



ROLE OF DIFFUSION WEIGHTED MRI IN ASSESSMENT OF TREATMENT RESPONSE TO CHEMOTHERAPY IN PATIENTS WITH OSTEOGENIC SARCOMA

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سببنا انك لا تعلم لنا
إلا ما علمتنا انك أنت
العليم العظيم

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List of Contents

Title	Page No.
List of Tables	i
List of Figures	ii
List of Abbreviations.....	v
Introduction	1
Aim of the Work.....	4
☞ Gross anatomy and MR anatomy of the bones	5
☞ Pathological Overview	10
☞ Different types of OS in Clinical, Pathological & Radiological view.....	15
Imaging Modalities of Osteosarcoma.....	36
Patients and Methods.....	42
Results	52
Cases Presentation.....	65
Discussion	106
Summary and Conclusion.....	113
References	114
Arabic Summary	\

List of Tables

Table No.	Title	Page No.
Table (1):	Primary tumor (T).....	13
Table (2):	Regional lymph nodes (N)	13
Table (3):	Distant metastasis (M)	13
Table (4):	Age of the patients (in years).....	52
Table (5):	Sex predilection in the study	52
Table (6):	Imaging Features of Osteosarcoma in our study group.....	56
Table (7):	Assessment of MRI criteria of 24cases of skeletal Osteosarcoma	57
Table (8):	Detailed analysis of ADC (mm ² /sec) values of Osteosarcomas in the study group	59
Table (9):	Lesions sizes assessed before and after chemotherapy	60
Table (10):	Enhancement pattern of the lesions before and after chemotherapy.....	61
Table (11):	MRI follow up of tumor breaking down.....	62
Table (12):	Analysis of mean ADC values in follow up of regressive cases of OS after 3 months of treatment.....	62
Table (13):	Analysis of mean ADC values in follow up of progressive cases of OS after 3 months of treatment....	63
Table (14):	ADC values of the tumours measured before and after chemotherapy.....	64

List of Figures

Fig. No.	Title	Page No.
Fig. (1):	Anatomy of long bone.....	7
Fig. (2):	Red to yellow marrow conversion in the femur.	8
Fig. (3):	(a) Normal anatomy. (b) Coronal T1-weightedMRimage (510/14) in a different 10-year-old girl shows epiphyseal conversion to fatty marrow.....	8
Fig. (4):	Coronal T1 of normal appearance of adult femurs and hips (yellow marrow and closed epiphysis).....	9
Fig. (5):	Coronal T2 of adult femurs and hips.....	9
Fig. (6):	Conventional osteosarcoma: AP distal femur.....	17
Fig. (7):	Lateral view of the same tumour	17
Fig. (8):	MR images of chondroblastic osteosarcoma in the left femur.	18
Fig. (9):	C, The computed tomography scan demonstrates that the borders are indeed well circumscribed and the lesion is confined to the bone.....	18
Fig. (10):	Drawings of low-grade central OS show that the tumor most commonly arises from the medullary canal of the metaphysis of the femur or tibia and has variable patterns of bone involvement.....	20
Fig. (11):	Gross examination of the tibial resection specimen.....	20
Fig. (12):	Low-grade central OS in a 51-year-old man.....	21
Fig. (13):	Drawing of small cell OS shows that the tumor most commonly arises from the metaphysis of a long bone and is permeative and lytic	22
Fig. (14):	Small cell OS in a 26-year-old man.....	22
Fig. (15):	Giant cell-rich osteosarcoma.....	23
Fig. (16):	Drawing of telangiectatic OS shows that the tumor usually arises from the metaphysis of a long bone and is expansile and lytic.....	24
Fig. (17):	Gross appearance of a telangiectatic osteosarcoma shows a predominantly cystic, blood-filled cavity.....	24
Fig. (18):	X-ray & MRI of TO.....	25
Fig. (19):	MRI of multicentric osteosarcoma.....	26
Fig. (20):	A diaphyseal cortically based mixed lytic and sclerotic lesion proved to be (Intracortical OS)	26
Fig. (21):	Drawing of parosteal OS shows that the tumor is typically lobular and arises from the outer periosteum of the metaphysis of a long bone	27
Fig. (22):	Parosteal OS of the distal femur in a 29-year-old mane	28
Fig. (23):	Parosteal OS of the proximal humerus in a 28-year-old man.	28

List of Figures (Cont...)

Fig. No.	Title	Page No.
Fig. (24):	Drawing of periosteal OS shows that the tumor most commonly arises from the inner periosteum of the diaphysis of a long bone and demonstrates perpendicular periosteal reaction.....	29
Fig. (25):	Periosteal OS in a 19- year-old man.	30
Fig. (26):	Drawing of high-grade surface OS	30
Fig. (27):	High-grade surface OS in a 19-year- old woman.....	31
Fig. (28):	Secondary osteosarcoma of the humerus in a 77-year-old woman with bong-standing Paget disease and new pain and a soft-tissue mass.	32
Fig. (29):	Extra skeletal osteosarcoma in an 87-yearold man with an enlarging soft-tissue mass in his left thigh.	33
Fig. (30):	Lateral radiograph of the femur shows medullary and cortical bone destruction associated soft tissue component	36
Fig. (31):	Spontaneous pneumothorax in an osteosarcoma patient with pulmonary metastases	37
Fig. (32):	Osteosarcoma of the mandible with clouds of mineralized osteoid.....	37
Fig. (33):	The sagittal T1WI (a) and Gd-enhanced T1W-image (b) with fat sat show a large tumor mass infiltrating the distal femur and extending through the cortex into the soft tissues	38
Fig. (34):	Coronal FDG PET of metastatic small cell OS of right femur showing metastatic lesions in the lung, mediastinal lymph nodes, right clavicle, spine and left iliac crest.....	40
Fig. (35):	(a) before treatment and (b) after treatment, Monitoring response to chemotherapy by MRI in a good responder	41
Fig. (36):	Location of Osteosarcoma in the study.	53
Fig. (37):	Anatomical location of Osteosarcoma of long bones of lower limb in the study.....	54
Fig. (38):	Anatomical location of Osteosarcoma of long bones of upper limb in the study.....	55
Fig. (39):	Lesions sizes assessed before and after chemotherapy	60
Fig. (40):	ADC values of the tumours measured before and after chemotherapy.....	64
Fig. (41):	Case 1: MRI images of 7 years old female, newly diagnosed as osteosarcoma of the left femur.	66
Fig. (42):	Case 1: Follow up MRI images after 3 months of treatment.....	68

List of Figures (Cont...)

Fig. No.	Title	Page No.
Fig. (43): Case 2:	MRI images of 14 years old female, diagnosed as osteosarcoma of the left tibia.....	71
Fig. (44): Case 2:	Follow up MRI images after 3 months of treatment.....	72
Fig. (45): Case 3:	MRI images of 9 year old female, diagnosed as osteosarcoma of the left iliac bone.....	75
Fig. (46): Case 3:	Follow up MRI images after 3 months of treatment.....	77
Fig. (47): Case 4:	MRI images of 11 years old male, diagnosed as osteosarcoma of the right tibia.....	79
Fig. (48): Case 4:	Follow up MRI images after 3 months of treatment.....	81
Fig. (49): Case 5:	MRI images of 9 year old female, diagnosed as parosteal osteosarcoma of left tibia.	83
Fig. (50): Case 5:	Follow up MRI images after 3 months of treatment.....	84
Fig. (51): Case 6:	MRI images of 34 year old female, diagnosed as chondroblastic osteosarcoma of left calcaneous.	87
Fig. (52): Case 6:	Follow up MRI images after 3 months of treatment.....	88
Fig. (53): Case 7:	MRI images of 17 year old male, diagnosed as osteosarcoma of right femur.	90
Fig. (54): Case 7:	Follow up MRI images after 3 months of treatment.....	92
Fig. (55): Case 8:	MRI images of 15 year old male, diagnosed as osteosarcoma of left femur.....	94
Fig. (56): Case 8:	Follow up MRI images after 3 months of treatment.....	96
Fig. (57): Case 9:	MRI images of 14 year old male, diagnosed as osteosarcoma of left femur.....	99
Fig. (58): Case 9:	Follow up MRI images after 3 months of treatment.....	101
Fig. (59): Case 10:	MRI images of 18 year old male, diagnosed as osteosarcoma of right humerus.	103
Fig. (60): Case 10:	Follow up MRI images after 3 months of treatment.....	105

List of Abbreviations

Abb.	Full term
<i>ADC</i>	<i>Apparent diffusion coefficients</i>
<i>ASU</i>	<i>Ain shams university</i>
<i>DWI</i>	<i>Diffusion weighted images</i>
<i>FNAC</i>	<i>Fine needle aspiration cytology</i>
<i>GCT</i>	<i>Giant cell tumor</i>
<i>IHC</i>	<i>Immunohistochemistry</i>
<i>MRI</i>	<i>Magnetic resonance</i>
<i>NVB</i>	<i>Neurovascular bundle</i>
<i>OS</i>	<i>Oseogenic sarcoma</i>
<i>RECIST</i>	<i>Criteria reposnse evaluation criteria in solid tumours</i>
<i>ROI</i>	<i>Region of interest</i>
<i>SPSS</i>	<i>Statistical package fro the social sciences</i>
<i>STIR</i>	<i>Short T1 inversion recovery</i>

INTRODUCTION

Osteosarcoma (OS) is the most common malignant bone tumor in children and adolescents. Currently, 10-year overall survival rates are 60% to 70% for all patients and only approximately 20% for patients with metastatic disease (*Flores et al., 2016*).

It affects the metaphysis of long bones and mostly the distal femur, proximal tibia, and humerus (*Isakoff et al., 2015*).

The most effective treatment seems to be neoadjuvant chemotherapy along with surgical resection of the tumor (*Isakoff et al., 2015*).

With chemotherapy, the therapeutic efficacy of osteosarcoma has been greatly improved since 1970s, and five-year disease-free survival rates have been raised from 15%, 20% to 70%, 80%. Limb salvage rate is obviously increased, but there are still 20%, 30% of patients with poor curative effect (*Wanget al., 2013*).

Traditionally, an assessment of solid cancer therapy effectiveness relies on comparison of changes in tumor size by images obtained before and after the therapeutic intervention (*Huang et al., 2016*).

For osteosarcomas there is a specific problem: during successful chemotherapy, tumour size does not diminish significantly because the therapy has only limited impact on the mineralized matrix of the tumour. On the other hand, in osteosarcomas, neoadjuvant chemotherapy has a significantly favorable impact on event-free survival. It is essential to monitor the response to chemotherapy to determine whether the prescribed treatment regimen is effective. Treatment response is considered successful if, histologically, more than 90% of tumour cells show necrosis (*Uhl et al., 2006*).

Apart from metastatic forms, the histological response to neoadjuvant chemotherapy remains the major prognostic criterion used for treatment of osteosarcoma (*Brisse et al., 2004*).

However; histological assessment of tumour response during the course of chemotherapy requires repeated biopsy (*Sanchez et al., 1990*).

MRI can provide clinically satisfactory information regarding tumour volume and extent, but does not yet gives sufficient information about the degree of tumour viability, the critical parameter in determining tumour response and prognosis (*Sanchez et al., 1990*).

A goal of oncology is the individualization of patient care to optimize therapeutic response and minimize toxicity. To achieve this non-invasive, quantifiable and early markers of tumour response are required (*Uhl et al., 2006*).

The use of water diffusion as a surrogate marker to probe tumour necrosis is compelling because the parameter is strongly affected by membrane permeability between intra- and extracellular compartments, active transport and directionality of cellular structures that impede water mobility (*Reichardt et al., 2009*).

Treatment with chemotherapy can result in the loss of cell membrane integrity which can be detected as an increase in mean diffusion value for the tumor. DW-MRI as biomarker has several advantages because it provides microstructural changes related to treatment effects over time. No ionizing radiation and no injection of isotope or any other contrast medium is necessary.

Furthermore, the acquisition time to perform diffusion-weighted MRI lasts only a few minutes, the method is easily repeatable providing quantitative information and information on spatial distribution including heterogeneity of the tumor and its response (*Thoeny et al., 2010*).

Therefore, DW-MRI for the evaluation of early treatment response is very promising (*Thoeny et al., 2010*).

AIM OF THE WORK

- 1- To investigate whether diffusion-weighted imaging (DWI) is useful for monitoring the therapeutic response after chemotherapy in osteosarcoma by comparing the ADC values pre and post chemotherapeutic treatment.
- 2- To determine if osteosarcomas change their water diffusion during preoperative chemotherapy in relation to the amount of tumour necrosis.

GROSS ANATOMY AND MR ANATOMY OF THE BONES

Structure of bone:

The adult human skeleton has a total of 213 bones, excluding the sesamoid bones. The appendicular skeleton has 126 bones, axial skeleton 74 bones, and auditory ossicles six bones (*Gray's Anatomy, 39th Ed., 2004*).

The four general categories of bones are long bones, short bones, flat bones, and irregular bones (*Taichman et al., 2005*).

The long bones are composed of a hollow shaft, or diaphysis; flared, cone-shaped metaphyses below the growth plates; and rounded epiphyses above the growth plates. The diaphysis is composed primarily of dense cortical bone, whereas the metaphysis and epiphysis are composed of trabecular meshwork bone surrounded by a relatively thin shell of dense cortical bone (*Eriksen et al., 1994*).

The adult human skeleton is composed of 80% cortical bone and 20% trabecular bone overall (*Eriksen et al., 1994*).

Cortical bone is dense and solid and surrounds the marrow space, whereas trabecular bone is composed of a honeycomb-like network of trabecular plates and rods interspersed in the bone marrow compartment. Both cortical and trabecular bone are composed of osteons (*Eriksen et al., 1994*).

Cortical bone has an outer periosteal surface and inner endosteal surface. Periosteal surface activity is important for appositional growth and fracture repair. Bone formation typically exceeds bone resorption on the periosteal surface, so bones normally increase in diameter with aging. The endosteal surface has a total area of approximately 0.5 m², with higher remodeling activity than the periosteal surface, likely as a result of greater biomechanical strain or greater cytokine exposure from the adjacent bone marrow compartment (*Kobayashi et al., 2003*).

The periosteum is a fibrous connective tissue sheath that surrounds the outer cortical surface of bone, except at joints where bone is lined by articular cartilage, which contains blood vessels, nerve fibers, and osteoblasts and osteoclasts. The periosteum is tightly attached to the outer cortical surface of bone by thick collagenous fibers, called Sharpeys' fibers, which extend into underlying bone tissue. The endosteum is a membranous structure covering the inner surface of cortical bone, trabecular bone, and the blood vessel canals (Volkman's canals) present in bone (*Kobayashi et al., 2003*).