© 2017 IJSRSET | Volume 3 | Issue 5 | Print ISSN: 2395-1990 | Online ISSN : 2394-4099
Themed Section: Engineering and Technology

Diffusion-Weighted Magnetic Resonance Imaging Procedure as a Cancer Diagnosis Application Tool

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ABSTRACT

Physical imaging technique described as Diffusion Weighted-Magnetic Resonance Imaging (DW-MRI) is based on classically principle of Brownian motion, where the molecules are thermal agitated and is highly influenced by the cellular availability of water. The aim of this study is to discuss the use of DW-MRI as a cancer diagnostic application tool using the basic physics principles as versus other available procedures and modalities in terms of accuracy and acceptability. Based on extravascular diffusion measurements where the measured signal is related to tissue cellularity, tissue organization and extracellular space tortuosity and on the intactness of cellular membranes that are intrinsically hydrophobic. The methodology involve the application of DW-MRI procedure, to qualitatively and quantitatively access DW-MR images to diagnose brain tumors, prostate and other organ cancers compared to other imaging modalities including other MRI procedures. It also include safety assessment and other consideration before, during and after imaging with MRI as compare to other radiological modalities. The results of the data of ten (10) MRI centers and 112 DW-MRI images and 99 other procedure and modalities were analysed, 34% were prostate cases, 27% were brain cases and 39% formed all other cases. In addition, DW-MRI compare to other single imaging procedure formed 53% of all diagnostic procedure that had 87% accurate predictability of prostate and brain cases. It can therefore concluded that DW-MRI is the best single imaging procedure that can be used to diagnose prostate cancers and brain tumors. It has a major advantage of non-ionizing radiation technique, with multiple planes image acquisitions, together with superior soft tissue contrast. In addition its perfusion allow for precise tissue characterization rather than merely 'macroscopic' imaging and superior visualization of both active parts of the brain during certain activities and understanding of the underlying networks. However, there are two outstanding challenges of DW-MRI scans in Ghana: it is expensive as compared to other modalities and not safe for patients with some metal implants. Despite these challenges, its advantages override its disadvantages and therefore it is recommended to clinicians as the first diagnostic tool to use in prostate cancer and brain tumor diagnoses.

Keyword : DW-MRI, Water Diffusion, Hydroscopic, Visualization, Brain Tumor, Prostate Cancer

I. INTRODUCTION

Magnetic Resonance Imaging (MRI) scanner consists of a large, powerful magnet in which the patient lies, which are connected to a radio wave antenna in order to send signals to the body and then receive signals back. These returning signals are converted into images by a computer algorithms attached to the scanner. Imaging of almost any part of your body can be obtained in multiple planes (Axial, Sagittal, Coronal, or Oblique) without repositioning the patient. In addition, it enable naturally occurring molecule, gene or characteristics by which a particular pathological processes or diseases to be identified. These are described as biomarkers and it's

classified as an important tools for the detection and characterization of cancers as well as for monitoring the response of its treatment [1]. With rapid technological developments, various techniques using MRI has been developed, these techniques and its methods appear rapidly and their utility requires systematic evaluation. One such unique technique of MRI is the physical imaging technique described as Diffusion-weighted magnetic resonance imaging (DW-MRI) depends on the microscopic mobility of water. Otherwise refers to as diffusion weighted imaging (DWI). DWI is a form of MR imaging based upon measuring the random motion of water molecules within a voxel of tissue. This technique depends on the mobility of water, which classically is based on the principle of Brownian motion. Basically, the water molecules are thermally agitated and highly influenced by the cellular availability of water molecules. Thus, findings on DW-MRI could be an early harbinger of biologic abnormality. For instance, the most established clinical indication for DW-MRI is the assessment of cerebral ischemia where DW-MRI findings precede all other MR techniques [2].

In oncologic imaging, several imaging modalities are available in diagnosing abnormal growth of cells or lesion and tumor response for therapeutic use, including the use of various techniques in Mammography, CT, conventional angiography and other MRI techniques. However, DW-MRI technique has been linked to lesion aggressiveness and tumor response, even though there is still no common grounds of its biophysical basis for its technique among researchers and clinicians partly due to understanding and hence acceptability [3].

In addition the fundamental bases that explained tissue diffusivity measurements are not always random due to tissue organization and therefore, have components that can be attributed both to the vascular and the extravascular compartments [4]. The tissue weighting technique is imparted by the experimental conditions used in measuring a quantity refers to as the b-values. The b-value is a factor that reflects the strength and timing of the gradients used to generate diffusion-weighted images. The higher the b-value, the stronger the diffusion effects. Classically, the low b-values of diffusion found in most tumors have been attributed to their increased cellular density; however, this remains a point of contention because diffusivity is influenced by extracellular fibrosis, the shape and size of the intercellular spaces, and by other microscopic tissue/tumor organizational characteristics such as glandular formations. Essentially, the imaging process is broken down into four parts: the Preparation, the Excitation, the Spatial Encoding and finally the Signal Acquisition [5].

II. OBJECTIVES

The aim of this study is to discuss the use of DW-MRI as a cancer diagnostic application tool from the basic principle of physics as against other available procedures and modalities in terms of accuracy and acceptability. This is focused on extravascular diffusion measurements where the measured signal is related to tissue cellularity, tissue organization and extracellular space tortuosity, and on the intactness of cellular membranes that are intrinsically hydrophobic. Based on which DW-MRI can be used to diagnose most cancers including prostate cancer and brain tumor [6].

III. LITERATURE

Several MRI techniques are available including; Diffusion-weighted MRI, Magnetic resonance angiography, Magnetic resonance spectroscopy, Functional MRI, Real-time MRI, Interventional MRI, and Magnetic resonance guided focused ultrasound. Of all this techniques DW-MRI, is one advance MRI technique for prostate cancer and brain tumor diagnostics study. DW-MR imaging is based on diffusion of water molecule between cells. However, the diffusion through the cells is hindered in a voxel of body tissue primarily by cell membrane boundaries which occurred in three compartments; including:

- Diffusion within the cytoplasm and organelles described as intercellular fluid diffusion
- Diffusion within the interstitial fluid, intravascular, lymphatic and various biological cavities, including ventricles of the brain generally referred to as extracellular fluid
- Finally diffusion between intracellular and extracellular compartments

In addition, the overall contribution of these three forms of compartmental diffusion of each one of these will depend on the tissue and the pathology. For instance, in an acute cerebral infarction it is believed that the decrease in **apparent diffusion coefficient** (ADC) values is the result of a combination of water moving

into the intracellular compartment, where the diffusion is impeded by organelles than it is in the extracellular space) and the resulting cellular swelling narrowing the extracellular space. Similar mechanisms result in low ADC values in highly cellular tumors as shown in askin tumor and retinoblastoma and high grade gliomas.

Diffusion coefficients are measure to represent the averages of the entire voxel and of each direction of diffusion. Therefore the word apparent is used to describe the values that are calculated with these measured average quantities. The signal of a particular tissue decreases exponentially with increasing b-value. Given an apparent diffusion coefficient D, the signal intensity I as:

$$I = I_0 * e^{-b * D} \quad (1)$$

where I_0 is the initial intensity.
Clinical application of DW-MRI involve three physical bases including;

- The DW-MRI technique is thermally driven of water molecules, which in vivo is impeded by cellular packing, intracellular elements, membranes, and macromolecules. In other words, DW-MRI provides insights to cellular architecture at the millimeter scale.
- Sensitivity to diffusion-based contrast is primarily controlled by the b value with the appropriate b-value range dependent on tissue diffusion properties, signal to noise ratio (SNR) and the need to suppress perfusion effects effectively at low b values.
- Tissues are known to exhibit Multiexponential signal decay over a broad range of b values, indicating the need for a better understanding to elucidate the fundamental biophysical properties of water movement within the cellular matrix.

To clearly understand the process and procedure in DW-MRI basic operation several factors including **ADC and** the b-value measurements must be understood.

The ADC is a measure of the magnitude of diffusion of water molecules within tissue and is commonly clinically calculated using MRI with diffusion weighted and b-value measures the degree of diffusion weighting application, thereby indicating the amplitude (G), time of applied gradients (δ) and duration between the paired gradients (Δ) and is calculated as:

$$b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3) \quad (2)$$

The term "b-value" derives from the landmark 1965 paper by Stejskal and Tanner in which they described their pulsed gradient diffusion method. This technique still forms the basis for most modern DWI pulse sequences and consists of two strong gradient pulses of magnitude (G) and duration (δ), separated by time interval (Δ). The formula for b, specific to this particular implementation only, is shown in figure 1.

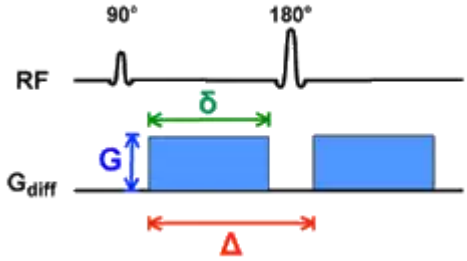

Figure 1: Stejskal-Tanner pulsed method.

During DW-MR imaging, a larger b-value is achieved by increasing the gradient amplitude, the duration and by widening the interval between paired gradient pulses. In other words increase in G, **δ** or **Δ** will increase the b-value as shown in equation 2. To sense slow moving water molecules and smaller diffusion distances, b-values 500 s/mm^2 or higher should be used. While apparent diffusion coefficient is calculated using a range of b-values between 0-1000 s/mm^2. These variations are shown in figure 2. The measurements of ADC from low group to high group are shown n figure 3.

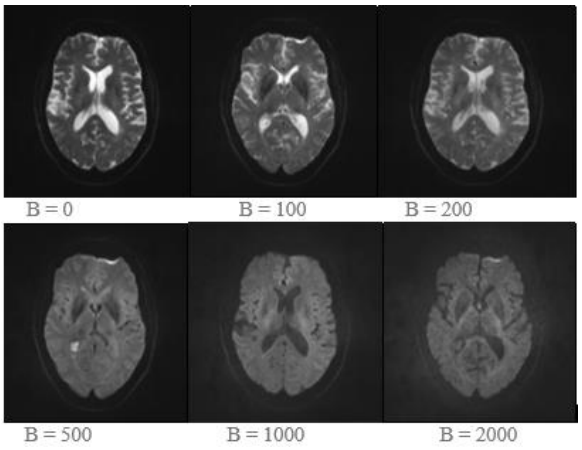

Figure 2 : Variation of b-value from 0-2000

It is extremely important and useful to apply the rule of thumb so as to choose the b value such that;

$$b * ADC \approx 1. \quad (3)$$

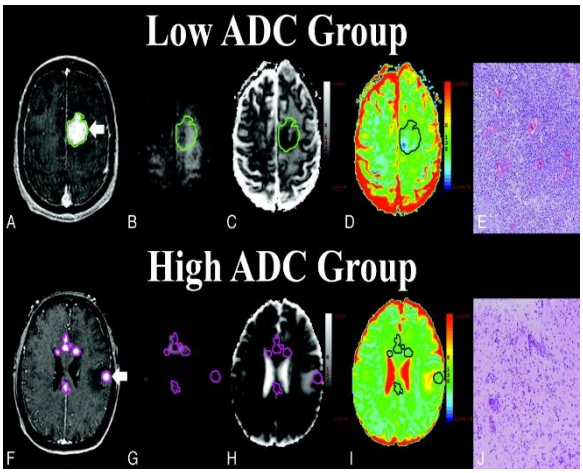

Figure 3. Low and High ADC groupings

The notion of using low or high b-values is relative and dependent on the tissue being studied and the ability to maximize or minimize diffusion contrast using SNR.

For instance in blood flow signal, which attenuate rapidly at low b-values between b-value of 100 and 150 sec/mm^2 and may be mistakenly attributed to diffusion. This is refer to as intravoxel incoherent motion (IVIM) phenomena, which are normally used to assess tissue perfusion [5]. Higher minimum b-values are required to suppress the perfusion in vascular-rich tissues, indicating that appropriate minimum b values may vary across applications depending on intrinsic vascularity. Even after elimination of perfusion effects, tissues are known to exhibit multiexponential signal decay.

Furthermore, very high b values between 1000 to 5000 sec/mm^2 are required to reliable quantify the biexponential decay constants, "Dfast" and "Dslow" [10, 11]. Alternatively, nonmonoexpential decay behavior may be fit to a stretched exponential model that yields a distributed diffusion coefficient and an index representing degree of intravoxel diffusion heterogeneity [12].

IV. MATERIALS

MRI modality is a fairly new imaging procedure in Ghana. DW-MRI are used for brain and prostate cases with varied acquisition techniques either with 1.5T or 3.0T field strength.

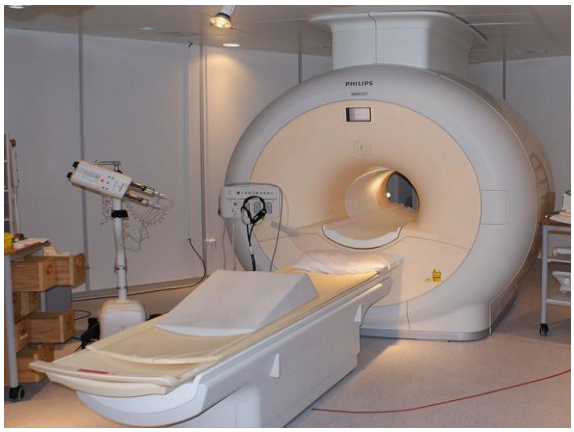

Figure 3: MRI machine

V. METHODOLOGY

The DW-MRI data acquisition techniques were done using the double spin-echo planar image (EPI) at either 1.5T or 3.0T field strength in all the centers. **DWI Pulse Sequence** DWI sequences are spin echo sequences, with 90- and 180-degree pulses. (Newer ways of performing DWI are being developed, not all of which use spin echo sequences.) The diffusion gradients are turned on before and after the 180-degree pulse (they are thus both positive gradients because the 180 degree pulse serves to reverse the effect of the second pulse). DWI sequences need to be extremely fast in order to eliminate any motion within the body part - since the entire purpose of the DWI sequence is to measure infinitesimal movements of water molecules, our images will be completely destroyed by macroscopic motions. For a long time, the fastest sequence available was echo-planar imaging (EPI), and virtually all currently used DWI sequences use EPI [7].

MeVisLab Digital Imaging Communication in Medicine image (DICOM) application software was used to view the images for both qualitative and quantitative analysis. The b-values was synthetically generated based on back-calculated from ADC/b-values with less noise which was used to extrapolate very high b-value images. The ability to segment a threshold high b-value/ADC images and then to obtain ADC values from "threshold ROIs" using histograms were done [8].

The most valuable images that were used for interpretation are high b-value images and ADC maps, which were evaluated with morphologic imaging. The high b-value were display by inverted grayscale whiles conventional grayscale colour levels were used to display ADC.

Three steps were used to analyze high-b value images by fusion imaging techniques with MVL. MVL image visualization software application works in three steps including: Superimposition, Alignment, and Visualization.

To ensure high quality images for both qualitative and quantitative assessments. The following two scanning factors was optimized to maximize SNR estimation and ensure a reduce artifacts in terms of motion, incomplete fat suppression, residual eddy currents induced by diffusion gradients and EPI-related artifacts.

- For visual qualitative analysis, DW-MRI was performed using appropriate b values, which result in sufficient background suppression to allow signal intensity differences in target tissues to be observed.
- For ADC quantification of a target tissue or lesion, two range of b values were used. The first set being values of greater than 100 sec/mm^2 and the second set being greater than 500 but less than 1000 sec/mm^2 with a monoexponential decay.

DW-MRI for Qualitative Assessment

To achieve the desire results of maximum tumor visualization and characterization, adequate suppression of background signals arising from normal tissue were done. These were performed with sufficient degrees of diffusion weighting by appropriate choices of b values, with considerations given for the anatomic region, tissue composition, and pathologic processes. This require the customization of DW-MRI protocols for different tumor types and tumor locations.

Both native high b value DW-MR images and the ADC maps were useful for qualitative visual assessments of DW-MRI data; both were evaluated with corresponding morphologic images.

DW-MRI for ADC Quantification

Meaningful comparisons of DW-MRI from different imaging centers with data acquired from different platforms were used to quantify DW-MR images. In addition, apparent diffusion coefficient quantification obtained using breath-hold DW-MRI is less reproducible compared with ADC obtained using free breathing techniques. However, ADC values obtained using free breathing techniques mask tissue heterogeneity owing to partial volume averaging effects. The relative balance between these two trends vary in different parts of the body thereby necessitating the different approaches.

Regions of Interest

To study diffusion properties of tumor, proper delineation of lesion boundaries are identified for subsequent quantification. The region of interest (ROI) were contoured around lesions using images with the highest contrast between lesion and normal tissue. In some instances, the DW images themselves offered strong lesion/tissue contrast, in which case these are sufficient for ROI definition.

The radiologist were made to choose which b-value image best delineates tumor from normal tissue/necrotic tissues. In cases where the ROIs were drawn on high-b value images for the estimation of ADC values, such ROIs were said to represent viable tumor because the detrimental effects of necrosis were ameliorated.
In the ADC calculation methods described, low SNR pixel values were eliminated before the ADC map calculation. The entire three-dimensional volume of interest (VOI), a composite of ROIs over multiple slices, of the lesion were delineated.

VI. DISCUSSIONS AND ANALYSIS

Table 1: Summary of data

Procedure	Brain	Prostate	Others	Total
DW-MRI	38	30	44	112
Others	35	28	36	99
Total	73	58	80	211

The diagnostic request by referring physicians and the diagnostic report of ten (10) radiologist were analysed as presented in Table 1. The results of the data of ten (10) MRI centers, 112 DW-MRI and 99 images of other procedures and modalities were analysed, of which 34% were prostate cases, 27% were brain tumors cases and 39% form the remaining other procedures and modalities. In addition, DW-MRI as compare to all other single imaging procedure form 53% of all diagnostic procedure analysed with 47% being all other procedure in cancer diagnostics. It had 87% accurate predictability of prostate and brain tumor. While others

modalities had an average accurate predictability of 48.5% (35%-62%) in prostate and brain tumor cases. It is of interest to state that other modalities and procedures outside brain and prostate tumor assessment where as high as 71% accurate predictability. These are summarized in Table 1. The qualitative and quantitative access of DW-MR images to diagnose brain tumors, prostate and other organ cancers were compared to other imaging modalities using the b-value and ADC in terms of SNR analysis.

Multiple b values are necessary to calculate the ADC. At least two b values were used for ADC calculations. The minimum and lower b value of 100 to 150 sec/mm^2 were used as a threshold to suppress perfusion effects depend on the vascular properties of tissues.

Furthermore, in applications where DW-MRI were acquired over larger ranges of diffusion sensitivities, its assuming perfusion effects were effectively removed by the proper choice of the lower b value. Usually, evidence of true multiexponential features (not related to perfusion effects) requires substantially higher b values (e.g., 2000–6000 sec/mm^2), much greater than is typically acquired in clinical studies owing to practical SNR limitations. Proper analysis of these data types requires multiexponential models where signal decays are modeled as weighted sums of two or more exponentials (provided that the signals at the highest b value are above the noise level) [11, 12] or alternative models such as stretched exponentials that allow a distribution of diffusion coefficients in each voxel [13]. As with other curve fitting challenges, reliability to accurately isolate multiple decay coefficients depends on the difference between the true Dfast and Dslow, SNR, b-value range, and number of b values acquired. Rejection of low SNR pixels and/or incorporation of SNR weights in the Multiexponential fitting routine should be used to mitigate fitting errors. An unfortunate tradeoff in acquisition of DW-MRI over many b values and/or averaging to increase SNR to support Multiexponential diffusion analysis is the commensurate increases in scan times which are not practical here.

Diffusion in some tissues is known to be directionally dependent, that is, anisotropic (e.g., in the central nervous system and in muscle). If it is known that the tissue of interest is isotropic (e.g., most tumor models) then a single gradient direction is sufficient to properly document diffusion properties. In general, however, it is safer to assume the lesion of interest and its surrounding tissues may have directional dependencies so it is best to measure water mobility along at least three orthogonal diffusion gradient directions yielding, say, ADCx, ADCy, and ADCz. The simple average of these into a mean diffusivity value effectively removes confounding influences of the relative orientation between tissue and the imaging system. This mean diffusivity bears the same desirable rotational independence as the trace of the full diffusion tensor without having to acquire or process DTI [11].

If further information is specifically desired regarding the strength and spatial patterns of anisotropy, at least six gradient directions are required to generate the full diffusion tensor, although additional gradient directions generally improve the quality of the tensor analysis results.

In conclusion, the study revealed that DW-MRI is commonly used for the following clinical indications: DW imaging has a major role in: early identification of ischemic stroke, differentiation of acute from chronic stroke, differentiation of acute stroke from other stroke mimics, differentiation of epidermoid cyst from arachnoid cyst, differentiation of abscess from necrotic tumors, assessment of cortical lesions in CJD, differentiation of herpes encephalitis from diffuse temporal gliomas, assessment of the extent of diffuse axonal injury, grading of gliomas and meningiomas (may require further study) and assessment of active demyelination. In data profiling based upon white matter tract orientation **diffusion tensor imaging, which** is an extension of diffusion weighted imaging (DWI) are used. DWI is based on the measurement of Brownian motion of water molecules. This motion is restricted by membranous boundaries. In white matter, diffusion follows the 'pathway of least resistance' along the white matter tract; this direction of maximum diffusivity along the white-matter fibers is projected into the final image. DWI are used to assess the deformation of white matter by tumors - deviation, infiltration, destruction of white matter, delineate the anatomy of immature brains, pre-surgical planning, Alzheimer disease - detection of early disease and schizophrenia.

VII. CONCLUSIONS

Diffusion-weighted MRI is an attractive noninvasive, quantitative technique that yields parameters that relate to tissue structure, cellularity, and necrosis. The plethora of existing methods in the current literature makes it impossible to conclude definitively that DW-MRI is qualified as a good diagnostic tool to enable a diagnostic decision. In addition, it is a good tool to monitor therapy response. DW-MRI give a clear precise clinical superiority in all cancer types and on the timing of imaging to address and answer clinical questions. It is established that data acquisition and analysis methods that yield water diffusion biomarkers, on calibration tools, and statistical methods for analyzing data is good enough to use.

The use of DW-MRI significantly improved the accuracy of tumor detection than what is achieve in other modalities. Although this task is complex, the potential benefits are enormous given the ease with which DW-MRI data can be incorporated for clinical application. It's therefore concluded that DW-MRI is the best single imaging procedure that can best be used to diagnose prostate cancers and brain tumor.

CHALLENGES

- Divergence among and between vendors on data measurements and analysis in addition to lack of transparency on how measurements are made
- As at now there is no accepted standards for measurements and analysis of data in DW-MRI.
- Multiple data acquisition protocols depending on body part and usage of data.
- There is high disagreement in the method for qualitative and quantitative assessments images.
- Lack of understanding of DW-MRI at a microscopic level
- Multiexponential decay components which affect the calculated ADC values
- Incomplete validation and documentation of reproducibility
- Divergent nomenclature and symbols
- Lack of multicenter working methodologies, accepted quality assurance (QA) standards, and physiologically realistic phantoms

VIII. RECOMMENDATIONS

- There is need to identify the best phantom materials to specify clearly QA procedures that can be used for SNR measurements. Improved phantoms mimicking the cellular environment of living tissue are required. Simple phantoms filled with liquids with different diffusion coefficients measure diffusion coefficients and ADC. Phantoms filled with beads of well-controlled size may help to understand the properties of diffusion of extracellular water, if susceptibility effects are negligible.
- It is recognized that improvements in SNR afforded by 3-T systems could be a boost for DW-MRI. It is accepted that diffusivity is likely to be independent of field strength; however, the effect of high field strengths on data acquisitions and analyses still needs to be systematically evaluated.

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