Accurate Monitoring of the Treatment Response in Whole-Body Bone Marrow Metastatic Cancers Based on ADC Histogram Analysis Employing an Automatic Multiparametric (T1/ADC) Registration/Segmentation Approach

Faezeh Sanaei Nezhad[1], Anahita Fathi Kazerooni[2,3], Anwar Padhani[4], Hamid Soltanian Zadeh[1], and Hamidreza Saligheh Rad[2,3]

[1]*School of Electrical and Computer Engineering (ECE), College of Engineering, University of Tehran, Tehran, Iran,* [2]*Medical Physics and Biomedical Engineering, Tehran University of Medical Sciences, Tehran, Iran,* [3]*Quantitative MR Imaging and Spectroscopy Group, Research Center for Cellular and Molecular Imaging, Tehran University of Medical Sciences, Tehran, Iran,* [4]*Paul Strickland Scanner Centre, Mount Vernon Cancer Centre, London, United Kingdom*

Target Audience: Oncologists, Radiologists, Physicists and Engineers Interested in Treatment of Bone Metastases

Introduction: Therapy goals for malignant cancers, such as bone marrow metastases in breast cancer, are to delay skeletal-related events, reduce the symptoms, improve the patients' quality of life and increase their survival **[1]**. Correct knowledge about the patients' state of disease in time is the key to achieve therapy goals. For this purpose, assessment, validation and monitoring of the patient response to the drug therapy over the shortest possible time-course seem to be essential. To this end, it has been proposed that monitoring the intensity alterations in diffusion-weighted (DW) images of the diseased bone marrow, or the changes of apparent diffusion coefficient (ADC)-values in the bone marrow over the treatment period could be a potent tool to indicate the outcome of the treatment **[2]**. In other words, the increase in some specific statistical properties of ADC-map histograms in the bone marrow, such as mean and standard deviation, computed in the whole bone marrow to be monitored over the treatment period, has been shown to be a sign of positive response to treatment in certain tissues **[2]**. Segregation of the bone marrow has been traditionally limited to the manual selection of regions-of-interest (ROI)s on the ADC-maps in the whole bone marrow. However, due to the heterogeneous nature of the tumors, the presence of cystic or necrotic areas before therapy, correct and complete separation of the overall border of the bone marrow is difficult. The manual ROI-placement process is irreproducible, too time-consuming and susceptible to errors caused by subjective assessment of the borders, contamination of the ROI placed on the bone marrow with surrounding tissues and misregistration of the images due to the complex motions in abdominal organs. This issue appears as both increase and decrease in ADC value changes in response to the treatment, leading in the decrease in the net mean of the histogram and compromising the detection of the true treatment-related changes on ADC-maps. Here, we proposed an automatic multiparametric approach to extract the whole bone marrow from the ADC-maps by segmentation in T_1-weighted (T_1-w) images and non-rigid registration onto the ADC-maps, resulting in its independency from human error and capability to perform superior to the ROI-based analysis.

Materials and Methods: Data Acquisition: Whole-body T_1- and diffusion-weighted images of a 56 years old female patient, with metastatic breast cancer under treatment, were carried out on a 1.5T MR scanner (Siemens, MMWPE31A), in four consequent time points with 4, 4 and 3 months follow-up intervals, respectively. Whole-body T_1-w images were acquired with the following specifications: *TR/TE* = 171/4.76 *m*s, matrix size = 256×151, field of view (FOV) = 326×430, slice thickness = 5*m*m, spaces between slices = 5.5*m*m. Whole-body DWI was acquired using a GE-EPI sequence with the following specifications: *TR/TE* = 5540/102*m*s, matrix size = 256×110, percent phase FOV = 84.375, slice thickness = 5*m*m, spaces between slices = 5.5*m*m, at *b*-values of 50, and 900 sec/*m*m^2. ADC-maps were then calculated from DW images. Image Processing and Analysis: Image processing and analysis consists of the following steps: 1) automatic non-rigid registration of the whole-body T_1–w MR images with the ADC-maps, for motion correction and image resizing, using SPM8 software **[3]**, by employing normalized mutual information (NMI) as the registration objective function and Trilinear interpolation method as the deformation model, 2) segmentation of the bone marrow in each slice from the T_1-w images using a specialized region-growing method implemented in MATLAB 7.14 (The MathWorks) with proper threshold settings, 3) using the result of step 2 as the mask for bone marrow extraction from the corresponding ADC-maps and 4) applying histogram analysis to the whole segmented bone marrow from the ADC-maps. For simplification, images of neck and head were excluded from the whole-body images. In order to show the feasibility of the automatic segmentation-based analysis, its performance in histogram analysis was compared to three various ROI-based analysis methods.

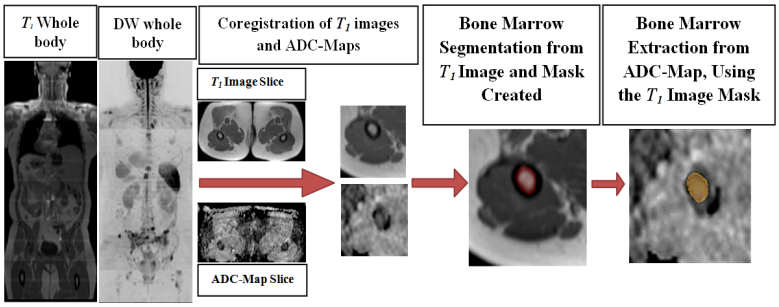

Figure 1. The diagram representing the bone marrow segmentation from T_1-w image and ADC-map.

Results and Conclusions: **Fig. 1** illustrates different steps of the bone marrow segmentation from one slice of T_1-w images and its corresponding slice from the ADC-map. As it can be inferred, the bone marrow is completely segmented and there is no need to manually define any ROIs. Based on the findings by Padhani *et al* **[2]**, in the bone marrow of a patient responding to treatment, the ADC histogram trend is bi-phasic: the first phase shows an increment of the ADC values, followed by a decrement after exceeding a certain threshold **[2]**. For this study case, the patient is in the ADC-increasing phase during the measurement period (until time point 4), thus we expect an increasing trend for the ADC mean values. As it can be observed from **Fig. 2**, the alteration trend of the mean value of the ADC-map histogram over time, obtained by different ROIs, shows large variations throughout a specific ROI and among various ROIs, implying the high dependency of this method on the shape and the size of the manually selected ROIs. In contrast, the calculated mean from the histogram of the automatically segmented bone marrow indicates a monotonous increasing trend, emphasizing its consistency with the expected trend. The mean and standard deviation calculations of the ROI-based analysis and automatic bone marrow segmentation methods are given in **Table 1**. In conclusion, the proposed automatic multiparametric approach combats motion artifact, caused in complex and moving organs, and avoids variations of the ADC histogram analysis, caused by manual selection of different ROIs in different slices. This method is accurate and robust, which can improve the design of the patient's treatment plan.

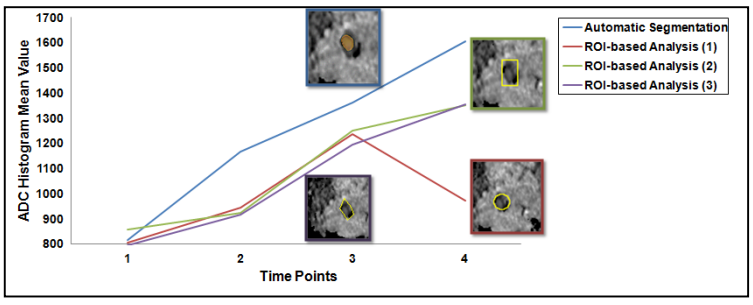

Figure 2. The calculated means of the ADC histograms obtained by automatic and the ROI-based bone marrow segmentation methods.

Method \ Time point	1	2	3	4
Automatic Segmentation	815 ± 179	1168 ± 287	1361 ± 317	1601 ± 327
ROI-Based Analysis (1)	806 ± 368	943 ± 294	1236 ± 293	972 ± 310
ROI-Based Analysis (2)	856 ± 426	922 ± 273	1252 ± 270	1352 ± 346
ROI-Based Analysis (3)	794 ± 381	917 ± 275	1195 ± 269	1354 ± 337

Table 1. The mean and standard deviation calculations for automatic segmentation and ROI-based analysis methods for bone marrow extraction

References: **[1]** Padhani A *et al*, *NEOPLASIA* 11, 102 (2009). **[2]** Padhani A *et al*, *JMRI* 19, 181 (2011). **[3]** SPM8, statistical parametrical mapping, http://www.fil.ion.ucl.ac.uk/spm/.