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

Thesis

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List of Abbreviations

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

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)***.