DIAGNOSTIC ACCURACY OF DIFFUSION TENSOR MAGNETIC RESONANCE IMAGING IN DIFFERENTIATING BETWEEN HIGH-GRADE AND LOW-GRADE PARTIAL ANTERIOR CRUCIATE LIGAMENT TEAR

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LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

3D	Three-dimensional
ACL	Anterior cruciate ligament
MRI	Magnetic resonance imaging
DWI	Diffusion weighted imaging
DTI	Diffusion tensor imaging
DTT	Diffusion tensor tractography
FA	Fractional anisotropy
ADC	Apparent diffusion coefficient
AD	Axial diffusivity
RD	Radial diffusivity
ROI	Region of interest
EPI	Echo Planar imaging
SENSE	Sensitivity-encoding
FOV	Field of view
TR	Repetition time
TE	Echo time
T1W	T1-weighted
T2W	T2-weighted
PDW	Proton density-weighted
SPAIR	Spectral attenuated inversion recovery
SPIR	Spectral presaturation with inversion recovery
STIR	Short tau inversion recovery
HUSM	Hospital Universiti Sains Malaysia

PACS	Picture archiving and communication system
RIS	Radiology information system
IBM	International Business Machines
SPSS	Statistical Product and Service Solutions
SD	Standard deviation
ROC	Receiver operating characteristics
AUROC	Area under receiver operating characteristics curve
AUC	Area under curve
ANOVA	Analysis of Variance
PPV	Positive predictive value
NPV	Negative predictive value
CD	Compact disc

Ketepatan Diagnostik Pengimejan Resonans Magnetik (MRI) dan Pengimejan Tensor Resapan (DTI) dalam Membezakan Antara Kecederaan Ligamen Silang Hadapan (ACL) Gred Tinggi dan Gred Rendah

ABSTRAK

Pengenalan: Ligamen silang hadapan (ACL) merupakan kecederaan ligamen lutut yang paling biasa ditemui dalam amalan harian bidang radiologi dan ortopedik. Tahap kecederaan ACL yang dikenalpasti melalui Pengimejan Resonans Magnetik (MRI) boleh dibahagikan kepada normal, koyakan separa atau koyakan lengkap. Koyakan separa ACL seharusnya dibahagikan lagi kepada koyakan separa gred tinggi dan gred rendah, untuk tujuan memberikan maklumat penting tentang keperluan pembedahan ACL. Pengimejan tensor resapan (DTI) dengan traktografi merupakan teknik baharu yang boleh digunakan untuk penilaian kuantitatif dan kualitatif dalam membezakan koyakan ACL separa gred tinggi dan gred rendah serta menilai tahap kecederaan ACL secara menyeluruh.

Kaedah Kajian: Sejumlah 260 pesakit berumur 16 hingga 45 tahun yang disyaki mengalami kecederaan ACL telah dimasukkan dalam kajian ini, termasuk kumpulan kajian 96 pesakit yang menjalani pemeriksaan lutut MRI dengan menggunakan gabungan teknik DTI dan teknik konvensional, dan satu lagi kumpulan kawalan 164 pesakit yang menjalani pemeriksaan lutut MRI dengan hanya menggunakan teknik konvensional. Teknik DTI dilakukan dengan menggunakan nilai-b 0s/mm^2, 400 s/mm^2 dan 800s/mm^2, serta 32 arah penyebaran yang berbeza. Semasa pemprosesan pasca

kajian DTI, empat parameter kuantitatif diperoleh, iaitu anisotropi pecahan (FA), pekali resapan ketara (ADC), resapan paksi (AD) dan resapan jejari (RD). Di samping itu, trakografi diffusion tensor telah dihasilkan untuk penilaian kualitatif kecederaan ACL. Keputusan MRI terhadap tahap kecederaan ACL dibahagikan kepada 4 kumpulan (gred), termasuk tiada koyakan (gred 0), koyakan separa gred rendah (gred I), koyakan separa gred tinggi (gred II) dan koyakan penuh (gred III). Nilai potongan FA dan ADC yang digunakan dalam membezakan kecederaan ACL gred tinggi daripada gred rendah ialah ⩽0.348 dan ⩾2.400 x 10-3mm2/s, masing-masing. Gred kecederaan ACL yang dikenalpasti melalui MRI telah dibandingkan dengan keputusan arthroskopi, yang bertindak sebagai piawai rujukan diagnostik. Analisis statistik dilakukan untuk menilai dan membandingkan ketepatan diagnostik antara kumpulan kajian dan kumpulan kawalan.

Keputusan: Kumpulan kajian pesakit yang menjalani pemeriksaan lutut MRI dengan menggunakan gabungan teknik DTI dan teknik konvensional menunjukkan ketepatan diagnostik yang lebih tinggi dalam membezakan koyakan ACL separa gred tinggi dan gred rendah (kadar ketepatan 86.4% dan 82.4% masing-masing); berbanding kumpulan kawalan pesakit. yang menjalani pemeriksaan lutut MRI dengan hanya menggunakan teknik konvensional untuk membezakan koyakan ACL separa gred tinggi dan gred rendah (kadar ketepatan 70.6% dan 68.4% masing-masing). Nilai FA berkorelasi negatif dengan tahap kecederaan ACL (r=-0.857, P<0.01) manakala nilai ADC, AD dan RD berkorelasi positif dengan tahap kecederaan ACL (r=0.899, P<0.01; r=0.689, P<0.01; dan r= 0.731, P<0.01 masing-masing).

Kesimpulan: DTI dengan traktografi dapat memberikan maklumat tambahan yang penting untuk penilaian kecederaan ACL secara kuantitatif dan kualitatif, serta meningkatkan ketepatan diagnostik. Oleh itu, teknik DTI seharusnya digunakan bersama dengan teknik konvensional dalam pemeriksaan MRI kecederaan lutut yang disyaki mengalami koyakan ACL.

Kata Kunci: pengimejan tensor resapan (DTI), traktografi tensor resapan (DTT), gred tahap kecederaan ligamen silang hadapan (ACL)

Diagnostic Accuracy of Diffusion Tensor Magnetic Resonance Imaging in Differentiating Between High-Grade and Low-Grade Partial Anterior Cruciate Ligament Tear

ABSTRACT

Introduction: Anterior cruciate ligament (ACL) tear is the most common knee ligament injury encountered in radiology and orthopedic practice. Magnetic Resonance Imaging (MRI) findings of ACL injury are categorized as intact, partial tear or complete tear. Partial ACL tear should be further classified into high-grade and low-grade partial tear, which provides useful information regarding the necessity of surgical reconstruction. Diffusion tensor imaging (DTI) with fiber tractography is a new technique which can be utilized for quantitative and qualitative assessment in differentiating high-grade and low-grade partial ACL tear as well as overall grading of ACL injury.

Methodology: A total of 260 patients aged 16 to 45 years old with suspected traumatic ACL injury were enrolled in this study, which include a study group of 96 patients who underwent MRI knee examination using combined DTI and conventional sequences, and another control group of 164 patients who underwent MRI knee examination using only conventional sequences. DTI sequence was performed using b-values of 0s/mm^2 400 s/mm^2 and 800s/mm^2, and 32 diffusion-encoding directions. During post-processing of DTI studies, four quantitative parameters were derived, namely fractional anisotropy (FA), apparent diffusion coefficient (ADC), axial diffusivity (AD) and radial diffusivity (RD). In addition, diffusion tensor tractography was generated for qualitative assessment of ACL injury. The MRI findings of ACL were categorized into

4 groups, which include intact (grade 0), low-grade partial tear (grade I), high-grade partial tear (grade II) and complete tear (grade III). The cut-off values of FA and ADC used in differentiating high-grade from low-grade ACL injuries are ≤0.348 and ≥2.400 x $10^{-3} mm^2/s$, respectively. The MRI grading of ACL injury was compared to arthroscopic findings as the diagnostic reference standard. Statistical analysis was performed to analyze and compare the diagnostic accuracy between the study group and the control group.

Results: The study group of patients who underwent MRI knee examination using combined DTI and conventional sequences demonstrated higher diagnostic accuracy in differentiating high-grade and low-grade partial ACL tear (86.4% sensitivity and 82.4% specificity) in comparison to the control group of patients who underwent MRI knee examination using only conventional sequences to differentiate high-grade and low-grade partial ACL tear (70.6% sensitivity and 68.4% specificity). FA values are negatively correlated with the severity of ACL injury ($r=-0.857$, $P<0.01$) while ADC, AD and RD values are positively correlated with the severity of ACL injury ($r=0.899$, $P<0.01$; $r=0.689$, $P<0.01$; and $r= 0.731$, $P<0.01$, respectively).

Conclusion: DTI with fiber tractography can provide useful additional information for both quantitative and qualitative assessment of ACL injury to improve diagnostic accuracy. Therefore, DTI sequence should be used in combination with conventional sequences in MRI examination of traumatic knee injury for suspected ACL tear.

Keywords: diffusion tensor imaging (DTI), diffusion tensor tractography (DTT), anterior cruciate ligament (ACL) injury grade

CHAPTER 1: BACKGROUND

1.1 Introduction

Anterior cruciate ligament (ACL) is one of the ligaments in the human knee, which consists of dense connective tissue. It originates from the medial side of the lateral femoral condyle and inserts at the medial tibial eminence. ACL is a key structure of the knee joint as it resists anterior tibial translation and rotational loads. ACL tear is the most common knee ligament injury encountered in radiology and orthopedic practice. ACL injury (including sprain, tear, and disruption) often results following traumatic knee injury, most commonly after sports activities, less commonly following road accidents or falls from height. The clinical assessment of ACL injury includes history taking, Lachman, pivot shift and anterior drawer tests.

In current radiological practice, magnetic resonance imaging (MRI) is the most widely used imaging modality to evaluate status of ACL injury. According to the published meta-analysis regarding MRI findings on ACL injury, the conclusions on ACL injury in previous publications are categorized as intact, partial tear or complete tear. However, not every patient who is diagnosed with partial ACL tear requires surgical reconstruction. The MRI diagnosis of partial ACL tear without quantitative assessment on severity, degree and stability of partial tear may lead to difficulty in decision making process among orthopedic surgeons regarding necessity of surgical reconstruction of ACL.

In current clinical practice, this decision (necessity of ACL surgical reconstruction in the case of MRI findings of partial ACL tear) is often based on clinical assessment of knee joint instability, patient's age and expected physical activities in the future. In order to provide useful information to orthopedic surgeons which assist in the decision on the necessity of ACL reconstruction, partial ACL tear can be categorized into high-grade partial tear and low-grade partial tear. High-grade partial ACL tears are defined as partial tears which are not stable and usually require surgical reconstruction. On the other hand, low-grade partial ACL tears are stable and generally does not require surgical reconstruction.

Currently, MRI knee examination in the evaluation of ACL injury is commonly performed using conventional sequences. These conventional sequences are generally similar with slight variation between different institutions and healthcare centers, which include proton-density weighted imaging, T2-weighted imaging, spectral attenuated inversion recovery (SPAIR), spectral presaturation with inversion recovery (SPIR) and short tau inversion recovery (STIR) (Li et al., 2017b). A few meta-analyses were performed to evaluate diagnostic accuracy of MRI in diagnosis of complete ACL tear using conventional sequences, with reported sensitivity and specificity range from 87% to 94% and from 90% to 95%, respectively (Li et al., 2017b; Phelan et al., 2016; Smith et al., 2012). The diagnostic accuracy of MRI in partial ACL tear is lower, with sensitivity ranges 40% to 75% and specificity ranges 62% to 89% (Smith et al., 2012). This leads to quantitative estimation of torn ACL fibers and differentiation between high-grade and low-grade partial ACL tears even more challenging for the radiologists.

Diffusion tensor imaging (DTI) with fiber tractography is a potential technique to provide additional information regarding laxity and integrity of ACL fibers as well as quantitative assessment of fiber disruption. DTI is a non-invasive MRI technique which is based on anisotropy in water molecules movement in human tissue. It can be used in quantitative characterization of heterogeneously oriented tissue through measurement of the following four parameters: fractional anisotropy (FA), apparent diffusion coefficient (ADC), axial diffusivity (AD) and radial diffusivity (RD).

Diffusion tensor tractography (DTT) can be reconstructed through post-processing mathematical algorithms of the diffusion tensors images. It is a useful technique which can be utilized to study and visualize the trajectories of fibers tracts of ACL in vivo.

The aim of this study is to determine whether DTI can be used to improve diagnostic accuracy of MRI in assessment of ACL injury as well as grading of partial ACL tear.

1.2 Objectives

1.2.1 General Objective

To study the diagnostic accuracy of conventional and DTI sequences of MRI knee examination in diagnosis of ACL injury.

1.2.2 Specific Objectives

1) To determine the diagnostic accuracy of conventional sequences of MRI knee examination in diagnosis of ACL injury using arthroscopy as the reference standard.

2) To determine the diagnostic accuracy of combined DTI and conventional sequences of MRI knee examination in diagnosis of ACL injury using arthroscopy as the reference standard.

3) To compare the mean values of DTI quantitative parameters (FA, ADC, AD and RD) between high-grade and low-grade ACL injuries based on arthroscopic results.

1.3 Research Questions and Hypothesis

Question 1:

What is the diagnostic accuracy of conventional sequences of MRI knee examination in differentiating between high-grade and low-grade partial ACL tear using arthroscopy as the reference standard?

Hypothesis:

The diagnostic accuracy of conventional sequences of MRI knee examination in differentiating between high-grade and low-grade partial ACL tear is expected to have a sensitivity ranges 40% to 75% and a specificity ranges 62% to 89% (based on the results in meta-analysis of the previous similar studies).

Question 2:

Can the diagnostic accuracy of MRI knee examination in differentiating between high-grade and low-grade partial ACL tear be improved by using combined DTI and conventional sequences (with arthroscopy as the reference standard)?

Hypothesis:

The diagnostic accuracy of MRI knee examination in differentiating between high-grade and low-grade partial ACL tear is higher by using combined DTI and conventional sequences, as compared to using conventional sequences only.

<u>Question 3:</u>

Is there any correlation between the DTI quantitative parameters, namely fractional anisotropy (FA), apparent diffusion coefficient (ADC), axial diffusivity (AD) and radial diffusivity (RD) with different grades of ACL injury?

Hypothesis:

The value of FA is negatively correlated with higher (more severe) grades of ACL injury while the values of ADC, AD and RD are positively correlated with higher (more severe) grades of ACL injury.

CHAPTER 2: LITERATURE REVIEW

2.1 Diffusion Tensor Imaging

2.1.1 Basic Principles

Diffusion tensor imaging (DTI) is an advanced MRI technique based on the water molecules diffusion in the tissues. The basic principle of water molecule diffusion was first introduced in the mid-1980s. Molecular diffusion refers to the random motion of molecules within human tissue, also called Brownian motion, driven by the thermal energy carried by these molecules (Figure 1). In a perfectly homogenous medium, the molecular diffusion is isotropic, which means equal probability of molecular movement in all directions. But in a complex environment of the human body, water molecules move on a small average distance, bouncing, crossing, or interacting with many different tissue components in the human body such as cell membranes, macromolecules or fibers (Le Bihan et al., 2001). This leads to water molecular diffusion having different probability in various directions, in a term coined as "anisotropy" (Figure 2) (Baliyan et al., 2016; O'Donnell and Westin, 2011).

In contrast to diffusion weighted imaging (DWI) which measures the movement of water molecule in one scalar direction, diffusion tensor imaging (DTI) utilizes the relationship between the movement of water molecules in different directions related to vector space using an algebraic object called tensor, hence the name diffusion tensor imaging (Huisman, 2010). The overall effects of the interaction between the moving water molecules and various tissues are observed in a voxel of several cubic millimeters. This observation provides information regarding the structure and geometry of the tissue or fibers (Le Bihan et al., 2001).

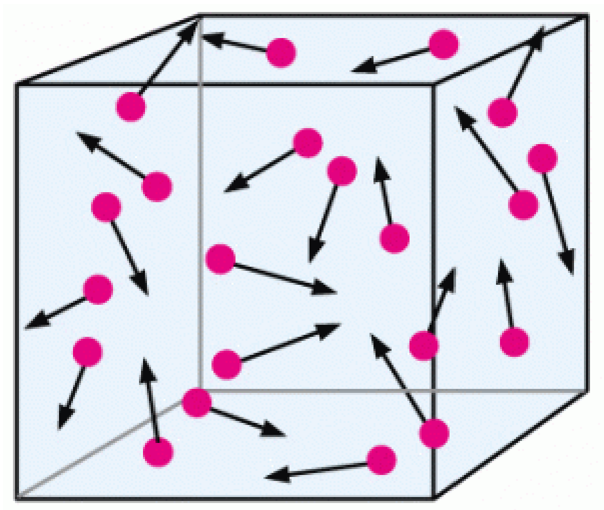

Figure 1 – A 3D model showing Brownian motion (random movement) of water molecules.

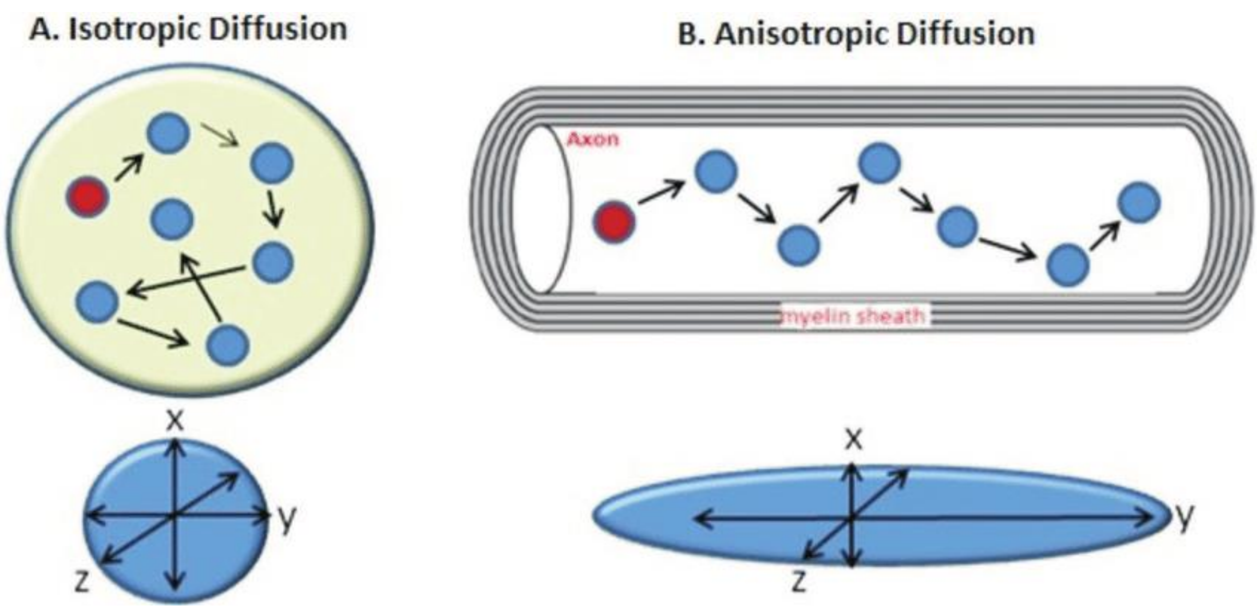

Figure 2 – Isotropic versus anisotropic diffusion. A – Isotropic diffusion is equal probability of water molecule movement in all directions. B – Anisotropic diffusion occurs due to different probability of water molecule movement in various directions.

2.1.2 Data Acquisition and Imaging Parameters

The diffusion tensor of tissue or fiber is considered as a three-dimensional structure with three principal diffusivities, which are known as eigenvalues, i.e., λ1, λ2, λ3. These eigenvalues are associated with three mutually perpendicular principal directions, which are termed as eigenvectors, i.e., *e1, e2, e2*. The tensor is represented by a 3×3 symmetric matrix, in the combination of the x-, y- and z-axis (Dxx, Dxy, Dxz, Dyx, Dyy, Dyz, Dzx, Dzy, Dzz) (Huisman, 2010). Since the tensor is a positive-definite matrix, this means that it has three orthogonal (mutually perpendicular) eigenvectors and three positive eigenvalues. The direction of the fastest diffusion determines the major eigenvector of the tensor (Figure 3) (O'Donnell and Westin, 2011).

Currently, single-shot echo planar imaging (EPI), is the most commonly used diffusion-sensitized MRI pulse sequence to measure the diffusion tensor, in view of short scanning time and reduced motion artifacts (Baliyan et al., 2016). The average diffusion or the degree of anisotropy in each voxel can be calculated using these imaging techniques. Subsequently, the major direction of diffusivities in each voxel and the associated diffusion values can be determined (Le Bihan et al., 2001).

On modern scanners, the typical scanning time is 5 minutes (in certain circumstances, up to 15 minutes time may be required, depending on the scanner and image acquisition parameters). High b-values in the range of 700-1000s/mm^2 (typically 1000s/mm^2) along at least 6 diffusion encoding directions with a T2-weighted image (b-value = 0 s/mm^2) are required to produce optimal DTI images. Other typical imaging parameters include slice thickness of 2-3mm, Field of View (FOV) of 256mm, acquisition matrix of 128x128, as well as Repetition Time (TR) of 8.5-12 seconds and Echo Time (TE) of 50-70ms (Soares et al., 2013).

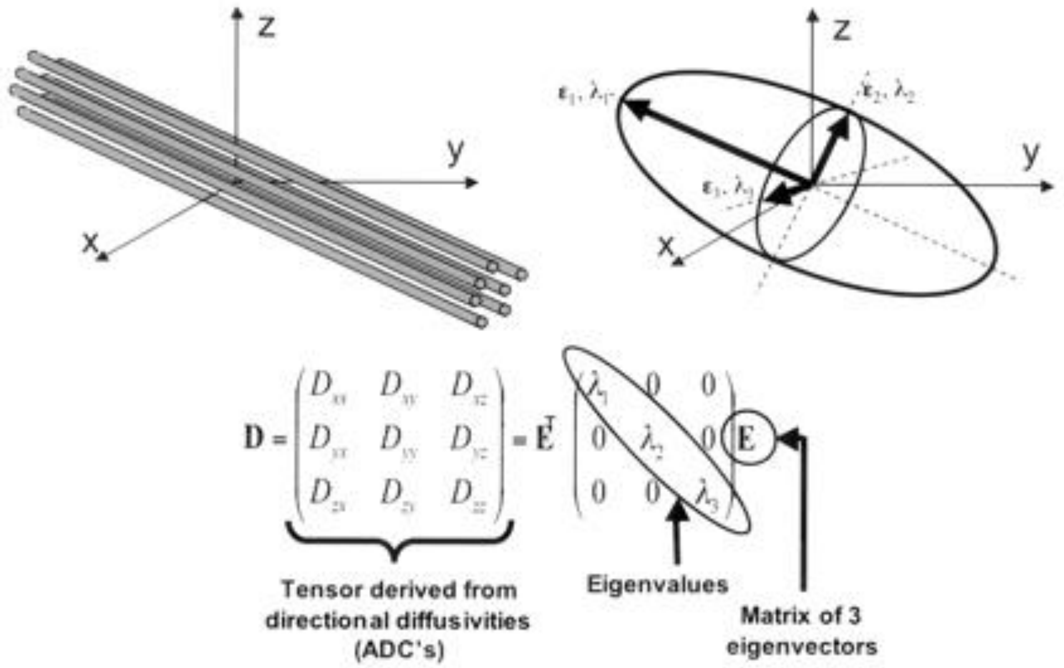

Figure 3 – Diffusion tensor model and image acquisition

Top left – Fiber tracts have an arbitrary orientation in relation to scanner geometry (x, y and z axes), which leads to directional dependence (anisotropy) on diffusion measurement

Top right – The three-dimensional diffusivity is modeled as an ellipsoid. The orientation of the model is characterized by three eigenvectors (*e1, e2, e2*) while the shape of the model is characterized by three eigenvalues (λ1, λ2, λ3)
Bottom – This ellipsoidal model is fitted into a set of at least six noncollinear diffusion measurements by solving a set of matrix equations. The major eigenvector (the eigenvector which is associated with the largest eigenvalue) reflects the direction of maximum diffusivity, which is the orientation of the fiber tracts.

2.1.3 Data Interpretation and Quantitative Parameters Derived From DTI

With DTI analysis and image interpretation, many diffusion properties in each voxel can be calculated. Through these calculations, there are four quantitative parameters that can be derived, namely mean diffusivity (MD), fractional anisotropy (FA), axial diffusivity (AD) and radial diffusivity (RD).

Mean diffusivity (MD) measures average molecular diffusion rate in all directions (higher value means higher diffusivity). In practice, it can be calculated by the mean of three eigenvalues (λ1, λ2, λ3). The sum of these eigenvalues is known as the *trace* of the tensor. The calculated mean diffusivity of each voxel can be presented as an apparent diffusion coefficient (ADC) map (Soares et al., 2013). This calculation can be expressed using the following formula:

$$MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} = \frac{D_{xx} + D_{yy} + D_{zz}}{3} = \frac{\text{Trace}}{3}$$

Where D_{xx}, D_{yy} and D_{zz} represent the diagonal terms of diffusion tensor.

Fractional anisotropy (FA) calculates the fraction of a tensor's magnitude due to anisotropic diffusion. This measurement is normalized and the calculated value ranges from 0 (isotropic diffusion) to 1 (anisotropic diffusion) (Soares et al., 2013). This measurement of anisotropy can be considered as the difference of a tensor's ellipsoid shape from a perfect sphere shape (O'Donnell and Westin, 2011). The following formula is used for the calculation of FA:

$$FA = \sqrt{\frac{3}{2}} \sqrt{\frac{(\lambda_1 - D)^2 + (\lambda_2 - D)^2 + (\lambda_3 - D)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

Where D is the mean diffusivity or (λ1 + λ2 + λ3)/3.

The three eigenvalues ($\lambda1$, $\lambda2$, $\lambda3$) of diffusivities can be delimited into parallel and perpendicular components, according to the diffusion direction with the fastest diffusion rate. Axial diffusivity (AD) measures parallel diffusivity, which is the magnitude of water molecular movement parallel to the tract of interest (O'Donnell and Westin, 2011; Wheeler-Kingshott and Cercignani, 2009; Winklewski et al., 2018). It is equal to the largest eigenvalue and can be expressed as the following:

$$\lambda_{\|} \equiv \lambda_1 > \lambda_2, \lambda_3$$

On the other hand, radial diffusivity (RD) calculates perpendicular diffusivity, which is the mean diffusion coefficient of water molecules perpendicular to the tract of interest (O'Donnell and Westin, 2011; Wheeler-Kingshott and Cercignani, 2009; Winklewski et al., 2018). It is equal to the mean of the two smaller eigenvalues and calculated using the following formula:

$$\lambda_{\perp} \equiv (\lambda_2 + \lambda_3)/2$$

The pathological process in human tissues (brain, tendon, ligaments, etc.) and the associated changes, including edema and inflammatory response, can affect the values of these quantitative parameters derived from DTI (Winklewski et al., 2018).

2.1.4 Diffusion Tensor Tractography

The calculated FA value which is derived from DTI interpretation is rotationally invariant, which provides no information regarding the direction and orientation of the diffusion. In order to represent the orientation of major eigenvectors, a color-coded FA map is used. The most commonly used color scheme works as follows: red color represents left-to-right direction, green color represents anterior-to-posterior direction and blue color represents superior-to-inferior direction (O'Donnell and Westin, 2011; Soares et al., 2013).

Glyphs are small three-dimensional (3D) graphical objects used to display a diffusion tensor through its location, size, shape and color (O'Donnell and Westin, 2011; Soares et al., 2013). Glyphs can provide useful 3D representation of an anatomical structure or tissue, as well as the information related to the pathological process.

Diffusion tensor tractography (DTT) refers to the technique used to study and visualize the trajectories of fibers tracts in human tissue (including white matter in the brain, axons in the nervous system, tendons and ligaments) in vivo through post-processing mathematical algorithms of the diffusion tensors images (Figure 4). Each tensor is represented by three eigenvectors both in direction and magnitude (Huisman, 2010).

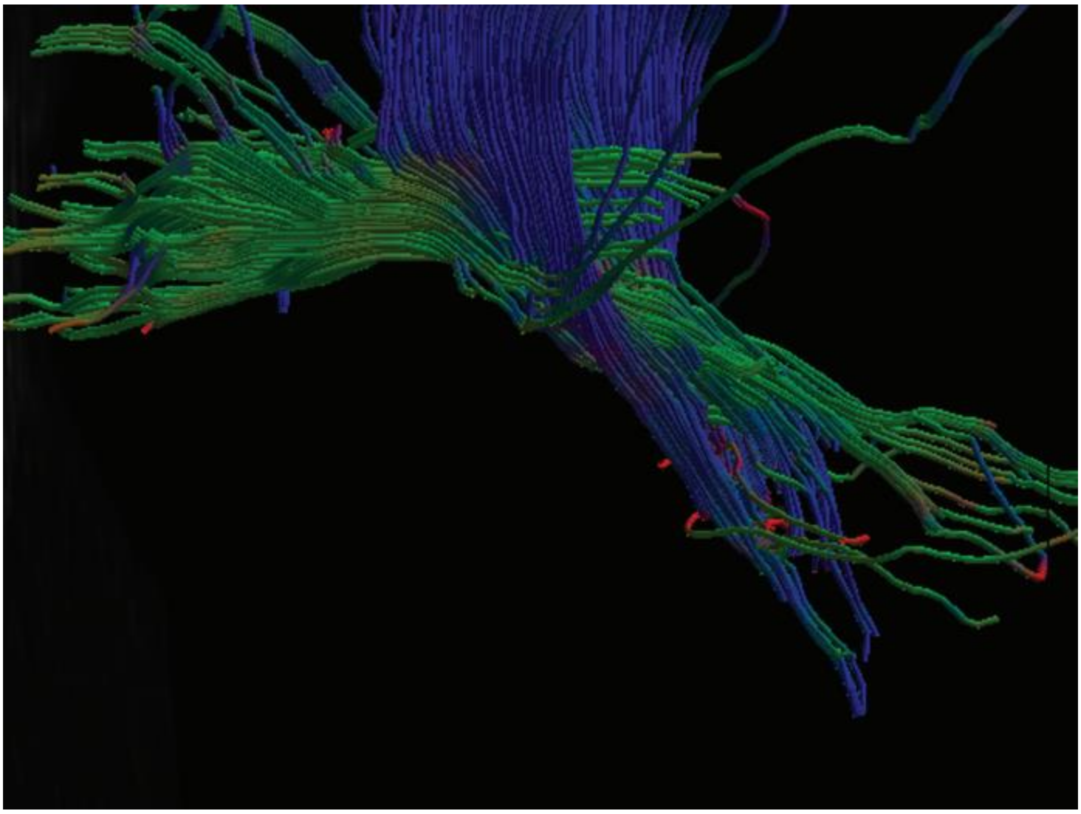

Figure 4 – Diffusion Tensor Tractography

The processing of tractography can be divided into three main stages, namely seeding, propagation and termination. Seeding is the process of specifying the points from which to draw the bundles of fibers, which can be done manually by identifying regions of interest (ROIs) or automatically by the post-processing software (Soares et al., 2013).

The fibers are produced progressively during the propagation stage. The last tractography step is the termination of the fiber tracking procedure based on termination criteria. These criteria are set up to avoid propagating the fibers in voxels where the robustness of the vectorial field is not guaranteed. The commonly used termination criteria are minimum FA thresholds and turning angle threshold (Soares et al., 2013). These termination criteria can be set up in the DTI fiber tractography software.

2.1.5 Clinical Application

Currently, the clinical application of DTI in diagnosing and assessing central nervous system pathology is well established. Advancements in DTI during the past two decades has led to its use to characterize the structural integrity of neural tissue and trace neuronal tracts in brain and spine non-invasively (Lerner et al., 2014).

One of the most successful applications of DWI/DTI is the early detection and diagnosis of acute brain ischemia. DWI/DTI can show tissue injury within 30 minutes after vessel occlusion, before any positive finding can be demonstrated using conventional T1 weighted and T2 weighted imaging (Baliyan et al., 2016; Huisman, 2010). The MD value first decreases in acute stroke, then renormalizes and subsequently increases. The FA value is reduced in acute stroke and remains low in chronic infarcts for up to 6 months (Tae et al., 2018; Trivedi et al., 2008).

In highly cellular brain tumors, such as high-grade glioma, medulloblastoma and lymphoma, MD value is markedly reduced. DTI is helpful for preoperative planning and intraoperative navigation to avoid injury of corticospinal tracts. Quantitative MD value can be used to predict therapeutic response of the tumors (Baliyan et al., 2016; Lerner et al., 2014).

DWI/DTI is particularly useful in the diagnosis of cerebral abscess, in which the MD value declines and FA value raises (Tae et al., 2018).

Other clinical applications of DWI/DTI in central nervous system include developmental disorders (such as heterotopia, callosal agenesis, cerebellar agenesis, polymicrogyria, etc.), HIV infection, amyotrophic lateral sclerosis, multiple sclerosis, neurodegenerative disorders, spinal cord injury, etc. (Tae et al., 2018; Trivedi et al., 2008).

Besides the central nervous system, diffusion anisotropy can also be observed in muscle fibers, tendons and ligaments. The implementation of DTI in the musculoskeletal system has increased in the past few decades. Water diffusion in the skeletal muscle prefers the direction along the longitudinal axis of the fiber rather than perpendicular to it, thus creating anisotropic properties. Muscles of the lower limb have been in-depth studied. The feasibility of in vivo DTI of human calf muscles also has been demonstrated (Khalil et al., 2010; Yanagisawa et al., 2009).

Recent studies have reported the feasibility of DTI in evaluation of the structural integrity of tendons and ligaments, as well as the degree of injury to these structures (Chianca et al., 2017; Guidetti et al., 2018; Wengler et al., 2018). The use of DTI in quantitative and qualitative assessment of ACL injury and its graft had also been studied and reported (Van Dyck et al., 2011; Yang et al., 2014).

2.2 Anterior Cruciate Ligament and Grading of Injury

Anterior cruciate ligament (ACL) is one of the ligaments in the human knee, which consists of dense connective tissue. It resists anterior tibial translation and rotational loads. ACL tear is the most common knee ligament injury encountered in radiology and orthopedic practice. The clinical assessment of ACL injury includes history taking, Lachman, pivot shift and anterior drawer tests (Kopkow et al., 2018).

According to the published meta-analysis regarding MRI findings on ACL injury, the conclusion on ACL injury in previous publications are categorized as intact, partial tear or complete tear (Phelan et al., 2016; Smith et al., 2012). In current clinical practice, this decision (necessity of ACL surgical reconstruction in the case of MRI findings of partial ACL tear) is often based on clinical assessment of knee joint instability, patient’s age and expected physical activities in the future (Paschos and Howell, 2016).

In order to provide useful information to orthopedic surgeons which assist in the decision on the necessity of ACL reconstruction, partial ACL tear can be further categorized into high-grade partial tear and low-grade partial tear. High-grade partial ACL tears are defined as partial tears which are not stable and usually require surgical reconstruction. On the other hand, low-grade partial ACL tears are stable and generally do not require surgical reconstruction.

To our knowledge, there is only one retrospective study that was performed to assess diagnostic efficacy of MRI in assessing the severity of ligament disruption in ACL partial tear using conventional sequences. In this study, the status of ACL injury is classified into 4 grades, namely, intact; low-grade partial tear; high-grade partial tear; and complete tear (Hong et al., 2003b).

2.3 Role of DTI in Grading of ACL Injury

Although the morphological features of ACL can be evaluated using conventional MRI sequences, only limited quantitative measurements are provided by this form of imaging (Yang et al., 2014).

A few meta-analyses were performed to evaluate diagnostic accuracy of MRI in diagnosis of complete ACL tear, with reported sensitivity and specificity range from 87% to 94% and from 90% to 95%, respectively. The diagnostic accuracy of MRI in partial ACL tear is lower, with sensitivity ranges from 40% to 75% and specificity ranges from 62% to 89% (Phelan et al., 2016; Smith et al., 2012). This indicates that quantitative estimation of torn ACL fibers and differentiation between high-grade and low-grade partial ACL tear can be very challenging for the radiologists.

DTI can be used to provide additional information regarding quantitative assessment and grading of ACL injury. For the purpose of ACL injury assessment, the results of DTI can be evaluated both qualitatively (visual assessment of the ligament fibers on post-processing tractography map) and quantitatively (using the values of parameters such as fractional anisotropy, mean diffusivity, axial diffusivity and radial diffusivity) (Chen et al., 2013; Liu et al., 2020; van Dyck et al., 2012).

Currently, there are a few published literature on studies of DTI on maturation and healing of ACL graft (Figure 5 and Figure 6) (Van Dyck et al., 2017; X. et al., 2015; Yang et al., 2014).

However, up to this date, the research on the usage of DTI in assessment of native ACL injury is very limited. As dated, there are 2 different published studies confirming the feasibility of DTI in evaluation of ACL by using post-processing fiber tractography map and parameters such as apparent diffusion coefficient (ADC) and fractional anisotropy (FA) values (Chen et al., 2013; Liu et al., 2020).

A study was performed by Liu et al., 2020, to investigate the role of DTI in quantitative assessment of ACL injury. The findings of this study demonstrated that FA values were negatively correlated with ACL injury grade ($r=-0.898$, $P<0.05$) while ADC values were positively correlated with ACL injury grade ($r=0.851$, $P<0.05$).

According to Liu et al., 2020, for differentiation between low-grade and high-grade ACL injury, the best cutoff threshold of FA value was 0.348 (95% CI, sensitivity 96.90%, specificity 87.00%) while the best cutoff threshold of ADC value was 2.400 $x10^{-3}mm^2/s$ (95%CI, sensitivity 100%, specificity 91.30%). This study was performed using b-values of 0 and 400 s/mm^2 with 20 diffusion directions.

To our knowledge, there is currently no study conducted to evaluate the diagnostic accuracy of MRI knee in ACL injury grading using combined DTI and conventional sequences.

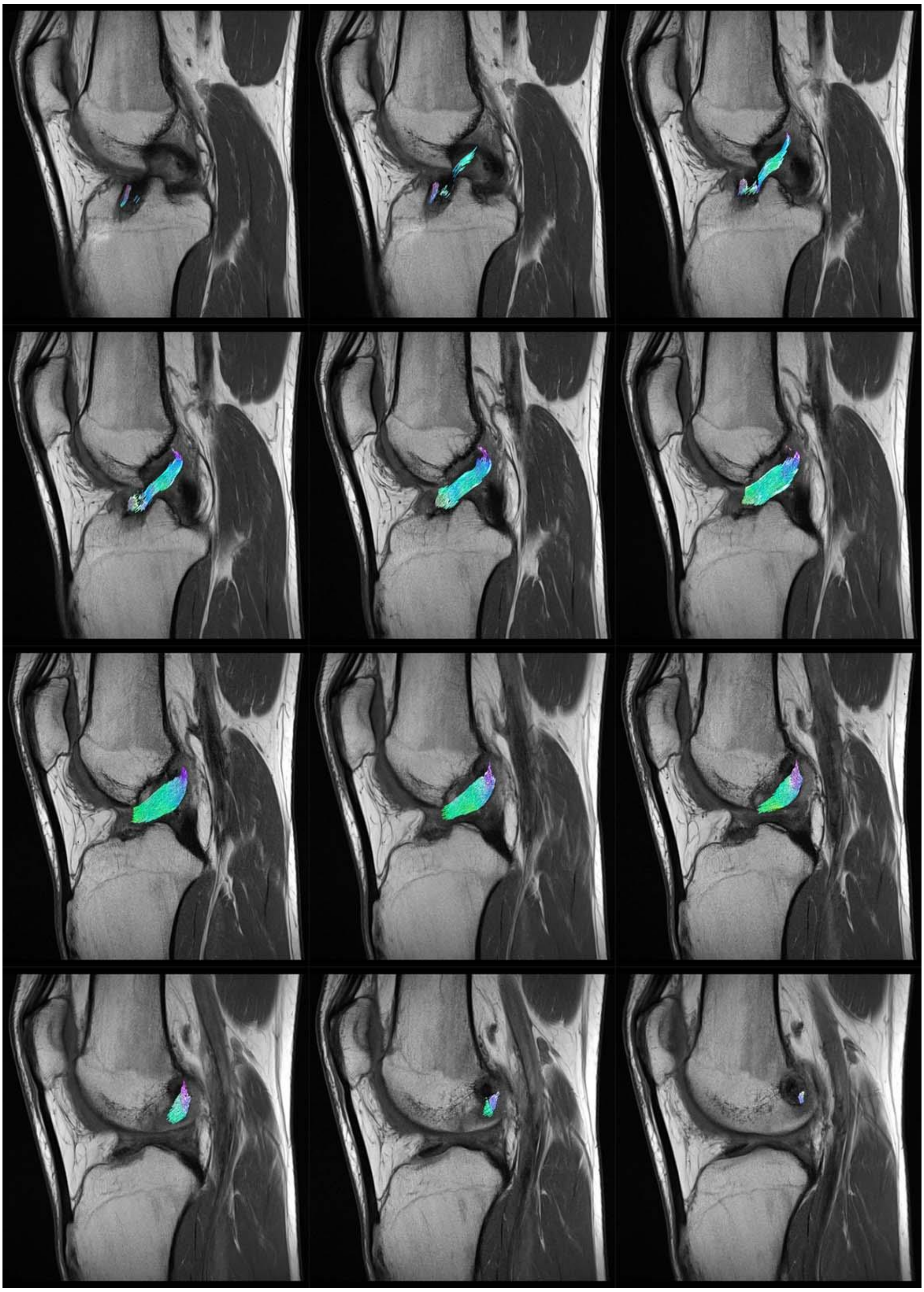

Figure 5 – Diffusion tensor tractography images of the ACL graft superimposed on sagittal proton density-weighted turbo spin echo images.

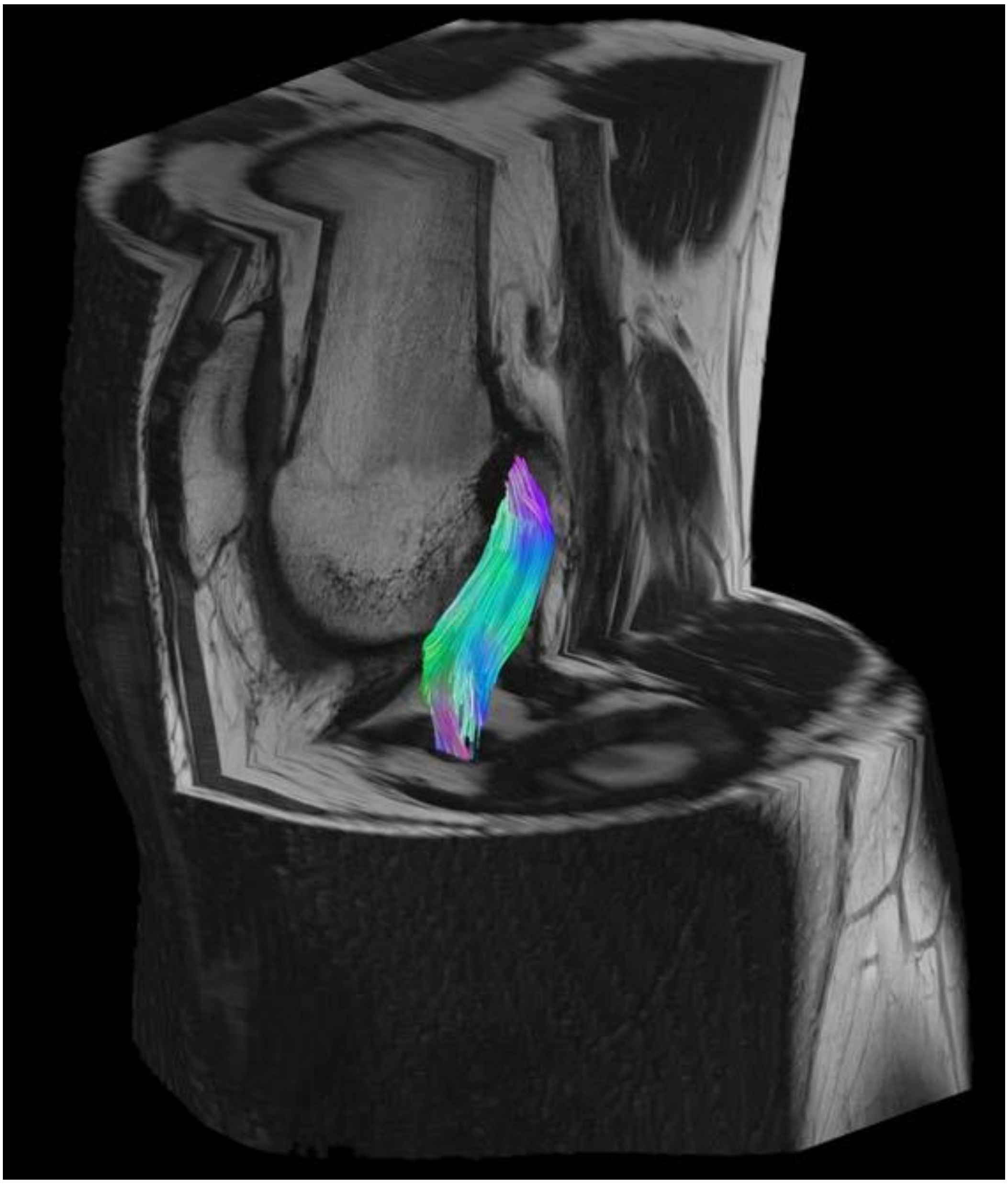

Figure 6 – 3D fiber tractography of the ACL from a medial view.

2.4 Problem Statement and Study Rationale

Although MRI knee is accurate in identifying complete ACL tear, the differentiation of complete tear and partial tear remains difficult. It is even more challenging for radiologists to estimate the degree or severity of partial tears quantitatively.

DTI is a non-invasive MRI technique which can be useful to provide additional information. The values of parameters including fractional anisotropy, apparent diffusion coefficient, axial diffusivity and radial diffusivity can be used for quantitative assessment of ACL injury. Besides that, diffusion tensor tractography (DTT) which is generated through post-processing software can be utilized for qualitative assessment of the ligament.