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Therapy response with diffusion MRI: an update

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Abstract

The efficiency of an oncological treatment regimen is often assessed by morphological criteria such as tumour size evaluated by cross-sectional imaging, or by laboratory measurements of plasma biomarkers. Because these types of measures typically allow for assessment of treatment response several weeks or even months after the start of therapy, earlier response assessment that provides insight into tumour function is needed. This is particularly urgent for the evaluation of newer targeted therapies and for fractionated therapies that are delivered over a period of weeks to allow for a change of treatment in non-responding patients. Diffusion-weighted MRI (DW-MRI) is a non-invasive imaging tool that does not involve radiation or contrast media, and is sensitive to tissue microstructure and function on a cellular level. DW-MRI parameters have shown sensitivity to treatment response in a growing number of tumour types and organ sites, with additional potential as predictive parameters for treatment outcome. A brief overview of DW-MRI principles is provided here, followed by a review of recent literature in which DW-MRI has been used to monitor and predict tumour response to various therapeutic regimens.

Keywords: *Diffusion-weighted MRI; ADC; treatment response; oncology.*

Introduction

The global cancer burden continues to increase due to a combination of factors including aging populations, population growth, and global increases in smoking, physical inactivity, and other cancer causing behaviours[1]. Therapeutic options include surgical resection, radiotherapy, various chemotherapeutic regimens and active surveillance in selected cases. While the ability to monitor the response or progression of a tumour throughout the therapeutic and follow-up cycle is desirable for the selection of effective treatment, standard tumour response criteria based on size reduction are not always timely as size reduction typically occurs after widespread cell kill and debris removal, which can occur over days and weeks with fractionated therapy regimens. An additional problem is that newer antiangiogenic, vascular, and molecular targeting chemotherapeutic agents act by other mechanisms apart from direct cell kill, leading to functional changes in the tumour microenvironment that are not directly detectable by tumour size criteria.

Positron emission tomography (PET), magnetic resonance spectroscopy (MRS), dynamic contrast-enhanced (DCE) and diffusion-weighted (DW) magnetic resonance imaging (MRI) can all be used to measure functional changes in the tumour microenvironment. PET can provide targeted functional information but is a relatively expensive method and is susceptible to false-positive results related to inflammation. The radiation burden of PET is also a consideration, particularly in young patients requiring multiple follow-up examinations. Magnetic resonance spectroscopy provides information about metabolites and tumour biochemistry. However, the limited spatial resolution can be problematic, particularly for metastases and heterogeneous tumours, and considerable expertise is required for effective data analysis and interpretation. DCE-MRI offers improved spatial resolution over MRS to visualize information about vascular perfusion, permeability, and/or interstitial volume. However, image analysis is also non-trivial, and the use of gadolinium-based contrast agents is a concern in patients with impaired renal function. DW-MRI is a non-invasive imaging modality that involves no radiation burden or contrast agent use. An increasing body of literature including several recent review articles indicates that DW-MRI is well suited to longitudinal monitoring of

tumour progression and response in a variety of tumour types[2–4]. This article is an update to a previously published review on the use of DW-MRI for monitoring tumour response to various treatment regimens[4], and focuses on recent developments in the field.

Principles of diffusion-weighted imaging

DW-MRI is a technique that measures the movement of free water molecules via the use of magnetic field gradients. The type of movement that is measured includes directed perfusion and passive thermal diffusion, which may be influenced by cell size, structure, and membrane integrity. Depending on the imaging parameters used, either one of these (or a combination) may be measured. Many treatments that act by functional mechanisms will affect water diffusion and perfusion in a detectable way long before tumour size reductions are seen. This ability of DW-MRI to detect early changes in the tumour microenvironment is the motivation behind the growing interest in DW-MRI for use in treatment monitoring.

The *b*-value used in a DW-MRI scan refers to the gradient durations and amplitudes used, and determines the extent of diffusion weighting in a scan. If DW-MRI images are acquired using a minimum of two *b*-values, the decay of the diffusion-weighted signal can be quantified to provide an estimate of the apparent diffusion coefficient (ADC). ADC values are typically lower in highly cellular tissues with impeded water diffusion, such as tumours, and are often increased in necrotic regions and tissues with damaged or permeable cell membranes. In many tissues, the diffusion-weighted signal exhibits a multi-exponential (rather than simple monoexponential) decay[5]. The more quickly decaying portion of the signal is attributed to tissue perfusion. If a bi-exponential model of diffusion is used, diffusion (D or ADC_d) and perfusion (D^* or ADC_p) related diffusion coefficients as well as the perfusion fraction (f) can be measured[5].

The selection of the optimal number and values for the *b*-values is an important technical consideration. Although there have been a number of articles on the topic, no consensus has yet been reached. A minimum of two *b*-values are required to measure the ADC assuming monoexponential signal decay and a minimum of four are required assuming bi-exponential signal decay; however, some groups routinely use more than this minimal number to minimize the effect of noise and motion on the data analysis[6], or to ensure full coverage of both low and high *b*-value ranges[7–9]. For clinical assessment of treatment response, monoexponential fitting with two or three *b*-values is the most commonly used model.

Clinical applications of DW-MRI for monitoring treatment response in different organ sites

DW-MRI can be used to detect microstructural changes that precede changes in tumour size as an indication of tumour response to therapy. For many organs and tumour types, a tumour initially demonstrates decreased ADCs relative to the surrounding tissue due to diffusion restriction caused by high cell density in the tumour. This should also correspond to high signal intensity on high-*b*-value diffusion-weighted images. Tumours containing necrotic regions will also demonstrate areas of high ADC, low perfusion fraction, and low signal on high-*b*-value images.

The change in DW-MRI signal and diffusion parameters observed after treatment will vary depending both on the individual tumour and treatment type. A positive response to treatment generally tends to result in an increase in ADC relative to pre-treatment values as apoptosis and necrosis begin and cell density decreases. However, ADC decreases may occur following the clearance of necrotic portions of the tumour, or in cases of fibrosis and scar formation concurrent with a decrease in the perfusion fraction. ADC decreases have been observed in response to therapy in rectal carcinoma [10–12] and bone metastases[13]. ADC may also decrease in response to treatments where cell swelling or vascular restriction are important mechanisms of action. Thus, to determine whether a change in ADC corresponds to response or progression, diffusion parametric maps should be evaluated along with DW-MRI signal intensity images and all other available clinical information. For many tumour types, low pre-treatment ADC values in the primary tumour indicating high cell density are predictive of favourable response to standard chemotherapy. However, this has not been confirmed in all tumours, and may not apply consistently in the case of metastases[13,14].

In the following sections, recent literature focusing on changes observed in DW-MRI parameters in a variety of extra-cranial tumours is summarized. The literature is categorized by anatomical site: head and neck cancer, breast cancer, primary lung cancer, liver metastases and hepatocellular carcinoma, osteosarcoma and soft tissue sarcoma, uterine cervical cancer, ovarian cancer, bladder cancer, prostate cancer, rectal cancer, and metastases imaged using DW whole-body MRI.

Head and neck cancer

Three recent studies evaluating the response to chemoradiation using DW-MRI have shown ADC increases in head and neck regions responding to therapy[15–17]. In one study, the ADC increase (both at 2 and 4 weeks during chemotherapy) was higher for non-recurrent lesions and correlated with loco-regional control at 2 years[15]. In another study, ADC increases at 3 weeks

did not correlate with loco-regional control at 6 months, however, parametric response mapping of ADC was predictive of 6-month clinical progression, showing ADC increases in a large percentage of the tumour volume for responding patients[16]. A third study showed that ADC decreases seen during or after treatment predict loco-regional failure with 100% specificity and 80% sensitivity[17].

Breast cancer

Monitoring response to neoadjuvant chemotherapy has been evaluated in a number of published reports on DW-MRI in breast cancer[18–27]. Incremental ADC increase over chemotherapeutic treatment cycles is consistently reported in a number of studies[18–23,25–27]. These ADC increases were more pronounced in responding patients than in non-responding patients[18–23,25–27]. In several studies, significant increases in ADC have been observed as early as after the first cycle of chemotherapy[19,25,26] and correlated with tumour volume reduction[18], while in one study anatomical response was only borderline significant after the 2nd cycle of chemotherapy[19].

While lower pre-treatment ADC has been correlated with eventual response to chemotherapy in several studies[18,20,21], this finding was not consistent in all studies[22,23]. Pre-treatment ADC was found to be lower in tumour lesions than in benign tumours[24] or normal breast tissue[25] and pre-treatment ADC cut-off values could be used to predict response with sensitivity of 94% and specificity of 71%[20]. Post-treatment ADC cut-off values were able to differentiate between responders and non-responders, or pathological complete and non-complete remission, respectively, with 88% and 100% sensitivity and 88% and 70% specificity[21,22].

Primary lung cancer

Recent trials reporting the use of DW-MRI in predicting and assessing lung cancer response show a consistent increase in ADC during and after chemotherapy, chemoradiation, and radiofrequency ablation[28–30]. Pre-treatment DW-MRI/ADC showed better specificity and accuracy than fluorodeoxyglucose (FDG)-PET/maximum standardized uptake value (SUV_{max}) in predicting tumour response[31]. Lower pre-treatment ADCs were found in partially responding lesions versus stable and progressive disease in one study[31], however no significant difference was seen in another study involving chemoradiation[28]. In contrast to the findings in uterine cervical cancer[32], pre-treatment ADC in lung was higher in squamous cell carcinoma than in adenocarcinoma[28–30]. This might be attributed to the fact that squamous cell carcinomas undergo necrotic change with consequent increases in ADC.

Liver metastases and hepatocellular carcinoma

Hepatic metastases, the most common malignant tumours of the liver, are only rarely eligible for surgical resection to achieve long-term tumour-free survival or cure. DW-MRI is a promising technique for the response of liver metastases and hepatocellular carcinoma to chemotherapy, radiotherapy, and local palliative treatment, particularly at early treatment time points when significant changes in tumour size have not yet occurred[33–38].

ADC increases correlated with response to systemic chemotherapy in all studies with liver metastases of breast and colorectal cancer[33,36–38]. The correlation of ADC increase with response of liver metastases of breast cancer was strongest on day 4, the earliest time point examined[33]. The findings of increased ADC after chemotherapy are consistent with studies of colorectal cancer liver metastases treated with chemotherapy via direct hepatic arterial infusion (HAIC)[34]. Using radiofrequency ablation, decreased ADC was observed in the periphery of the ablation zone and correlated with local tumour progression[35]. Two studies found that for liver metastases of colorectal cancer, non-responding lesions had significantly lower pre-treatment mean ADCs than responding lesions[36,37], but this was not confirmed in a third study[38].

Several clinical studies evaluating response to treatment for hepatocellular carcinoma using DW-MRI have been published. A post-treatment increase in ADC was reported in most of the studies[39–44] as early as 1–2 weeks after treatment[39], while a correlation between ADC and response as assessed pathologically in terms of percent tumour necrosis was also demonstrated[40]. The use of DW-MRI seems to be an important contributor to treatment monitoring in these tumours, as morphologically a change in tumour size could not yet be observed at 4 weeks after transarterial chemo-embolization (TACE), the last time point measured in one study[39]. In another study, a 4% decrease in tumour size and 15% increase in ADC were observed 1 month after therapy[41]. An association was found between post-treatment ADC increase and RECIST response in a further study[42]. Pre-treatment ADC values proved not to be reliable for identification of eventually responding lesions in one study[43]. While sensitivity improved and specificity decreased for distinguishing recurrence versus benign lesions when adding DW-MRI to DCE-MRI[45], sensitivity was lower for DW-MRI than for DCE-MRI for distinguishing recurrence versus necrosis in this study, albeit with an equal specificity in another study[44].

Osteosarcoma and soft tissue sarcomas

Studies on primary tumours of the bone and one study on soft tissue sarcoma have shown good results for the use of DW-MRI in assessing response to cytotoxic chemotherapy[46–49]. Post-treatment increases in ADC

were observed in all studies. The ADC differential ($ADC^{post} - ADC^{pre}$) had 100% sensitivity and 57% specificity for predicting poor responders in osteosarcoma in one study[46], while in another study the minimum ADC ratio ($[ADC^{post} - ADC^{pre}]/ADC^{pre}$) was significantly higher in responding versus non-responding patients[47]. For soft tissue sarcomas, a significant negative correlation between ADC and changes in tumour volume was found[48].

Uterine cervical cancer

Several recent studies have investigated the use of DW-MRI in evaluating response to radical external beam radiotherapy or chemoradiation in uterine cervical cancer[50]. ADC was found to be lower in cancer versus normal tissue[32,51], and lower for squamous cell carcinomas than for adenocarcinomas[32]. While a relationship between decreased pre-treatment ADC values and eventual tumour response was found in one study[52,53], this was not confirmed in a second study[54]. ADC was found to be negatively correlated with cellular density and tumour grade[32], and also correlated with tumour stage[51].

Ovarian cancer

Response to chemotherapy in ovarian cancer has been evaluated by DW-MRI in two recent studies[14,55]. In a study evaluating distinct anatomical tumour sites, mean pre-treatment ADCs were lowest for peritoneal deposits, followed by omental and primary ovarian lesions; post-treatment ADCs were significantly increased for ovarian, but not for omental and peritoneal lesions[14]. While RECIST responders showed an ADC increase for ovarian lesions, Gynaecologic Cancer InterGroup (GCIG) CA125 serum marker responders did not[14]. Significant increases in ADC as well as in histogram skewness and kurtosis were observed after the 1st cycle in responders; the ADC change of the 25th percentile proved to be the best discriminant of response[55].

Bladder cancer

Recent studies using DW-MRI to evaluate response to neoadjuvant chemotherapy showed that ADC was a significant and independent predictor of sensitivity to chemoradiation[56], with chemoradiation-sensitive tumours showing lower pre-treatment ADC compared with resistant tumours[56]. In a multiparametric evaluation, DW-MRI was superior to T2-weighted (T2w) and DCE-MRI in specificity and accuracy, albeit with comparable sensitivity to DCE-MRI[57].

Prostate cancer

The potential of detecting prostate cancer and the effect of external beam radiotherapy, antihormonal treatment, and ultrasonic ablation of locally progressing, recurrent, and advanced prostate cancer has been evaluated in a number of recent studies[58–64], with a growing interest in applying multiparametric MRI techniques.

While in one study ADC was lower in recurrent cancer than in benign tissue after radiotherapy[58], a difference was only found before but not after radiotherapy in a second study[59]. ADC increased in response to both radiotherapy[59] and antihormonal therapy[60].

Multiparametric MRI, including DW-MRI, can achieve accuracy levels of 80–90% in the detection of recurrent cancer after radiation therapy[61]. While the combination of DW-MRI with T2w-MRI was found to be more specific than DCE-MRI alone[62], and more sensitive than T2w-MRI alone[58], DCE-MRI proved to be more sensitive than T2w-MRI combined with DW-MRI in detecting recurrent cancer[62]. The sensitivity, specificity, and area under the curve (AUC) of qualitative detection of prostate cancer can be improved by including DW-MRI with T2w imaging; the best results were seen on high-*b*-value images (2000 s/mm^2) rather than at $b = 1000$ s/mm^2[64]. Furthermore, a recently published study showed the potential of DW-MRI to detect tumour recurrence after radical prostatectomy that could not be assessed on computed tomography (CT) or conventional MRI[65].

Rectal cancer

Although the rectum can be a difficult area for DW-MRI due to physiological motion, a growing number of studies investigating the use DW-MRI in monitoring response of rectal cancer to neoadjuvant chemotherapy and chemoradiation show indications that DW-MRI is sensitive to early changes in response to treatment[10–12,66–72].

It has been found that the combination of DW-MRI with T2w-MRI improves the prediction of surgical tumour clearance of the mesorectal fascia over the use of T2w-MRI alone[66]. Low pre-treatment ADC correlated with eventual response to therapy in two studies[10,67], while in two other studies pre-treatment mean ADCs were identical in responders versus non-responders and pathological complete response versus non-complete response, respectively[68,69]. Post-treatment ADC increase was observed in a number of recent studies[12,67–71] and was observed as early as 1 week after initiation of therapy[12]. However, it should be noted that ADC decreases have also been observed: in one study, the ADC of responders decreased after chemotherapy and rose after chemoradiation[10], while in another study the ADC of responders increased 1 week after chemoradiation therapy followed by a decrease in subsequent weeks[12]. Some authors have suggested that this may occur if a treatment results in the loss of a necrotic luminal component of the tumour in response to treatment, leaving a tumour with a proportionately greater viable cell fraction behind[10]. Another explanation is that when tumours eventually showing pathological complete remission were analysed, those with reduced

post-treatment ADC more often developed proctitis or fibrosis[11].

A correlation with both pre-treatment and post-treatment ADC and Mandard regression grade[70] of the tumour was found; low pre-treatment ADC correlated also with more advanced disease (i.e. extramural invasion and positive lymph nodes after chemoradiation)[72]. ADC cut-off values proved helpful in predicting complete response with a sensitivity of 100% and a specificity of 79% in one study[71]. Interestingly, in another study the post-treatment ADC showed higher accuracy in determining pathological complete response than relative change in ADC[69].

Whole-body DW-MRI and metastases

Recent technological advances in scanner technology have improved the ease of whole-body MRI examination. Whole-body DW-MRI is being increasingly used in the detection of bone and organ metastases from various tumours and for the assessment of lymph node and bone marrow involvement in lymphoma[13,73–80], in many cases showing comparable sensitivity and specificity to scintigraphy and PET/CT with no radiation dose to the patient.

One study showed superior sensitivity but inferior specificity for DW-MRI compared with scintigraphy for metastasis detection[73], while in another study the specificity was higher but sensitivity was comparable for DW-MRI compared with scintigraphy and PET-CT[74]. The detection rate of bone metastases was 92% for DW-MRI compared with 57% for [^{11}C]methionine-PET and 23% for bone scintigraphy[75]. For the detection of distant metastases in breast cancer, DW-MRI proved less sensitive and specific than FDG-PET/CT[76].

A comparison of DW-MRI with PET/CT in lymphoma staging showed that the two modalities agreed in 94% of cases[77], and a second study confirmed that staging results for whole-body T1-weighted (T1w) and DW-MRI were comparable with CT[78]. The use of whole-body DW-MRI for the diagnosis of lymphoma had a sensitivity of 100% in a study of 31 patients, but a specificity of only 31% when compared with histopathology[79]. It is not clear whether DW-MRI provides an advantage over standard whole-body MRI; for the detection of bone marrow involvement DW-MRI gave a sensitivity of 42% compared with 46% for whole-body T1w-MRI[80], and similar results were found for whole-body T1w and DW-MRI in lymphoma staging[78].

In studies measuring mean ADC in bone metastases before and after treatment, ADC rose in most lesions[13,81]. However, in one study, the ADC maps of bone metastases revealed areas of both central ADC increase and peripheral ADC decrease within metastases[81], and in another study, the mean ADC fell in some lesions, which included both responding and non-responding lesions, indicating that mean ADC should be used with caution to monitor bone metastasis response[13].

Conclusions

While ADC increases are seen in response to many therapies, care must be taken as post-treatment decreases can also be seen with selected therapies, imaging time points and tumour types (notably, rectal cancers and bone metastases). The predictive value of ADC is not yet clear for all tumour types, and care should be taken when using ADCs for prediction of individual patient response.

DW-MRI continues to show promise as a method of detecting early changes in the tumour microenvironment in response to a variety of treatment regimens. The advantage of DW-MRI over other methods of monitoring response include its sensitivity to tumour function, good spatial resolution, and lack of radiation burden. One potential caveat for DW-MRI is that imaging protocols, *b*-values, and time of examination relative to therapeutic interventions must be tailored to individual tumour types, organs, and therapies. However, with careful application of appropriate DW-MRI protocols, the use of DW-MRI in treatment monitoring presents a large potential benefit to the patient.

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Conflict of interest

MZ is a paid advisor for Roche Inc and Teva Inc. The other authors have no conflicts of interest to declare.

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