European Journal of Radiology 83 (2014) 1655–1664

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Very early indicators of response to systemic therapy in lymphoma patients based on alterations in water diffusivity—A preliminary experience in 20 patients undergoing whole-body diffusion-weighted imaging

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ARTICLE INFO

Article history:
Received 15 November 2013
Received in revised form 14 May 2014
Accepted 18 May 2014

Keywords:
Lymphoma
MRI
DWI
Response evaluation

ABSTRACT

Objective: To assess feasibility of whole-body diffusion-weighted MRI (wbDWI) for very early evaluation of response to therapy in different lymphoma subtypes.
Materials and methods: 20 patients (10 male, 10 female; mean age 50.7 ± 16.1 ± 17.2 years) underwent wbDWI (calculation of apparent diffusion coefficient [ADC] with $b = 0, 800$ s/mm^2) at baseline and within a median of 7 days after therapy onset. Lymphoma manifestations were evaluated with respect to changes in ADC and size at follow-up with up to six of the largest lesions per patient undergoing quantification. An increase in ADC as well as a decrease in size at follow-up was classified as responder, whereas neither change in ADC nor in size (or progression) was considered non-responder. Results were confirmed at interim measurements (after 3–4 chemotherapy cycles) and 6 months after treatment.
Results: 90 lymphoma lesions were analyzed. 18 patients were classified as responders and 2 as non-responder at FU (mean, 1 week). DWI results accurately (100%) correlated with the subsequent interim course of all lesions. $_{\text{mean baseline}}$ ADC was $0.79 \pm 0.28 \times 10^{-3}$ s/mm^2. For responders mean $_{\text{follow-up}}$ADC increased by 64.6 ± 56.5% ($p < 0.001$) whereas lesions size decreased by mean 14.4 ± 13.3% ($p < 0.001$). In the non-responder, both values did not significantly change.

In patients classified as responders six months after treatment, $_{\text{mean}}$ADC increase at FU was 70.3 ± 57.8% ($p < 0.001$) whereas mean size decrease vs. baseline was 15.8 ± 13.6% as compared to non-responders (22.4 ± 39.9%) and 5.4 ± 0.9%, respectively.
Conclusion: wbDWI with ADC analysis represents a feasible diagnostic tool for very early response assessment in lymphoma patients enabling also prediction of long-term response.

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http://dx.doi.org/10.1016/j.ejrad.2014.05.027
0720-048X/

1. Introduction

Lymphomas arise from cells of the immune system at different stages of differentiation resulting in a broad range of histological subtypes with many common imaging and clinical findings. They range from the most indolent (e.g. follicular lymphoma-FL) to the most aggressive types (e.g. diffuse large B-cell lymphoma-DLBCL) [1]. For staging and response monitoring purposes, contrast enhanced CT is currently the most often used technique. However, many authors have suggested the need for more sensitive imaging modalities for staging and treatment monitoring, recommending the use of fluorine [^{18}F]-fluorodeoxyglucose (FDG) alone or in combination with CT (PET/CT) because of its higher sensitivity compared to CT alone [2–4]. Alternative techniques exist and rely on the additional acquisition and evaluation of functional data derived from perfusion measurements (dynamic contrast-enhanced MRI [DCE-MRI] or CT, diffusion-weighted MR imaging (DWI) and/or proton MR-spectroscopy [5–7]. The goal of lymphoma treatment, especially in highly aggressive NHL and in HL is to achieve the highest cure rate with the least morbidity and mortality. Response to treatment is therefore probably the most important prognostic factor for the individual patient. At this point, FDG-PET studies performed before and early after could demonstrate that in patients with no residually increased FDG-uptake there no cases of refractory disease and the frequency of early relapse is lower, whereas a modest early lymphoma response often heralded mid-term relapse [8]. However, such studies were performed relatively late, after 2–4 chemotherapy cycles [2]. Especially, with regard to life quality under aggressive systemic therapy, early response monitoring is desired. Another imperative demand at successful imaging techniques is that they should display all lymphoma manifestations as they might behave differently (e.g. Richter transformation in chronic lymphocytic leukaemia-CLL) which qualifies only whole-body imaging techniques for this task.

Diffusion-weighted magnetic resonance imaging (DWI) is an emerging imaging modality that measures water diffusivity in tissues and is known for its high sensitivity for detection of restricted diffusion in tumors that are highly cellular and present high nuclear-to-cytoplasm ratio. Lymphomas fulfil all these requirements and are therefore pertinent for serial DWI examinations. Some reports about the role of DWI in oncologic imaging and especially in lymphoma diagnosis exist, confirming its strengths on this field [9,10]. Little information, however, exists with respect to the temporal evolution of morphologic and functional changes in lymphoma shortly after chemotherapy onset. Moreover, lymphoma treatment is very well dependent on the histological subtype, expression of certain surface proteins, especially CD20, aggressiveness and risk stratification which makes therapies quite variable. Consequently, knowledge about the benefit of using DWI for very early therapy monitoring of different lymphoma subtypes as well as prognosis assessment is lacking at this time.

Hence, our study addresses the feasibility of performing whole-body DWI (wbDWI) very early after therapy onset for evaluation of short- and middle-term response to treatment in various lymphoma subtypes independent on therapeutic regimen.

2. Materials and methods

2.1. Patients

This prospective study was approved by our institutional review board. Patients with histologically proven lymphoma that were scheduled for immediate specific chemotherapy and gave their written informed consent were eligible. The exclusion criteria were patients with contraindications to MRI, such as claustrophobia, implanted pacemakers or such refusing to participate in the study. Between February 2011 and May 2013, 20 consecutive patients (10 male, 10 female; mean age 50.7 ± 16.1 years, range 20–77 years) meeting the inclusion criteria underwent wbDWI, both, in the baseline setting and approximately one week (median 7 days, range 2–13 days) after therapy onset. Five patients were excluded as they refused to enroll in this study. Interim imaging diagnosis (e.g. CT [n = 15], FDG-PET/CT [n = 4], wbMRI [n = 3] was performed in all patients after the 3rd or 4th chemotherapy cycle (median, 10 weeks; range 6–25 weeks) according to clinically established response monitoring imaging recommendations. No patient received radiation therapy during the control interval. The following histologic lymphoma subtypes were enrolled: follicular lymphoma (n = 4 grade II and n = 2 grade IIIa), Hodgkin's lymphoma (n = 7 nodular sclerosing subtype), diffuse large B-cell lymphoma (n = 3), mantle cell lymphoma (n = 1) and chronic lymphocytic leukemia/small lymphocytic lymphoma B-CLL/SLL (n = 3) (Table 1). Grade II FL were classified low/intermediate-grade whereas DLBCL and MCL were classified high-grade. For statistical purposes, Hodgkin's lymphomas were added to the aggressive group of non-Hodgkin's lymphomas.

Patients received the following therapy regimens at a median of 2.5 days (range, 0–18 days) after baseline examination (Table 1).

2.2. Whole-body DWI protocol design

Examinations were performed on a 1.5 Tesla MR scanner (MAGNETOM Avanto; Siemens Healthcare, Erlangen, Germany) capable to perform wbMRI and wbDWI (gradient performance amplitude, 40 mT/m, slew rate, 170 [mT m^{-1}]/ms). The patients were positioned supine and head-first in the magnet bore, with multiple sets of phased-array surface coils installed simultaneously to cover the head, neck, chest and abdomen, and the pelvis to the middle of the thighs (total imaging matrix coil technology).

Our wbDWI consisted of a multi-step protocol. Images were acquired in transversal orientation. For better visualization of findings, coronal multi-planar reconstructions as well as maximum intensity projections were generated (b = 800 s/mm^2). ADC maps were automatically generated taking into account both acquired b-values and assumption of a linear signal decay by the MR software. As DWI sequence, a modified version of the single-shot EPI DWI technique used in [11] was applied: for diffusion encoding, a monopolar scheme was applied in this study and instead a spectral fat saturation, suppression of fatty tissue was achieved with a spectral inversion recovery technique (SPAIR) resulting in homogenous fat saturation also in challenging areas like the neck.

B-values at 0 and 800 s/mm^2 were acquired using diffusion gradients along the three orthogonal axes of the magnet. The lower b-value was set to 0 s/mm^2 to allow best correlation of morphological changes between the CT and MR imaging modalities. The higher b-value of 800 s/mm^2 was chosen in order to maximize tumor visualization and achieve adequate suppression of undesirable background signals arising from normal tissue. Lymphomas generally consist of densely packed cells with predominantly homogenous consistency and minimal expected necroses and are therefore optimally suited for DWI using higher v-values (750–1000 s/cm^2). Perfusion effects cannot be ruled out by applying b-values of 0 s/mm^2; however, to keep the wbDWI examination time short, no further b-values were acquired.

Sequence parameters were: TR/TE = 11,900 ms/52 ms, averages = 4, averaged 3-scan trace, matrix = 117 × 192, FOV = 324 × 399 mm^2, slice thickness = 5 mm and 10% gap between slices. In all cases, the patients did breathe freely. We decided to include up to six of the largest lesions for ADC and size calculation, but considered all lesions (up to 60 involved sites [lesions] pro patient)