CHARACTERISATION OF MALIGNANT AND BENIGN MUSCULOSKELETAL SOFT TISSUE LESIONS USING THE DIFFUSION WEIGHTED MAGNETIC RESONANCE IMAGING

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMNS

MRI	Magnetic resonance imaging
ADC	Apparent diffusion coefficient
DWI	Diffusion weighted imaging
HPE	Histopathology examination
ROI	Region of interest
ROC	Receiver operating characteristic

ABSTRAK

Pengenalan :Terdapat pertindihan ciri-ciri yang sama bagi ketumbuhan tisu otot dan sokongan tulang melalui rutin imbasan magnetic (MRI).

Objektif : Tujuan kajian ini adalah untuk membezakan ketumbuhan tisu otot and sokongan tulang yang merbahaya dan tidak merbahaya menggunakan nilai ADC dan untuk menentukan ketepatan ADC dengan keputusan kajian histopatologi tisu ketumbuhan tersebut.

Metodologi: Kajian terhadap pesakit yang disyaki mempunyai ketumbuhan tisu otot, dirujuk untuk MRI dan memenuhi kriteria untuk terlibat dalam kajian ini. DWI dan peta ADC dikaji untuk mendapatkan bacaan nilai ADC. Kaitan antara nilai ADC dan jenis ketumbuhan telah dianalisa dengan ujian statistik. Nilai p kurang daripada 0.05 dikira sebagai signifikan.

Keputusan: Sejumlah pesakit (n=40) dengan ketumbuhan tisu otot dan sokongan telah menjalankan pemeriksaan rutin MRI. Hanya 23 pesakit yang menepati kriteria untuk kajian ini dan mempunyai keputusan kajian tisu histopatologi terlibat dalam kajian ini. Sejumlah tiga belas pesakit (n=13) disahkan ketumbuhan merbahaya dan sepuluh pesakit (n=10) disahkan ketumbuhan tidak merbahaya melalui analisia tisu histopatologi. Pesakit dengan ketumbuhan merbahaya mempunyai nilai ADC yang lebih rendah daripada ketumbuhan tidak merbahaya. Perbezaan ini adalah ketara mengikut kajian statistik Mann-Whitney test (nilai p <0.001). Nilai ADC untuk ketumbuhan merbahaya adalah 1.04×10^{-3} mm/sec (SD 2.38) and ketumbuhan tidak merbahaya

adalah 1.61 $x10^{-3}$ mm^2/sec (SD 0.51). Sensitiviti and spesifisiti nilai ADC untuk menentukan ketumbuhan merbahaya dan ketumbuhan tidak merbahaya berbanding keputusan analisa tisu adalah tinggi iaitu 90.1% dan 100% dengan nilai aras pada ADC 1.30 x 10^{-3} mm^2/sec.

Kesimpulan: Wujud perbezaan ketara antara nilai ADC ketumbuhan merbahaya dan tidak merbahaya. DWI juga mempunyai sensitiviti and specifisiti yang tinggi untuk menentukan ketumbuhan merbahaya dan tidak merbahaya berbanding dengan keputusan tisu analisis. DWI berpotensi membezakan ketumbuhan tisu otot dan sokongan tulang kepada merbahaya dan tidak merbahaya.

Kata kunci: ketumbuhan tisu otot dan sokongan tulang, diffusion weighted imaging (DWI), apparent diffusion coefficients (ADC)

ABSTRACT

Introduction : Conventional magnetic resonance imaging (MRI) shows some overlapping features of malignant and benign musculoskeletal soft tissue tumour.

Objectives : The purpose of this study is to characterise malignant and benign or tumour-like musculoskeletal soft tissue lesions using apparent diffusion coefficients (ADC) and to determine the accuracy of the ADC with histopathological examination (HPE) result.

Methodology : Cross sectional study on patients referred for conventional magnetic resonance imaging (MRI) for suspected musculoskeletal soft tissue lesions and full-filled the inclusion and exclusion criteria. Diffusion weighted imaging (DWI) and ADC maps were evaluated to obtain the mean ADC value. The relationship between the ADC value and type of tumours were analysed with statistical tests. The p value of less than 0.05 was taken as statistically significant.

Results : From all the forty (n=40) subjects who came for routine conventional MRI imaging for musculoskeletal lesions, only twenty-three (n=23) subjects full-filled the inclusion and exclusion criteria and histologically proven musculoskeletal soft tissue lesions were included in this study.

Thirteen patients (n=13) had histologically proven malignant lesions and ten patients (n=10) had histologically proven benign or tumour-like lesions. Patients with malignant lesions demonstrated lower mean ADC value in comparison with the patient with benign or tumour-like lesions. Based on Mann-Whitney test, the mean ADC was

significantly different ($p<0.001$). The median ADC for malignant lesions was 1.04×10^{-3} mm^2/sec (SD 2.38) and benign lesions was 1.61×10^{-3} mm^2/sec (SD 0.51). The sensitivity and specificity of mean ADC in predicting type of musculoskeletal soft tissue lesions comparing to histopathology examination report was 90.1% and 100% respectively with cut off point of 1.3×10^{-3} mm^2/sec.

Conclusion: There was statistically significant difference of mean ADC value of malignant and benign or tumour-like lesions. DWI was also highly sensitive and specific as compared to tissue analysis to determine type of lesions. Thus**,** DWI has potential in differentiating malignant and benign soft tissue lesions.

Keywords: musculoskeletal soft tissue tumour, diffusion weighted imaging (DWI), apparent diffusion coefficient (ADC)

CHAPTER 1 : BACKGROUND

1.1 Introduction

Musculoskeletal soft tissue lesions are commonly encountered in our daily practice. Patient usually presents with palpable lump and bumps. The initial imaging is plain radiograph to look for osseous involvement, to locate the lesion and to look for nature of mineralization. Further imaging includes ultrasound for superficial lesion, and computed tomography (CT) scan and magnetic resonance imaging (MRI) for further characterisation of the lesion. Soft tissue lesions are categorised into tumour and tumor-like lesion. Tumour or neoplastic lesion is a growing lesion which can further subdivide into benign; the harmless lesion and malignant; the dangerous and rapidly growing lesion. The tumour-like lesions are non-neoplastic and hence harmless. They include infection, inflammation, abscess or cyst.

The standard protocol MRI has an important role in characterisation of musculoskeletal soft tissue lesions depending on their signal intensity. It is the imaging modality for diagnosis, staging and follow-up of much musculoskeletal pathology. Some lesions demonstrate typical signal intensity on routine imaging such as for lipoma or cyst. However, there are also some overlapping features for benign and malignant lesions. The dermoid tumour for instance, a benign tumour, demonstrates imaging features of malignancy. The tumour-like lesion such as inflammatory or infection may appear as aggressive lesion on routine MRI imaging.

Diffusion weighted imaging (DWI) is a recent addition to the conventional MR protocols, provides the functional information concerning the microscopic movements of water at the cellular level. It is a noninvasive method for evaluation of

musculoskeletal soft tissue lesions. Apparent diffusion coefficient (ADC) values, which are obtained from the DWI images, represent cellularity activity and extracellular water content. Decreased ADC value reflects high cellularity and low extracellular water content as seen in malignant lesion whereas increased ADC value reflects breakdown of cell membrane integrity causing high extracellular water content. These features make DWI valuable tool for differentiating benign and malignant lesion. Thus, the diffusion weighted imaging (DWI) imaging might improve the diagnostic imaging accuracy.

DWI is very commonly used in brain imaging. However, there are emergences and evolving usage of DWI in breast, liver and musculoskeletal imaging. A number of musculoskeletal disorders have been evaluated by using DWI, which includes vertebral fractures, bone marrow infection, bone marrow malignancy, bone and soft tissue tumours and post-treatment follow-up. The earlier studies showed overlapping ADC value of benign and malignant lesions. However, some recent studies showed significant difference between the ADC value of malignant and benign lesion. The ADC value of malignant lesion is lower as compared to benign lesion, reflecting restricted diffusion due to increased cellularity and limited extra-cellular space.

Therefore, the aim of this study is to characterise the malignant and benign musculoskeletal soft tissue lesions using the DWI and ADC value. As the Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan is the Malaysia's East Coast referral center for musculoskeletal lesions and reconstruction unit. The study was using 3 Tesla MRI, and it is expected that DWI will be obtained with better signal-to-noise ratios (SNRs) hence, higher accuracy. Thus adding DWI to routine MRI protocols may improve diagnostic accuracy.

1.2 Objectives

1.2.1 General Objective:

To differentiate malignant and benign musculoskeletal soft tissue lesions using diffusion weighted imaging (DWI).

1.2.2 Specific Objectives:

i. To compare mean apparent diffusion coefficient (ADC) between malignant and benign musculoskeletal soft tissue lesions.
ii. To determine the accuracy of ADC in differentiating between malignant and benign musculoskeletal soft tissue lesions.

CHAPTER 2 : LITERATURE REVIEW

2.1 Musculoskeletal Soft Tissue Lesions

Musculoskeletal soft tissues are tissues that connect, support and surround the skeletal system. They include from superficial to deeper structures; skin, adipose tissue, fascia, muscle, tendon, nerve, blood vessels and joints. They hold our bodies together with the skeletal system or bones and help to move. There are lesions arising from the soft tissues, which can be broadly classified as congenital and acquired. Congenital lesions develop before or at birth. It also can manifest during the first few months of life. Acquired conditions develop over a course of one's life. It includes tumour or tumour-like lesions.

Musculoskeletal soft tissue tumours or neoplasms are generally classified into 2 main groups, which are benign and malignant or known as soft tissue sarcomas. They are derived from ectodermal and mesodermal layer and can occur at any age and site (Hochman, 2009; Zou *et al.*, 2016). Benign tumours are generally harmless while malignant tumours are cancerous. Tumour-like lesions are non-neoplastic such as infection, abscess, inflammation or cysts (Bloem and Reidsma, 2012).

2.2 Imaging of Musculoskeletal Soft Tissue Lesions

The initial approach starts with clinical history, physical examination and location of the lesion. It is further characterised by imaging features such as mineralisation on plain radiographs, the nature of superficial lesion on ultrasound and signal intensity and enhancement pattern on CT scan and magnetic resonance imaging MRI (Mark J. Kransdorf, 2000).

A study published by Gruber *et al.,* (2017) showed that the most predictive features of malignant potential of unknown mass were heterogeneity on ultrasound, CT and MRI, lesion roundness, restricted diffusion, presence of cystic or necrotic intralesional areas, higher patient age, surrounding extensive oedema and intralesional Doppler hypervascularity (Gruber *et al.*, 2017).

Plain radiographs are cheap and readily available. Two standard views, frontal and lateral projections are required on imaging to locate the lesion. They also provide the information regarding mineralisation, underlying skeletal deformity or co-existing osseous involvement such as periosteal reaction or bone remodeling. However, plain radiographs are suboptimal to assess the small lesion and to detect subtle radiological features such as obliteration of fascia planes (Mark J. Kransdorf, 2000). CT is a useful adjunct in lesion that radiograph inadequately depict or characterise the lesions. As compared to plain radiographs, CT is beneficial for lesion in deeper structures such as in the pelvis.

MRI is the mainstay of diagnosis, staging and follow-up of much musculoskeletal lesion. Compared to CT scan, MRI provides superior soft-tissue contrast, allows multiplanar image acquisition, obviates iodinated contrast agents and ionising radiation, and is devoid of streak artefacts commonly encountered with CT **(Khoo *et al.*, 2011)**. However, not all the medical centers are equipped with MRI. MRI scanners are more expensive than CT scans. The imaging duration is longer thus susceptible to motion artefacts. MRI scanning is also not safe for patients with MRI non-compatible metal implants and foreign bodies, which can induce local heat and possibility of migration. Careful attention to safety measures is necessary to avoid

serious injury to patients and staff, and this requires special MRI compatible equipment and stringent adherence to safety protocols. MRI is a preferred modality for evaluating soft tissue tumour, to assess the origin, morphology and signal intensity, extension and the anatomical relationship with the neurovascular bundle and joints (Khoo *et al.*, 2011). MRI also beneficial at determining cystic versus solid components of the lesion and for characterising common tumour subtypes such as lipoma, vascular malformation and peripheral nerve sheath tumour (Fisher *et al.*, 2016).

A systemic imaging approach of soft tissue tumour and tumour-like lesions remains problematic due to overlapping and indeterminate characteristic of the lesions except for the simple lipoma and cyst that have unique signal intensity on conventional protocol (Song *et al.*, 2017). However, there are advances and emergences of imaging to improve the characterisation of the lesion.

In view of overlapping imaging features of the soft tissue lesions, they are recent emergences of functional and metabolic imaging, namely the MR diffusion, MR perfusion or dynamic perfusion enhancement, MR spectroscopy and in-phase/opposed-phase MRI (Drapé, 2013; Fisher *et al.*, 2016; Laura M Fayad, 2012; Mark J. Kransdorf, 2000). For the MR perfusion or dynamic perfusion enhancement, the main contributions for identification of viable tissue are depending on the types of MRI enhancement time versus intensity curves after the gadolinium injection. There are 5 types of curves which are type 1: no enhancement such as in lipoma or hematoma, type 2: faint and gradual enhancement as in benign tumours, type 3: rapid early enhancement followed by plateau as in benign vascular tumour, desmoid tumour or abscess, type 4: rapid early enhancement followed by washout as in highly vascular tumour and type 5: rapid early

enhancement followed by slow gradual enhancement as in tumours post radiotherapy of chemotherapy. These techniques are widely used in monitoring response post chemotherapy or to detect residual or recurrent tumour (Drapé, 2013).

For in-phase and opposed-phase imaging, it relies on the lipid/water ratio in a given tissue voxel particularly in bone marrow which consist of equally high water and fat contents. The simultaneous existence of water and fat in normal marrow results in signal suppression on opposed-phase images. However, in bone marrow infiltration that replaces the fat component, there is loss of signal suppression on opposed-phase images. Thus, it can differentiate pathological fracture from the acute mechanical fracture (Drapé, 2013). For in-phase and opposed-phased imaging or known as chemical shift imaging, it is widely used for liver, adrenal glands and bone tumours. However, little study was performed in imaging of soft tissue tumour possibly due to heterogeneity of fat and water content of the lesion. MR spectroscopy is also widely used for brain imaging. The lesions are characterized based on their metabolic constituents such as choline, which is found in cell membrane. An increased in choline level, indicated increased cell membrane turnover, which is indirect marker for malignancy. Apart from that, MR spectroscopy has been used in bone and soft tissue tumours, breast cancer, prostate cancer and cervical cancer (Drapé, 2013).

2.3 Diffusion Weighted Imaging: Concept

Diffusion weighted imaging (DWI) or MR diffusion serves the qualitative and quantitative characterisation of lesions by means of signal intensity on diffusion weighted images and ADC value on ADC maps. It assesses the tissue cellularity and

integrity of cell membrane. The basic concept of DWI is measuring the random movement of water molecules in vivo such as in the extracellular, intracellular and transcellular compartments. For highly cellular tissues, there is smaller extracellular compartment thus the water restriction is greater. This is applied in the malignant tumour. Restriction of water molecule is inversely proportionate to tissue cellularity. For benign lesion, the extracellular compartment is still adequate in view of lesser degree of cellularity, thus the water movement is less restricted (Bhojwani *et al.*, 2015; Drapé, 2013).

2.4 Diffusion Weighted Imaging: Technique

There are five main types of DWI sequences: (1) spin- echo DWI: the simple sequence with relatively high signal-to-noise ratio (SNR) but a long acquisition time; (2) single-shot echo planar imaging (SS-EPI): quicker acquisition times while maintaining relatively high SNR; but vulnerable to susceptibility artefacts, particularly at tissue interfaces; (3) Multi- shot echo planar imaging (MS-EPI): EPI sequence that divides the echo train into shorter parts, provides higher spatial resolution and is less susceptible to artefacts or distortions; however, it has a longer acquisition time; (4) single-shot fast spin-echo (SS-FSE): this sequence has similar speed and spatial resolutions to echo planar sequences, and are less sensitive to susceptibility artefacts; (5) steady-state free precision imaging (SS-FPI): a gradient-echo MRI pulse sequence with fat saturation. The most commonly used sequence is single shot EPI as it is simple and has short acquisition time and thus eliminate risk of motion artefacts (Drapé, 2013; Yao and Troupis, 2016).

DWI used the diffusion gradients to filter water signal in conventional T2-weighted images. Thus it improves the detection of water molecule diffusion and mobility and gives the greatest ADC value. To improve the accuracy of interpretation the diffusion, at least 2 different b values are generally used (0 and 600, or 0 and 1000 s/mm2). The b-value reflects the diffusion force. Cystic tumours exhibit greater signal attenuation on high *b*-value images. The higher diffusion force, the less restricted of water molecule movement. Whereas for solid masses and cellular tumours with restricted diffusion, they continue to generate a high-intensity signal independent on the diffusion force (Drapé, 2013). The different b-values reflect the qualitative characteristic of the lesion rather than quantitative characteristic, the ADC value. Many studies are using b value of ranging 0 until 800 s/mm^2.

2.5 Diffusion Weighted Imaging: Applications

MRI diffusion is widely used in neuro-imaging particularly in cerebral pathology such as stroke and tumour. However, its usage is expanding involving imaging of the breast, liver and musculoskeletal system (Vinit Baliyan, 2016). MR diffusion is easily available sequence in addition to the conventional routine MRI sequences for imaging of musculoskeletal soft tissue. A number of musculoskeletal disorders have been evaluated by DWI and hence the ADC including vertebral fractures (Bhojwani *et al.*, 2015; Dallaudiere *et al.*, 2015; Geneidi *et al.*, 2016; Khoo *et al.*, 2011; Yao and Troupis, 2016), bone marrow infection and malignancy (Subhawong *et al.*, 2014), primary bone lesions (Dallaudiere *et al.*, 2015; Geneidi *et al.*, 2016; Hayashida *et al.*, 2006a; Khoo *et al.*, 2011; Kotb *et al.*, 2014; Oh *et al.*, 2017; Pekcevik *et al.*, 2013; Subhawong *et al.*, 2014; Yao and Troupis, 2016), soft tissue lesions (Dallaudiere *et al.*,

2015; Einarsdottir *et al.*, 2004; Jeon *et al.*, 2016; Khoo *et al.*, 2011; Subhawong *et al.*, 2014; van Rijswijk *et al.*, 2002a) and post-treatment follow-up to monitor for residual or recurrent disease, due to its ability to discriminate necrosis from viable tumours (Bhojwani *et al.*, 2015; Dallaudiere *et al.*, 2015; Einarsdottir *et al.*, 2004; Hayashida *et al.*, 2006b; Khoo *et al.*, 2011; Yao and Troupis, 2016). Additionally, the lesions with decreasing ADC values can suggest malignant transformation and increasing ADC values post chemotherapy can suggest reduction in tumour size (Dudeck *et al.*, 2008).

A number of studies have been performed to characterise benign and malignant bone tumours There is significant difference of ADC value between benign and malignant bone tumours with lower ADC value in malignant tumour as compared to benign tumours (Ahlawat *et al.*, 2015; Geneidi *et al.*, 2016; Kotb *et al.*, 2014; Neubauer *et al.*, 2012; Oh *et al.*, 2017; Pekcevik *et al.*, 2013). The lesions were confirmed by HPE and clinical confirmation. They defined clinical confirmation by means of no underlying malignancy, no change in tumour size and extension; and no clinical evidence of disease progression in 6 months after the initial MRI (Oh *et al.*, 2017). DWI is non-invasive method to evaluate tumour histological content. The tissue histopathological analysis is invasive method and yet being the gold standard for the final diagnosis (Fisher *et al.*, 2016). There was some overlap in ADC values between benign and malignant bone tumours. The mean minimum ADC values of benign and malignant of chondroid tumours were high. Giant cell tumor, non-ossifying fibroma and fibrous dysplasia showed lower ADC values (Pekcevik *et al.*, 2013). The other study reported overlapping in the ADC values of chondrosarcomas, solitary bone cyst, and fibrous dysplasia (Hayashida *et al.*, 2006a).

There are also several studies to characterise benign and malignant soft tissue tumour using the DWI. The initial studies showed overlapping ADC value (Einarsdottir *et al.*, 2004; van Rijswijk *et al.*, 2002b). However, recent studies showed significant difference between the ADC value of benign and malignant soft tissue tumour. The patients diagnosed with malignant soft-tissue tumours have low ADC values of DWI compared to those with benign soft-tissue tumors (Jeon *et al.*, 2016; Neubauer *et al.*, 2012; Song *et al.*, 2017; Zou *et al.*, 2016). A study by Song *et al.*, (2017) also reported that ADC values for myxoid tumours were significantly higher than those of non-myxoid tumour. However, the myxoid component can be characterised well using conventional MRI due to their distinguishing features such as fluid-like signal intensity on T2-weighted imaging and variable degree of enhancement of the myxoid component (Song *et al.*, 2017).

Another study by Pekcevik *et al.* (2015) showed the mean ADC values were different between benign and malignant soft tissue tumors ($p = 0.031$). The mean ADC value of benign and malignat tumous were $2.31 \pm 1.29 \times 10^{-3}$ mm^2 / s and $0.90 \pm 0.70 \times 10^{-3}$ mm^2 / s respectively. Benign cystic tumours had significantly higher ADC values than benign solid or mixed tumours and malignant solid or mixed tumours (p values were 0.001 and 0.003, respectively). Malignant solid or mixed tumours had lower ADC values than benign solid or mixed tumours ($p = 0.02$) (Pekcevik *et al.*, 2015).

Another study by Subhawong *et al.* (2013) showed higher mean ADC values in cysts than solid soft tissue masses respectively (2.31 vs 1.45×10^{-3} mm^2 / s, $p < 0.005$) (Subhawong *et al.*, 2013). However, the findings of solid and cystic masses are easily