Whole-body diffusion-weighted magnetic resonance imaging for staging and early treatment response assessment in malignant lymphoma

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SUMMARY

Diffusion-weighted magnetic resonance imaging (DW/MRI) is a radiation-free functional imaging technique reflecting tissue cellularity by probing the diffusion of water molecules on a microstructural level. This can be assessed visually, but also quantified by calculating the apparent diffusion coefficient (ADC). Although established in many solid tumours and multiple myeloma, its role in disease assessment in malignant lymphoma has yet to be determined. Therefore, the main purpose of this work was twofold: exploring the performance of whole-body DW/MRI (WB-DW/MRI) in staging malignant lymphoma and assessing treatment response early during treatment with 18F-FDG-PET/CT in combination with bone marrow biopsy results serving as the gold standard. Regarding staging, we found that WB-DW/MRI is a feasible imaging technique. Visual image analysis sufficed to accurately detect extranodal disease, while adequate nodal characterisation required ADC calculations. Lymph node characterisation was further improved by using a more elaborate quantitative analysis based on ADC parameters derived from whole-lesion ADC histogram analysis next to the commonly used mean ADC. In the context of treatment response assessment, mean ADC changes between the baseline and interval scan performed after one cycle of (immuno)chemotherapy significantly correlated with progression-free-survival in patients with aggressive non-Hodgkin lymphoma (NHL). For Hodgkin lymphoma, taking into account the typical intralesional heterogeneity, an advanced 3-D texture analysis was performed, which demonstrated that ADC parameters associated with tumour heterogeneity (energy, local homogeneity, and entropy) were predictive of outcome in contrast to conventional ADC parameters.

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INTRODUCTION

Imaging plays an essential role in determining disease extent and treatment response in malignant lymphoma. The most commonly used imaging technique in aggressive lymphoma and follicular lymphoma is Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG-PET/CT), which has proven to be superior to contrast enhanced computed tomography (CE-CT) owing to the combined functional and anatomical information this technique provides.[1] Nevertheless, disease assessment in indolent lymphoma subtypes with low FDG-avidity still relies on anatomical CE-CT findings.[2] Furthermore, the metabolic response induced by immunotherapy can generate false positive 18F-FDG-PET/CT results, hampering accurate early treatment response assessment.[3]

In the last decade, diffusion-weighted magnetic resonance imaging (DW/MRI) has become a cornerstone in oncological imaging. Diffusion of water molecules on a microstructural level can be assessed both visually and quantitatively by determining the apparent diffusion coefficient (ADC). Restricted diffusion of extracellular water molecules in hyper cellular tissue such as tumours can be appreciated as high signal on DW/MRI images, and will generate low ADCs.[4] This quantification of DW/MRI allows for objective treatment response assessment as ADC changes during treatment can be monitored.[5] Furthermore, more advanced quantitative

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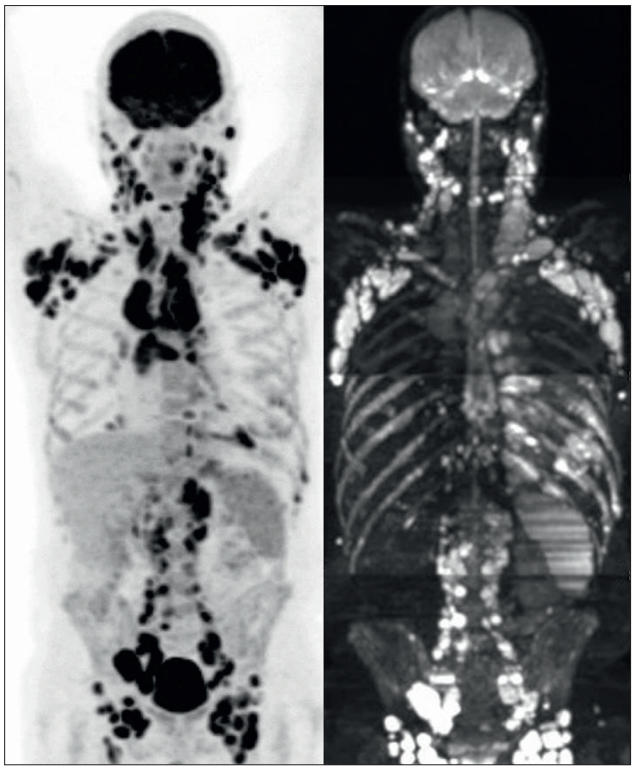

FIGURE 1. 18F-FDG-PET/CT (left) and WB-DW/MRI (right) in a patient with stage IV disease illustrates that although both techniques are based on different principles to visualise tumour, resulting images are comparable.

analyses could unravel tumour heterogeneity and improve tumour assessment.[6] Therefore, the purpose of this research was to determine the role of whole-body DW/MRI (WB-DW/MRI) for staging and early treatment response in malignant lymphoma with 18F-FDG-PET/CT and bone marrow biopsy as the gold standard.

STAGING

The results of this work demonstrated that WB-DWI/MRI is a useful tool to stage malignant lymphoma. In a first explorative study in sixteen patients with aggressive non-Hodgkin lymphoma (NHL), we found WB-DWI/MRI to agree on Ann Arbor stage with the gold standard (FDG-PET/CT and bone marrow biopsy) (*Figure 1*) in 94% of cases (15/16). Visual assessment sufficed to correctly detect bone and soft tissue lesions. In contrast, accuracy of lymph node characterisation was considerably lower, yet improved when nodal mean ADC was determined with accuracy increase from 68% to 92%. In a subsequent larger-scale prospective study including Hodgkin lymphoma (HL), aggressive and indolent NHL, we showed that WB-DW/MRI performed better than CE-CT and agreed on Ann Arbor stage with the gold standard in 76% (64/84) and 88% of cases (82/93), respectively. Better performance of WB-DW/MRI was due to a higher detection rate of bony lesions. Again, we noted that nodal misclassification was the main cause of incorrect WB-DW/MRI staging, emphasising the need for quantitative analysis. To improve the quantitative analysis consisting of mean ADC calculations, we added ADC histogram analysis. Histograms were constructed for every node plotting per-pixel ADC values, and histogram derived parameters describing the shape of this histogram were calculated. ADC skewness, a feature describing the asymmetry of the histogram shape, proved to be a more accurate and robust parameter for lymph node characterisation than the commonly used mean ADC, regardless of lymph node size.[7]

RESPONSE ASSESSMENT AND TREATMENT PREDICTION

Treatment response induces a decrease of tumour cells, which can be detected by WB-DW/MRI as an increase in mean ADC. We demonstrated that in patients with aggressive NHL, a mean ADC increase between the baseline WB-DW/MRI and one performed after two weeks of treatment was significantly higher in responding than non-responding lesions (*Figure 2*) and was associated with longer progression-free-survival (PFS).[8] These findings were confirmed in a larger-scale study including 45 patients with aggressive NHL, demonstrating that early WB-DW/MRI was an accurate and independent prognostic factor of treatment outcome in comparison with interim and end-of-treatment 18F-FDG-PET/CT as well as prognostic clinical (international prognostic index (IPI), histopathological (germinal versus non-germinal B-cell centre) and immunohistochemical features (Ki-67, BCl-2, BCl-6). For a similar study in HL, we took into account the inherent intralesional low tumour cell density and heterogeneity, and performed advanced 3D texture quantitative analysis. In contrast to interval changes of mean ADC or ADC histogram derived parameters, texture analysis parameters reflecting tumour heterogeneity, such as ADC energy, ADC local homogeneity and ADC entropy, were significantly different between responding and non-responding lesions with the latter demonstrating higher heterogeneity, and poorer PFS.

CONCLUSIONS

WB-DW/MRI is a promising imaging technique for staging malignant lymphoma and to assess and predict treatment response after only cycle of (immuno)chemotherapy without exposing patients to ionizing radiation and without the need for contrast injection.

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KEY MESSAGES FOR CLINICAL PRACTICE

1. **WB-DW/MRI is a radiation-free functional imaging technique reflecting microstructural tissue features.**
2. **WB-DW/MRI is a feasible imaging method for staging malignant lymphoma and could be particularly useful in indolent lymphoma, young or pregnant patients.**
3. **WB-DW/MRI performed after only one cycle of treatment showed good correlation with treatment response and outcome.**

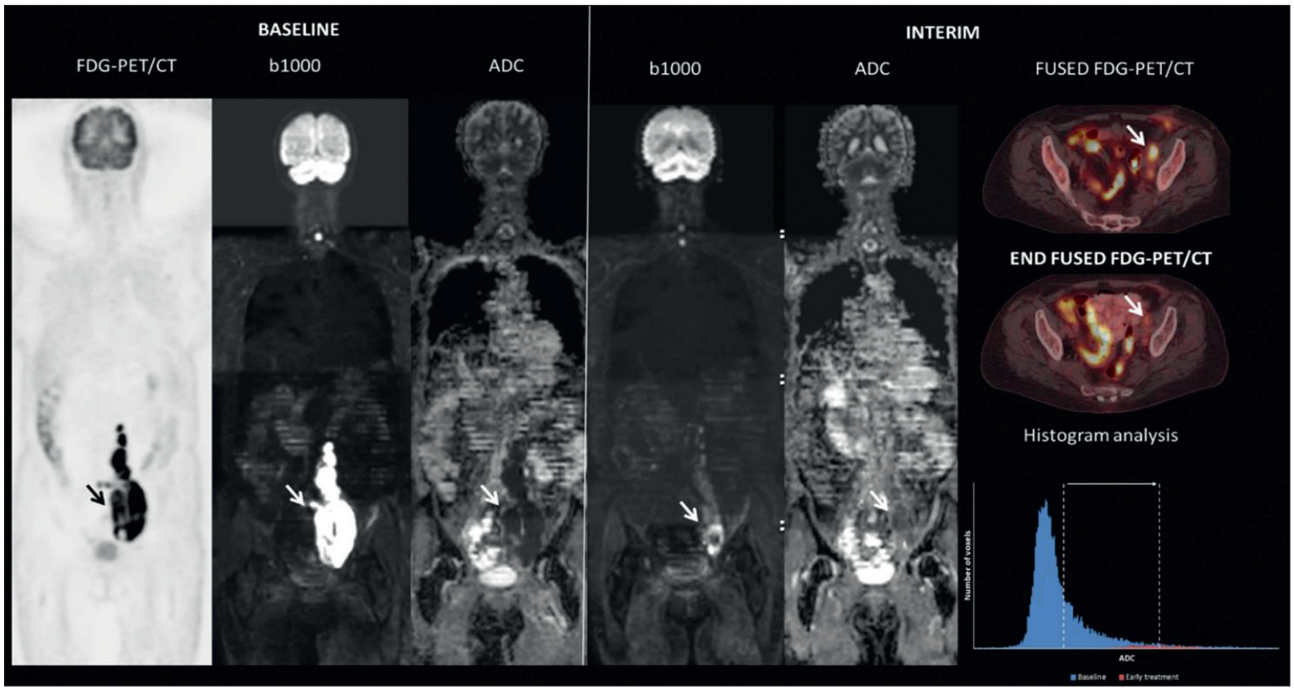

FIGURE 2. Example of a patient with diffuse large B-cell lymphoma (DLBCL) showing a large retroperitoneal-iliac mass, which demonstrated good treatment response. At baseline, the mass shows high FDG-uptake, high b1000 signal intensity and inversely low ADC value on the calculated ADC-map. After three weeks of therapy (one cycle of R-CHOP), b1000 SI of the mass has clearly decreased (and increased on the ADC-map), with the associated ADC histogram showing a significant ADCmean increase of the lesion, rendering this a responding patient. In contrast, the lesion demonstrated persistent FDG-uptake on both interim (after three cycles) and end-of-treatment FDG-PET/CT, and was consequently categorised as non-responder. No further therapy was initiated owing to reassuring clinical findings and blood results, and the patient has remained in complete remission till the end of follow-up (48 months).

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