to conventional radiography surveys [27]. Based on the evolving research in this area, it is likely that DW-MRI will play an increasing role for the detection and evaluation of malignant bone disease.

Disease Characterization

DW-MRI has been applied to distinguish between benign and malignant lesions. However, the success of this has

been limited, since both benign and malignant solid lesions will show high signal intensity impeded diffusion on DW-MRI. Furthermore, although the ADC values of malignant lesions are often lower than benign lesions, there is substantial overlap. For example, in the liver, both visual assessment and ADC quantification were found to have limited accuracy in differentiating benign from malignant focal liver lesions [28]. Furthermore, using DW-MRI alone to characterize focal liver lesions can erroneously classify benign lesions as malignant in up to 49 % of cases [29]. For this reason, lesion characterization should be made after reviewing other imaging sequences, to improve the diagnostic confidence and lesion analysis [30].

However, once the diagnosis of malignant disease has been made, the quantitative ADC values of several tumor types appear to reflect tumor aggressiveness, biological behavior or histological features. A few tumor examples are discussed below.

Liver

Radiological and histological correlation of HCC was recently investigated in a study by Nakanishi et al. [31], who evaluated the mean and minimum ADC of tumors within 30 days of resection and quantitatively demonstrated that lower ADC values were histologically associated with poorly differentiated HCC.

Urinary Tract

A study by Wang et al. [32] conducted at 3.0 T demonstrated that clear cell renal cell carcinoma (RCC) could be differentiated from non-clear cell tumors as the ADC values of clear cell tumors were significantly higher than those of non-clear cell (chromophobe and papillary) histologies. Papillary tumors returned the lowest ADC values.

In urothelial tumors, ADC values were found to be significantly lower in higher grade (grade 3) upper tract urothelial carcinomas than in lower grade (grade 1–2) tumors [33]. Furthermore, ADC was demonstrated to correlate inversely with Ki-67 LI expression, a tumor proliferative index [34]. In the same study, the cancer-specific survival was lower in the high Ki-67 LI group, suggesting that ADC could be a quantitative marker of tumor aggressiveness. In this regard, quantitative ADC may therefore have a future role in stratifying patients into high and low risk of cancer-specific related deaths.

The correlation of tumor grade with ADC value was also observed in prostate cancer, where the ADC value has been found to have an inverse relationship with the Gleason score [35, 36•, 37, 38]. As such, the ADC value is likely to help the identification of the index lesion within the

Fig. 2 Disease detection. **a** Tc99 m Bone Scan demonstrates an area of increased uptake at T8 (*black arrow*), which was interpreted as a fracture. The DW-MRI **b** sagittal and **c** coronal maximum intensity projection images demonstrate extensive bony metastases in the ribs

and spine. **d** The CT shows only a few areas of sclerosis and the pathological T8 fracture. All three studies were performed within the same week, and the DWI MRI study showed the extent of disease, not appreciated on either the bone scan or the CT

Fig. 3 Prostate cancer. **a** Anatomical T2 sequence shows a mid-glandular peripheral 2×1 cm area of low signal intensity abutting the capsule and distorting it (*arrow*). The tumor returns **b** a low ADC

value on the ADC map and **c** shows high signal intensity impeded diffusion on the $b = 900 \text{ s/mm}^2$ image

prostate gland (Fig. 3), and may also be used to guide tissue sampling of the most probable biologically aggressive disease [39], so that appropriate management decisions can be undertaken.

DWI Characterization of Lymph Nodes

The assessment of lymph nodes remains challenging on DW-MRI. This is because normal and non-pathological

lymph nodes demonstrate impeded diffusion on account of their cellularity, and there is an overlap in the ADC values between malignant and non-malignant nodes. Although a few studies have indicated that the ADC value of malignant nodes tends to be lower compared with benign nodes, there is no consistent threshold that can be applied across different disease types for practical deployment. The diagnostic accuracy of characterizing non-enlarged lymph nodes may be improved by the administration of lymphotrophic contrast medium (ultrasmall iron oxide particles, USPIO), which is not yet licensed for commercial use, but may be available for research trials. Preliminary work combining DW-MRI with USPIO enhanced MRI showed a very high diagnostic accuracy of 90 % in characterizing normal size lymph nodes in patients with pelvic urological malignancies [40]. This is because the susceptibility effects of USPIOs taken up by normal lymph nodes suppresses the diffusion signal, making it possible to more confidently differentiate between malignant and non-malignant nodes.

Evaluation of Treatment Response

Tumor cell death by cellular lysis, necrosis or apoptosis from a variety of treatments results in less impeded water motion in the tissue, leading to an increase in ADC value, which may be detected as early as 1–4 weeks after the commencement of therapy. The disease may, however, remain of high DW-MRI signal intensity, especially in areas of necrosis, due to the effect of T2 shine-through. However, the temporal evolution of ADC following initial cell death appears to be variable, depending on the type of treatment administered and the tissue repair processes that ensue. More work is needed to understand these changes and relate them to underlying pathophysiological processes. Nonetheless, emerging literature contributes to our further understanding of ADC as a potential response, predictive and prognostic biomarker in different disease settings.

Gastrointestinal

There has been a relative paucity of data on the clinical use of DW-MRI in upper gastrointestinal cancers. A recent study found that the percentage change in ADC values with treatment of gastro-esophageal tumors had a negative relationship with the tumor regression observed in response to neoadjuvant chemoradiotherapy [41]. Responders to neoadjuvant treatment had a lower pre-treatment tumor ADC value and a higher post-treatment ADC value. Furthermore, even though the responders demonstrated an increase in the mean tumor ADC value, the mean tumor

volume did not significantly change after treatment in this group [41], demonstrating the potential value of ADC as both a response and a predictive biomarker.

In rectal cancer, studies have shown the potential predictive and prognostic value of ADC in the primary tumor. In one study [42], a lower pre-treatment ADC value was associated with poor tumor regression (tumor regression grade of 4) and the presence of extramural venous invasion. However, in other studies, a lower pre-treatment ADC value has been observed in responders to chemoradiotherapy [43, 44], which mirrors observations made in colorectal cancer metastases [45]. In another study, the pre-treatment tumor volume defined by high *b* value tumor diffusion signal intensity showed a strong correlation with the tumor regression grade [46]. Clearly, these parameters will need to be further validated in a wider clinical setting.

Malignant Bone Disease

The lack of robust tumor response criteria for disease confined to the bones remains one of the major limitations in oncologic imaging. In this regard, ADC measurement shows substantial promise as a response and predictive biomarker in patients with metastatic bone disease and multiple myeloma. Significant increase in tumor ADC values has been reported in responders to chemotherapy [47] and hormonal therapy [48] and as early as 1 month following the initiation of therapy [48]. In multiple myeloma, trials are on-going in applying WB-DW-MRI technique for evaluating treatment response in metastatic bone disease and multiple myeloma (Fig. 4). Patients with marrow disease remission after treatment showed significantly higher ADC values [49], with the increase in ADC being observable at even 3 weeks after initiating therapy [50].

Beyond ADC: Accounting for Non-mono-exponential Diffusion in Tissues

The ADC calculated on most vendor MR platforms, which are in routine clinical use, assumes a mono-exponential relationship between the measured signal intensity and the diffusion-weighting (*b* value). However, in tissues, the signal attenuation with increasing *b* value is non-linear, with an increased signal attenuation at lower *b* value, which is ascribed to tissue microcapillary perfusion. By performing DW-MRI using multiple *b* values (including low *b* values of typically $<200 \text{ s/mm}^2$), it is possible to characterize or estimate both the “true diffusion” from the “pseudodiffusion” (related to microcapillary diffusion) by applying the principles of IntraVoxel incoherent motion (IVIM [51]), which assumes a bi-exponential relationship between the measured signal intensity and the *b* value.

Fig. 4 Disease response assessment in metastatic prostate cancer. **a** Baseline radionuclide bone scan shows predominant right hemipelvic disease. **b** After 3 months of treatment, the repeat bone scan shows reduced uptake inferiorly (*thick arrow*), but increased uptake at the anterior superior iliac spine (*thin arrow*). **c** The baseline DWI-MR

and corresponding ADC map demonstrate the extent of disease in the bone, but also show hepatic metastases (*arrow head*). **d** The 3-month DWI-MR shows that the bone disease has significantly improved with a marked rise in the ADC of the right hemi-pelvis (*chevron*). The hepatic metastases have also almost all resolved

Parameters derived using this approach include the perfusion fraction (f , a simplified view is that it represents the fraction of vascular flow in tissue), the pseudodiffusion coefficient (D^* , the rate of vascular flow) and the diffusion coefficient (D , representing tissue water diffusivity), the product, fD^* , providing an estimate of perfusion.

The ability to provide both diffusion and perfusion quantification using a single imaging study, without the need for intravenous contrast injection, appears highly attractive. Others see bi-exponential data fitting by IVIM analysis as a way of obtaining a potentially more robust and accurate measurement of tissue diffusion by accounting for the perfusion component. For these reasons, there has been a significant output of research in this area in the past few years, exploring DW-MRI derived diffusion and perfusion parameters for disease assessment [52–64].

Studies have already demonstrated that the renal cortex and medulla have different ADC values, and the f of the medulla has been proven to be lower than the cortex [65]. Recently, it has been shown that using IVIM analysis, the f together with the D showed the highest diagnostic

accuracy for the diagnosis of clear cell renal carcinoma ($Az = 0.78$), and this was able to reliably distinguish between papillary cell carcinoma from cystic RCC [66]. In another study, the D showed a higher diagnostic accuracy than mono-exponential ADC in discriminating between clear cell and non-clear cell renal cancers [57]. IVIM analysis has been used in differentiating pancreatic carcinomas from the mimicking focal pancreatitis and surrounding normal pancreatic tissues [55, 67, 68]. More recently, the D was found to have a higher diagnostic performance compared with conventional ADC in discriminating between malignant and benign focal hepatic lesions (Az 0.96 versus 0.93) [53]. Furthermore, the f and D^* were also significantly higher in hypervascular liver lesion compared with non-hypervascular lesions [53].

Despite these varied and positive results, a word of caution should be made. The IVIM analysis requires imaging acquired using multiple b values (typically six or more), with good image signal-to-noise ratio, to provide confidence in the results. Even then, because the diffusion model is fitted with three parameters, the pseudo-diffusion

coefficient derived can be unstable, and some authors have thus chosen to fix this value a priori [68]. A study evaluating liver parenchyma and liver metastases has shown that the measurement reproducibility of the D is good in both normal liver and metastases, but in hypovascular metastases, the estimation of the f and D^* is associated with very large measurement uncertainty (50 % or greater) [56•]. This poor measurement reproducibility in lesions with low f suggests that the technique may not be reliable in disease with inherently low pseudodiffusion phenomenon at low b values. For these reasons, IVIM analysis is still regarded as a research tool and has not filtered into mainstream clinical application.

More recently, other non-mono-exponential diffusion models have been applied for DW-MRI evaluation, including Gaussian model [69], stretched exponential model [70] and the kurtosis model [71]. The IVIM model remains the most widely used, as it links the bi-exponential signal attenuation behavior in tissues to the specific underlying biological underpinning of microcapillary perfusion.

Interest in the kurtosis model (also called kurtosis diffusion in the literature) is, however, increasing. The diffusion kurtosis (K) measures deviation from Gaussian water diffusion behaviour, which is observed in free water or homogenous solutions. In tissues, the presence of microstructure and microcapillary perfusion results in deviation from this behavior. Hence, diffusion kurtosis (K) measurements can be thought of as measuring diffusion heterogeneity, thus reflecting tissue “complexity”, with higher K values having been reported in tumors [72, 73]. Early work suggests that the technique may be able to distinguish between tumor and benign pathologies; between low and high grade tumors; as well as between native and treated tumor tissues [72, 73]. Clearly, the role of diffusion kurtosis imaging (DKI) needs to be further clarified with future research, including studies to establish its measurement reproducibility across different body sites and tumor types.

Future Development and Challenges

The last decade has seen an exponential growth in the use of body DW-MRI in both research and clinical practice, especially in oncology, and there is little doubt that the technique will continue to be relevant and useful in the future. In terms of image acquisition, technical refinement is likely to ensue in the coming years, with algorithms to further improve the speed of image acquisition without comprising image quality. As the degree of image distortion associated with echo-planar DW-MRI is accounted for and corrected, we are likely to see translation of DW-MRI

imaging to provide biological targets for radiotherapy planning. Various initiatives by professional bodies (e.g. QIBA, EORTC, ECMC) are addressing methods to standardize DW-MRI quantification, which will become increasingly relevant to drug development and clinical trials. Last but not least, DW-MRI is likely to find its place as an important response, predictive and prognostic biomarker across different tumor types. In particular, DW-MRI is likely to be highly relevant for the evaluation of metastatic bone and bone marrow diseases. However, more work is needed to understand how the evolution of normal bone components (e.g. fat and calcification) in disease and treatment affect the diffusion signal and the ADC value. There are clearly research endeavors being undertaken in these areas.

Conclusion

DW-MRI has evolved considerably since its inception. It is now used routinely along other MRI sequences in tumor detection in the body. With the increasing volume of studies demonstrating a correlation between ADC with tumor subtype, grade and response to treatment, confidence in its application in routine diagnosis and follow-up is widening. Future research and professional initiatives will underpin the importance of quantitative ADC value as a response biomarker in oncology.

Acknowledgments We would like to acknowledge the support of the NIHR Biomedical Research Centre at the Royal Marsden Hospital/ Institute of Cancer Research.

Compliance with Ethics Guidelines

Conflict of Interest Venus Hedayati, Nina Tunariu, David Collins, and Dow-Mu Koh have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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