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Diffusion-Weighted MRI for Assessment of Early Cancer Treatment Response

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Abstract

Recent clinical practice for the management for cancer patients has begun to change from a statistical “one-size fits all” approach to medicine to more individualized care. Pre-treatment biomarkers (i.e. genetically and histologically based) have a growing role in providing guidance related to the appropriate therapy and likelihood of response; they do not take into account heterogeneity within the tumor mass. Thus, a biomarker which could be utilized to measure actual tumor response early following treatment initiation would provide an important opportunity to evaluate treatment effects on an individual patient basis. Diffusion weighted magnetic resonance imaging (DW-MRI) offers the opportunity to monitor treatment-associated alterations in tumor microenvironment using quantification of changes in tumor water diffusion values as a surrogate imaging biomarker. Results obtained thus far using DW-MRI have shown that changes in tumor diffusion values can be detected early following treatment initiation which correlate with traditional outcome measures. Sensitive imaging biomarkers are providing for the first time a means of assessing 3 dimensional tumor response early in the treatment cycle which may also provide opportunities to visualize spatial heterogeneity of response within the tumor which could open up further opportunities for spatially modulating therapy. This review highlights the development of DW-MRI and its proposed usefulness in the clinical management of cancer patients. The utility of DW-MRI for assessing therapeutic-induced response is further evaluated on tumors residing in the brain, head and neck and bone.

Keywords

DW-MRI; apparent diffusion coefficient; imaging biomarker; cancer; treatment response

Overview of Clinical Assessment of Cancer Treatment Response

Advances in medical imaging instrumentation have fundamentally changed clinical management of cancer patients. A key component is magnetic resonance imaging which is involved in diagnosis, treatment planning, and assessment of response or recurrence of solid

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malignancies. With high spatial resolution and soft tissue contrast, MRI allows precise non-invasive radiographic measurements of tumor location and size.

The need for an objective measure of cancer response has been realized since the 1960s[1]. In 1979 the World Health Organization published its cancer assessment criteria that has been the standard for patient management and clinical trials[2]. Realizing that there were deficiencies in the WHO criteria, a series of investigators have set up the Response Evaluation Criteria in Solid Tumors (RECIST)[3], which has been adopted for clinical protocols. This new method for assessing solid tumor response to treatment is based on a single linear summation of specific lesions. Although this approach provides a means for rapid and reproducible measurements for cancer assessment, there continues to be a growing concern that response measurements may not be adequately addressed when tumors are treated with molecularly targeted agents that may provide therapeutic benefit without significantly reducing the tumor volume [4-6]. These concerns underscore the urgency for the development of reliable response biomarkers linked to clinical outcome that can evaluate response to treatment earlier than current imaging methodologies.

Principle of Diffusion Measurement

First demonstrated in 1965, Stejskal and Tanner[7] measured water diffusivity by acquiring water signal using a spin echo sequence in the presence of bi-polar time-dependent field gradients. The principle behind this MR technique is that the initial position of a water molecule within a sample region can be encoded using the gradient. Water molecules which experience displacement, due to thermal motion (i.e. diffusion), from the initial location over a short time period, during the decoding process, will have a detectable loss of signal. Stejskal and Tanner showed that water signal attenuates at a rate proportional to the diffusivity of the molecule as expressed in the equation:

$$S=S_0\exp\left(-D\cdot(\gamma\delta g)^2(\Delta-\delta/3)\right) \quad (1)$$

As observed in Eq. (1) the degree of diffusion (D) sensitivity, commonly referred to as the b-value, is dependent on the gyromagnetic ratio of the nuclei (γ), gradient amplitude (g), gradient pulsewidth (δ) and the temporal separation of gradient pulses used to encode and decode molecular positions (Δ). Thus higher b-values yield higher diffusion weighting in the resultant MR signal[8-9]. Separation of diffusion effects from other MR imaging contrast typically requires the acquisition of diffusion weighted images using two or more b-values. There exists a complex interplay of factors in vivo that restrict the ability of direct measurement of the actual diffusion coefficient of water by MRI[10-11]. Consequently, water diffusion coefficient is typically acquired by MRI using three orthogonal diffusion sensitive gradients. The measured diffusion value is commonly reported as an “apparent diffusion coefficient” (ADC) [8-9] since water molecules reside in intra- and extra-cellular regions separated by semi-permeable membranes. ADC can be analytically obtained from diffusion weighted images (S_i) acquired at low ($b_1=0$ s/mm²) and high ($b_2=1000$ s/mm²) b-values.

$$ABC = \ln \left(\frac{S_{b1}}{S_{b2}} \right) / (b_2 - b_1) \quad (2)$$

This approach has been found to be sufficient in providing adequate diffusion sensitivity for most cancer applications.

Cancer Treatment Assessment by DW-MRI

Image-based treatment response assessment for cancer patient management continues to be an active area of research. MRI is a versatile imaging technique capable of acquiring anatomical, functional, metabolic and biophysical information of intact living tissues. The capability of measuring water diffusivity in a viable tumor by MRI provides a means for monitoring relatively subtle alterations in cellular density that can yield corresponding changes in the diffusion rate of water molecules in those spatially localized regions. This provides DW-MRI with the potential for application as a sensitive imaging biomarker for detecting therapeutic intervention in solid tumors [9,12].

The principle behind the application of using water diffusivity for monitoring cancer treatment response is the ability of the water molecule to sample the subcellular structures (e.g. cell membranes, organelles and extracellular matrix) within the tumor that may hinder water diffusion. The success of DW-MRI is based on the concept that, during their random, diffusion driven displacement (also referred to as Brownian motion), water molecules probe tissue structure at a microscopic scale (~10µm) over the diffusion measurement interval, which is well beyond the usual image resolution (~100µm). Anderson and colleagues have investigated the relationship between cell volume fraction and ADC as measured by DW-MRI [13]. In a packed array of glial cells, a rise in the ADC was found to occur when cells shrank, which results in an increase in cell volume fraction. Conversely, a decline in ADC was observed in the presence of cell swelling, where increasing cellularity of the sample lead to increased hindrance of water mobility. In general, the free mobile water molecules undergo a larger net loss in signal relative to a more immobile water molecule. As presented in Eq(2), the acquisition of signal at multiple diffusion gradient values can be used to measure molecular mobility, as expressed as ADC, that can be spatially quantified in heterogeneous tissues such as tumors. As illustrated in Fig. (1), cellular/tissue interactions and restrictive sub-cellular barriers, as in a solid tumor, reduce the water mobility resulting in a lower ADC measurement within a tissue region. Conversely, as the density of cellular and macromolecular structures decreases water mobility will increase resulting in elevated ADC values for that spatial region. Following a treatment-induced alteration in the tumor, ADC values have been shown to correlate inversely with cell density in a variety of tumor types providing evidence for its use as a non-invasive imaging biomarker of cell density [14-16].

As an early tumor treatment response biomarker, tumor ADC values from DW-MRI measurements are quantified in an individual patient prior to and during therapy. The goal is to use the change in ADC values as a surrogate for clinical efficacy in a manner that conventional anatomical imaging cannot. Two methodologies are used for quantification and

reporting of tumor treatment response using ADC values: (1) the percent change in the mean ADC value and (2) the voxel-by-voxel change in ADC.

Monitoring cancer treatment response by DW-MRI requires a baseline or pre-treatment diffusion scan followed by a serial scan mid-therapy. Quantitative ADC maps are generated for each of the interval scans. By delineating the tumor margins one can specify a volume-of-interest (VOI) on quantitative ADC maps, all of the ADC values from the individual voxels comprising the tumor mass can then be obtained to generate a histogram for the tumor at each time interval. Mean ADC values can be obtained from the temporally resolved histogram distributions and used to report a percent change in the mean ADC at mid-therapy from baseline values. The main advantage of this approach is the simplicity of the procedure assuming quality data was reasonable and adequate delineation of the tumor margins. However, significant heterogeneity of response (diffusions values increased and decreased within the tumor following treatment) in the tumor may attenuate the sensitivity of detecting changes in treatment-associated ADC values.

An alternative approach for measuring tumor response to a therapeutic intervention was developed with the motivation of compensating for the potential heterogeneity in ADC values. The functional diffusion map (fDM) was conceived on the premise that a voxel-by-voxel comparison of tumor changes over time would elicit a more sensitive measure of response[17]. Analogous to the histogram-based approach data is collected from which ADC maps are generated and VOI are contoured on tumor margins. However, the fDM approach requires spatial alignment of serial pre-treatment and mid-treatment ADC maps from the same patient using a computer registration algorithm as shown in Fig (2). Thus each voxel consists of two temporally resolved ADC values from which a difference map can be generated. Voxels are then categorized based on a pre-determined threshold of statistically significant change which allows for quantification of the tumor volume fractions which had a significant increased or decreased in ADC values or had remained unchanged. These regions are encoded as a color map and overlaid on an anatomical MR image providing spatial information of therapeutic-induced change within the tumor. In principle, fDM provides an opportunity for a “real-time” assessment of the spatial alterations within the tumor following treatment that would aid in adapting therapy for an individual patient.

Applications of DW-MRI as a Surrogate Imaging Biomarker of Cancer

Treatment Response

Brain Cancer

The Macdonald criteria, based on radiographic measurements of tumor size, continue to be the primary method for assessing treatment response in central nervous system (CNS) tumor patients [18-19]. Patients with grade III/IV gliomas typically have a median survival of 12-14 months from the time of diagnosis [20]. A deficiency of the Macdonald criteria is that response is typically assessed 8-10 weeks from the start of therapy, which may be one month following the completion of treatment. Early identification of tumor response to therapy would allow for an ineffective treatment regimen to be modified in a more timely

fashion. DW-MRI provides an opportunity to monitor intratumoral response to therapy which has been shown to precede gross volumetric changes in the tumor size.

Initial preliminary data reported that changes in tumor ADC were detectable weeks prior to standard clinical volumetric measurements in two patients with high-grade primary brain tumors [21]. ADC changes to convection-enhanced delivery of chemotherapy directly into the tumor were detected as early as 1 day post-treatment initiation [22]. The same investigators had also reported a significant increase in diffusion as early as 3 days after treatment in 6 out of 10 metastatic or primary brain tumors treated with radiotherapy [23]. These same six patients showed tumors regression up to 35-89% ($P < 0.006$). Additional studies of CNS tumors have reported that changes in ADC values are predictive of response following chemotherapy [24-26] or radiotherapy [27-28].

Consequent to the high spatial heterogeneity found in gliomas, the conventional approach of monitoring tumor response by percent change in mean tumor ADC does not provide adequate sensitivity to changes in mean water diffusivity following a therapeutic intervention. In an effort to develop an analytical approach which would potentially improve the ability to use ADC measurements as a prognostic imaging biomarker of response, fDM was developed and evaluated in three different studies [17,29-30]. In these prospective trials of DW-MRI on patients with primary brain tumors, MRI scans were performed one week before the start of treatment followed by mid-treatment scans at 1, 3 and 10 weeks. Therapy consisted of 6 weeks of fractionated radiation with or without chemotherapy.

In the first of these studies, Moffat and colleagues investigated the sensitivity of the fDM analysis in discriminating between patients who had progressive disease, stable disease, or a partial response compared to the conventional approach of monitoring percent change in mean ADC over the tumor volume [17]. For the first time changes in ADC were evaluated voxel-wise by co-registering serial ADC maps acquired pre and mid-therapy. The tumor volume fraction that exhibited a significant increase in mid-treatment ADC from baseline values were found to be predictive of 10 week radiological response in a cohort of 20 glioma patients as early as three weeks into therapy. In contrast the percent change in the mean ADC provided no predictive value.

A companion study consisting of 34 patients with WHO grade III/IV glioma were evaluated by fDM at 3 weeks into fractionated radiation therapy [29]. The fDM measurement was found to correlate with radiographic response as well as progression-free and overall survival [29]. Patients designated by fDM as having progressive disease had a median survival of 8.2 months whereas patients designated as favorable had an improved median survival of 18.2 months ($P < .008$).

The predictive value of fDM was further validated in a cohort of 60 glioma patients [30]. In this study, a correlation of fDM with patient one-year survival was validated using a receiver operating characteristic curve analysis. Patients alive at 1 year were found to have a larger tumor volume fraction with increased diffusion values in response to therapy than those who died as a result of disease. This predictive value was observed for fDM when assessing overall survival using Cox and log-rank proportional hazards models. In Fig (3) the fDM

analysis is demonstrated on responding and non-responding glioma patients. The fDM analysis was found to be most predictive of patient one-year survival by week 3 mid-therapy, with a larger tumor volume fraction with significantly increased ADC (red voxels) predicting longer median survival (52.6 versus 10.9 months; log-rank, $P < .003$). A similar prognostic value was observed for radiologic response (RR) measured at 10 weeks (median survival, 31.6 versus 10.9 months). These studies have shown that compared with conventional neuroimaging techniques for determining tumor response to therapy, fDM provided equal predictive value with an earlier assessment of response.

Head and Neck Squamous Cell Carcinoma

Head and neck squamous cell carcinoma (HNSCC) accounts for 2.5% of all patients newly diagnosed with cancer [31]. For these patients, functionality (e.g. swallowing and speech) is preserved, while maintaining the current survival rate, by non-surgical organ preservation therapy (NSOPT). DW-MRI may be useful for providing information on tumor status following chemoradiotherapy in this patient population. Recent work by others has found DW-MRI to be useful as a surrogate biomarker for early treatment response in HNSCC patients[32]. In this report, they demonstrated that changes in whole-tumor mean ADC from pre-therapy to one week into chemoradiotherapy correlated with clinical or pathological assessment of disease. Thus, changes in ADC values as measured by DW-MRI may serve as an imaging biomarker for quantifying therapeutic efficacy in patients with HNSCC that can be incorporated into clinical head and neck cancer treatment protocols.

A prospective trial involving 15 patients with HNSCC investigated the predictive value of DW-MRI measurements obtained at baseline and three weeks post-treatment initiation of NSOPT using concurrent radiation and chemotherapy [33]. Tumor response to therapy was determined by monitoring the percent change in whole-tumor mean ADC and fDM and correlating these results with tumor control at 6 months. T₂-weighted, contrast-enhanced images and ADC maps were found to provide adequate contrast for visualizing tumors. Regions within the tumor volume where water mobility increased are observed by a voxel-by-voxel analysis using the fDM approach. This trend was also observed in the analysis of tumor ADC histograms which revealed a significant increase in mean ADC at the three week time interval. However, the percent change in tumor volume and mean ADC did not correlate with tumor control at 6 months as assessed using a receiver operator characteristic curve analysis. In contrast, the fDM analysis was found to correlate with tumor control (partial response (PR) and complete response (CR) at 6 months (Fig. (4)). These results revealed that DW-MRI when assessed by fDM has potential to provide both prognostic and spatial information related to treatment effects during NSOPT of head and neck cancer. In addition, DW-MRI may also have the potential to aid in the individualization of head and neck cancer treatment regimens.

Bone Malignancies

At present there are no accepted methods for assessing response of primary or metastatic cancers within skeletal sites. In fact, response is considered unmeasurable by RECIST [3]. The ability to determine response of osseous lesions to therapy would provide a major breakthrough for imaging as well as having a major impact on the clinical treatment and

management of patients with metastatic cancer to the bone. This deficiency provides an interesting opportunity for investigating DW-MRI as an imaging biomarker of cancer treatment response assessment.

Assessing response to therapy by plain radiography, bone scanning, and conventional anatomical MR imaging has not proven satisfactory. A recent study investigated the application of DW-MRI for evaluating signal intensity changes of bone marrow for assessing response to therapy in metastatic disease of the spine [34]. A cohort of 24 patients were imaged prior to and following radiation therapy. Changes in the MRI signal intensity of the metastatic disease of the vertebral bone marrow were monitored before and following treatment were compared between conventional spin-echo and diffusion-weighted MR images. In 23 patients with clinical improvement following therapy, diffusion values were found to increase in the follow-up scans by approximately 56%. Neither signal intensity from T1- or T2-weighted images nor the volume of the abnormality correlated with clinical improvement. In contrast, in the one patient who had symptoms that had progressed after radiation therapy, the mean ADC decreased. This study concluded that increased ADC as measured by DW-MRI correlates with effective therapy in metastatic disease of the vertebral bone marrow [34].

In a recent study, preliminary work was performed to determine the feasibility of clinically translating the functional diffusion map (fDM) imaging biomarker for quantifying bone tumor response in a patient treated for metastatic prostate cancer to the bone [35]. A patient was scanned using DW-MRI prior to treatment and again at 2 and 8 weeks post-treatment initiation to quantify changes in tumor diffusion values. Three metastatic lesions were identified for fDM analysis (Fig (5)), which all demonstrated early changes in diffusion values at 2 weeks. ADC values were found to increase further by week 8 post-treatment initiation. Significant regions of increased (red voxels) and decreased ADC (blue voxels) within each of the monitored tumors are evident in the fDM color overlays (Fig. (5)). The percent change in mean ADC using whole tumor volume statistic (i.e. histogram analysis) were compared with the tumor volume fraction with increased ADC changes quantified using voxel-by-voxel analysis (i.e. fDM). This analysis revealed that fDM offered improved sensitivity over the histogram-based approach when tumors have heterogeneous changes over time. The fDM changes were also found to correlate with changes in patient's prostate-specific antigen (PSA) levels, which is suggestive of patient response. In contrast, CT, bone scans, and anatomic MRI images obtained post-treatment were not useful for the assessment of treatment efficacy. This study presents the feasibility of applying the fDM approach in osseous lesions following treatment and provides intriguing data warranting further investigation of fDM as a quantitative imaging biomarker of response in patients with metastatic bone cancer.

Summary

Overall, each of the studies reviewed have presented data which independently supports the concept of DW-MRI as an early surrogate biomarker for tumor response. In a growing body of work, every one of these studies has shown that changes in tumor diffusion values correlated with response to therapy. This is quite remarkable considering the different tumor

types, tumor sites, MRI manufacturers, institutions and analysis approaches reportedly used in these studies.

In general, tumor ADC tended to increase following a successful intervention. Although this trend appears to be the norm there have been cases where a decrease, rather than an increase, in ADC measurements were reported to correlate with positive response [36-39]. The tumor mass may respond dynamically over the course of therapy. Consequently, timing of the acquired DW-MRI measurement may impact the finding of the study. For example, two studies that investigated the efficacy of DW-MRI on treated rectal cancer [37-38] in fact showed a brief, transient increase in ADC in the first week post-treatment initiation. Subsequently, a decrease in ADC was observed over the next several weeks. Histology confirmed that chemoradiation of rectal carcinoma resulted in increased interstitial fibrosis which may have an effect of reducing ADC values in those tumor regions[37]. The authors had also drawn attention that regions of obvious necrosis as observed by MRI within the tumor mass were not included in the volume of interest prescribed over the tumor mass. Omission of the necrotic regions would bias the measurement to lower ADC values. Therefore, the reported decreased ADC values that correlated with response appear to be primarily related to the timing of the measurement as well as fibrotic formation following tumor cell death.

Presently, clinical cancer studies on the efficacy of DW-MRI as a surrogate imaging biomarker of tumor treatment response demonstrate that treatment-induced cell death can be detected in responding tumors as an increased ADC value in those regions. Due to variability in DW-MRI acquisition and analytical post-processing protocols, efforts have been made to reach a consensus to provide for standardization across institutions [40]. These standards are needed for data acquisition, post-image processing, timing of evaluation, and the method used to generate the quantifiable metric used to report treatment response. Validation of DW-MRI as a surrogate imaging biomarker of response will require a large, prospective, multi-institutional trial that is performed in a standardized fashion between sites. Future opportunities in employing DW-MRI in the clinical management of cancer patients may include adapting chemo and radiotherapy protocols based on intra-therapy evaluation of early ADC changes allowing for alteration of agents or doses or for quantifying multi-focal disease response using whole-body DWI techniques [41].

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Figure 1.

A schematic of the change in cellularity (left) and increased molecular water mobility measured as an apparent diffusion coefficient (ADC; right) as a tumor responds to treatment (top to bottom). For a tumor responding to therapy, an increase in extracellular space/membrane permeability allows greater water mobility and an increase in the ADC. (Reprint from Ref. [12] with permission from Journal of Clinical Oncology)

Figure 2.

Pictorial description of the functional diffusion map (fDM) analytical process. DW-MRI data undergo digital image postprocessing and analysis that involves coregistration of images before and during treatment. Data are used to generate a three-color overlay representing regions in which tumor ADC values are unchanged (green voxels), significantly increased (red voxels), or significantly decreased (blue voxels). This data can also be presented in a scatter plot and percentages assigned to the three defined ADC regions, allowing quantitative assessment of overall changes in tumor ADC values. (Reprint from Ref. [17] with permission from PNAS)

Figure 3.

Representative functional diffusion map (fDM) analysis over time. Functional diffusion maps at 1, 3, and 10 weeks for two patients treated with fractionated radiation therapy. The patient on the left was scored as responsive by fDM at 3 weeks but progressive disease by radiologic response at week 10 and had overall survival (OS) of more than 33 months. The patient on the right was scored as nonresponsive by fDM at 3 weeks but stable disease by Macdonald criteria and OS of 7 months. Depicted images are single slices of the T1 postcontrast scans at each time point with a pseudocolor overlay of the fDM. Red voxels indicate regions with a significant rise in apparent diffusion coefficient (ADC) at each time point compared with pretreatment, green regions had unchanged ADC, and blue voxels indicate areas of significant decline in ADC. The scatter plots display data for the entire tumor volume and not just for the depicted slice at each time point, with the pretreatment ADC on the *x*-axis and post-treatment ADC on the *y*-axis. The central red line represents unity, and the flanking blue lines represent the 95% CIs.

(Reprint from Ref. [30] with permission from Journal of Clinical Oncology)

Figure 4.

Representative slices of fDM for patients whose conditions were diagnosed as (A) CR and (B) PR; color-coded VOIs are overlaid on contrast-enhanced T1-weighted MR images before therapy and corresponding scatter plots for quantification and distribution of ADC before and 3 weeks after treatment initiation for the entire tumor volume. Unity and threshold designating significant change in ADC within the scatter plot are presented by red and black lines, respectively. Voxels with significant increased, decreased, or unchanged ADC values were assigned as red, blue, and green, respectively. (Reprint from Ref. [33] with permission from Translational Oncology)

Figure 5.

Regional changes of ADC generated from fDM analysis are plotted on the image to provide a visual representation of areas with increased ADC (red voxels), decreased ADC (blue voxels), and areas where ADC did not change significantly (green voxels).

fDM analysis of the femoral head lesion at (A) 2 and (B) 8 weeks after treatment initiation revealed distinct regions of red voxels signifying areas with significant increases in ADC ($>26 \times 10^5 \text{ mm}^2/\text{s}$). fDM analysis of the sacral lesion at (C) 2 and (D) 8 weeks after treatment revealed significant regions of increased ADC as depicted by the red voxels. fDM analysis of the ilium lesion at (E) 2 and (F) 8 weeks after treatment show large regions of increased ADC values (red voxels). (Reprint from Ref. [35] with permission from Neoplasia)