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Whole-body diffusion magnetic resonance imaging in the assessment of lymphoma

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Abstract

The current evidence regarding the usefulness of whole-body diffusion-weighted magnetic resonance imaging (diffusion MRI) in the assessment of lymphoma is reviewed. Diffusion MRI combining both anatomical and biophysiological information is currently under investigation as a valuable tool in the oncology field including lymphoma, not only for staging but also for the assessment of response. Representative images for each purpose are shown. Diffusion MRI requires no administration of contrast medium and does not use ionizing radiation, which could be particularly advantageous for repeat follow-up surveillance in lymphoma patients. Diffusion MRI may prove to be a useful biomarker in clinical decision making for patients with lymphoma. Large-scale prospective studies are warranted to further establish its complementary value to the current standard of care, [^{18}F]fluorodeoxyglucose positron emission tomography/computed tomography.

Keywords: *Whole-body diffusion MRI; lymphoma; staging; response assessment; FDG-PET/CT.*

Introduction

Imaging biomarkers are important tools for the detection and characterization of cancers as well as for monitoring the response to therapy. Whole-body molecular imaging, in particular using [^{18}F]fluorodeoxyglucose (FDG)-positron emission tomography (PET), has been proved to be useful in the evaluation and management of lymphoma patients. FDG-PET has evolved as a valuable biomarker in aggressive lymphomas, which is the current state-of-the-art imaging technique for response assessment at the end of treatment[1,2]. Thanks to rapid technical development, whole-body functional magnetic resonance imaging (MRI), in particular diffusion-weighted MRI (diffusion MRI) reflecting cell density, is now feasible in the clinical setting. In addition to qualitative anatomical information, the so-called apparent diffusion coefficient (ADC) quantitative parameter can be derived, which may potentially help in the characterization of lesions. Lymphoma lesions are usually well visualized on diffusion MRI, because of their high cellularity and high nuclear-to-cytoplasm ratio. Lymphomas have been shown to have significantly lower ADC values compared with other tumour types in different body regions[3–5]. The use of whole-body diffusion MRI in the lymphoma setting, where extensive nodal and extranodal involvement is common, promises to be of great clinical importance.

Whole-body diffusion MRI protocol

Ever since Takahara et al. introduced whole-body diffusion-weighted imaging with background body signal suppression (DWIBS)[6], the concept of obtaining PET-like images has gained much attention. Short-tau inversion recovery (STIR) theoretically gives more homogeneous fat saturation because of its insensitivity to magnetic field heterogeneity, and is commonly used as the fat suppression method[7]. Thin axial images (usually 4–5 mm in thickness without gap) are acquired under free breathing, allowing multiple signal averaging and volumetric three-dimensional image reconstruction[7]. However, since anatomical details are lacking in these images, conventional T1- and T2-weighted sequences remain indispensable in

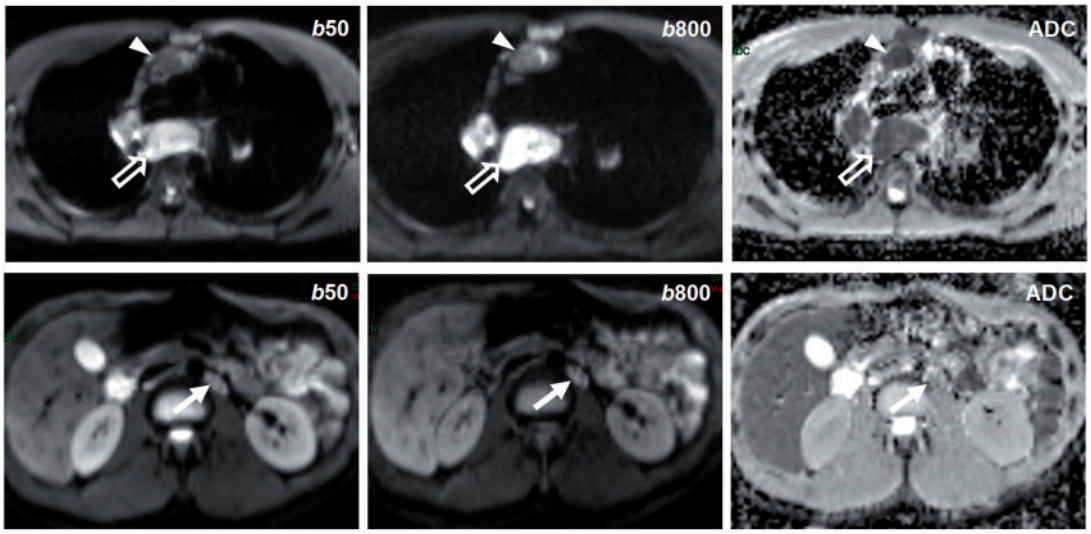

Figure 1 **3-T diffusion-weighted images with *b* values of 50 and 800 s/mm^2 (*b*50 and *b*800) and their corresponding apparent diffusion coefficient (ADC) map in a 22-year-old patient with Hodgkin lymphoma. (Upper row) the subcarinal mass (open arrow) is more conspicuous on *b*800 image but with higher ADC value, 0.794 × 10^{-3} mm^2/s, than the anterior mediastinal one (arrowhead), ADC 0.655 × 10^{-3} mm^2/s. (Lower row) the para-aortic nodes (arrow) are visible on the *b*800 image but show no restricted diffusion on the ADC map (signal intensity similar to that of back muscles, ADC 1.464 × 10^{-3} mm^2/s).**

acting as an anatomical reference for the DWIBS images, therefore adding another acquisition time to the entire MR examination[7,8]. Whole-body diffusion MRI using DWIBS is mostly evaluated qualitatively on inverted-gray images with a single *b* value in the range of 800–1000 s/mm^2. However, it should be noted that lesion conspicuity does not always parallel the ADC values (Fig. 1, upper). In addition, lesions depicted on diffusion-weighted images with high *b* values (either inverted or not on the grey scale) do not always indicate the presence of restricted diffusion (Fig. 1, lower). Therefore, recently quantitative ADC analysis was also attempted, and it is recommended that diffusion MR images should be interpreted in association with the ADC maps[8].

Although ADC measurement of a large, relatively uniform organ such as the liver appears to be accurate with free breathing, respiratory motion can still result in ADC errors for small focal lesions such as lymph nodes because of signal contamination by adjacent tissues[9]. To minimize slice-position mismatch between different *b* values and different excitations, we designed a whole-body "respiratory-gated" diffusion MR 1.5-T (Avanto; Siemens Healthcare, Erlangen, Germany) protocol using exclusively a single-shot spin-echo echo-planar imaging sequence[10]. Three trace *b* values, 50, 400 and 800 s/mm^2 (*b*50, *b*400 and *b*800; instead of the commonly used two data points), were used to more reliably assess the ADC values from the skull base to upper thighs (or lower in the case of a lesion). Image analysis was performed on native diffusion-weighted images and their corresponding axial ADC maps but not on reconstructed images, the same way as for all kinds of MR studies. Diffusion-weighted *b*50 images not only provide anatomical information equivalent to the conventional T2-weighted images but also eliminate signals from vessels, therefore allowing more selective visualization of adjacent lymph nodes[11]. Moreover, most perfusion effects can be reduced in this case in comparison with ADC calculation with the lowest *b* value set at 0. Spectrally selective fat saturation was used to obtain a reasonable total acquisition time (30–45 min) and a higher signal-to-noise ratio (SNR) than STIR (acquisition time twice as long)[10]. Therefore, the acquisition time for the conventional MR sequences can be saved, resulting in a shorter total time than those in common DWIBS protocols. Signal reception can use the machine's integrated body coil, but better-quality images can be obtained with local surface coils[8,10]. The respiratory gating can be waived for body regions with negligible motion, therefore saving total acquisition time; however, the repetition time should be kept at about the duration of a respiratory cycle, i.e., approximately 3000 ms, in order to keep adequate T2 contrast.

Several studies have shown the potential of whole-body diffusion MRI in lymphomas for staging and response assessment on 1.5-T MR systems[10,12–16]. Whole-body diffusion MRI at 3.0 T has the potential to improve image SNR but is more technologically challenging because of the greater frequency of susceptibility artefacts at the air–tissue interface, i.e., the supraclavicular region, and poorer fat suppression over large fields of

view[8]. To date two published studies, one for staging and the other for early response assessment, have been successfully performed on 3.0-T systems[17,18]. Our own experience on 3.0-T MR systems (Verio and Trio; Siemens Healthcare) showed decreased mean total time of acquisition, from 25 to 40 min depending on patients' respiratory cycles and the gradient performance of each system. Image quality was rated good to excellent (score 3 or 4 over 4), with equivalent diagnostic performance to that of the 1.5-T system. These initial experiences clearly demonstrated the clinical feasibility of a 3.0-T whole-body diffusion MRI protocol. Compared with our previous 1.5-T protocol, the major difference would be for the "neck" region, where the inversion recovery method was indispensable in achieving optimal fat suppression. In addition, manual shimming was carefully applied; for example, the shoulders with sharp air–tissue interfaces were placed at the centre of a station and also at the isocentre of the magnet. Patients were instructed not to swallow during the acquisition of the neck region.

Lesion detection/staging

Nodal involvement

Since pathological confirmation of each lymphoma lesion is both ethically and technically not feasible, our diffusion MR findings for patients with diffuse large B-cell lymphoma (DLBCL) have been compared with those of FDG-PET/computed tomography (CT) as the reference standard. Although it is known that size criteria lack the desired accuracy for characterizing lymph nodes[8,12,19], our results showed that for the purpose of pre-treatment staging, the ability of diffusion MRI for detection of lymph node involvement based on size criteria alone (i.e., node larger than 10 mm in the "greatest" transverse diameter according to Cheson et al.[20]) was comparable with that of FDG-PET/CT[10]. Studies of whole-body MRI using only T2-weighted images for paediatric lymphoma staging also corroborated this point[21,22].

In addition to size measurement, the signal intensity of lymph nodes on ADC maps was also visually assessed in comparison with that of back muscles on the same image slice. A signal hypointense to muscle was designated as having restricted diffusion[10,16]. The majority of the lymphoma nodes appeared with restricted diffusion except under circumstances of huge mass, where the signal may be heterogeneous because of focal necrosis, or in Hodgkin lymphoma where fibrosis comprised part of the tumour mass (Fig. 2). When visual ADC analysis was combined with the size criteria, the diffusion MRI specificity increased to 100% but with decreased sensitivity of 81%[10]. Although ADC analysis may potentially help in depicting subcentimetric lymph node involvement[10], the reliability of ADC values in such small lesions under current imaging resolution and slice thickness warrants further investigations. Moreover, the clinical significance of involved subcentimetric lymph nodes is less important in lymphoma patients who have larger masses and require systemic chemotherapy than in those with cancer types that require local treatment, such as head and neck cancers.

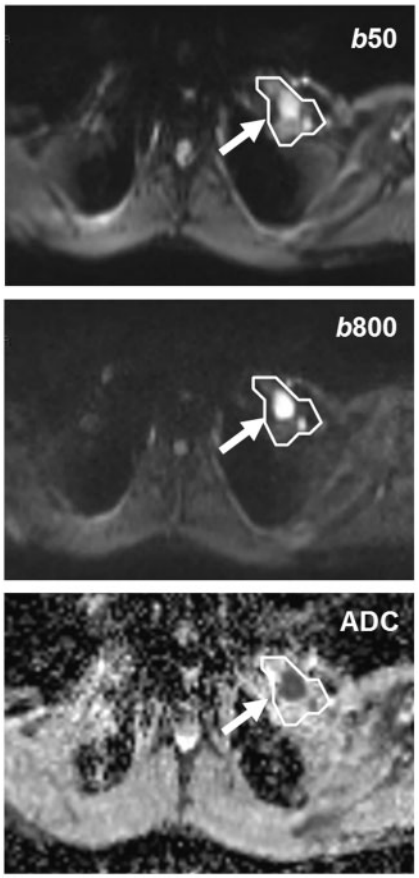

Figure 2 **Same patient with Hodgkin lymphoma as in Fig. 1. The left supraclavicular mass (arrow) is present with heterogeneous signal intensity on the 3-T diffusion-weighted images (*b*50 and *b*800), as well as on the ADC map.**

It should be noted that not all FDG-PET-positive lymph nodes had low ADC values. Small lymph nodes adjacent to the lungs, heart or diaphragm may show falsely high ADC values probably related to susceptibility artefacts and heart or respiratory motion[10], and therefore are not well visualized on DWIBS images with high *b* values[12] (Fig. 3). Finally, currently the diffusion MRI has limited ability in differentiating low-grade from high-grade lymphoma subtypes, since they all present with increased cell density; however, this could potentially be complementary to FDG-PET in estimating tumour burden from non-FDG-avid subtypes, e.g., low-grade follicular lymphoma[10].

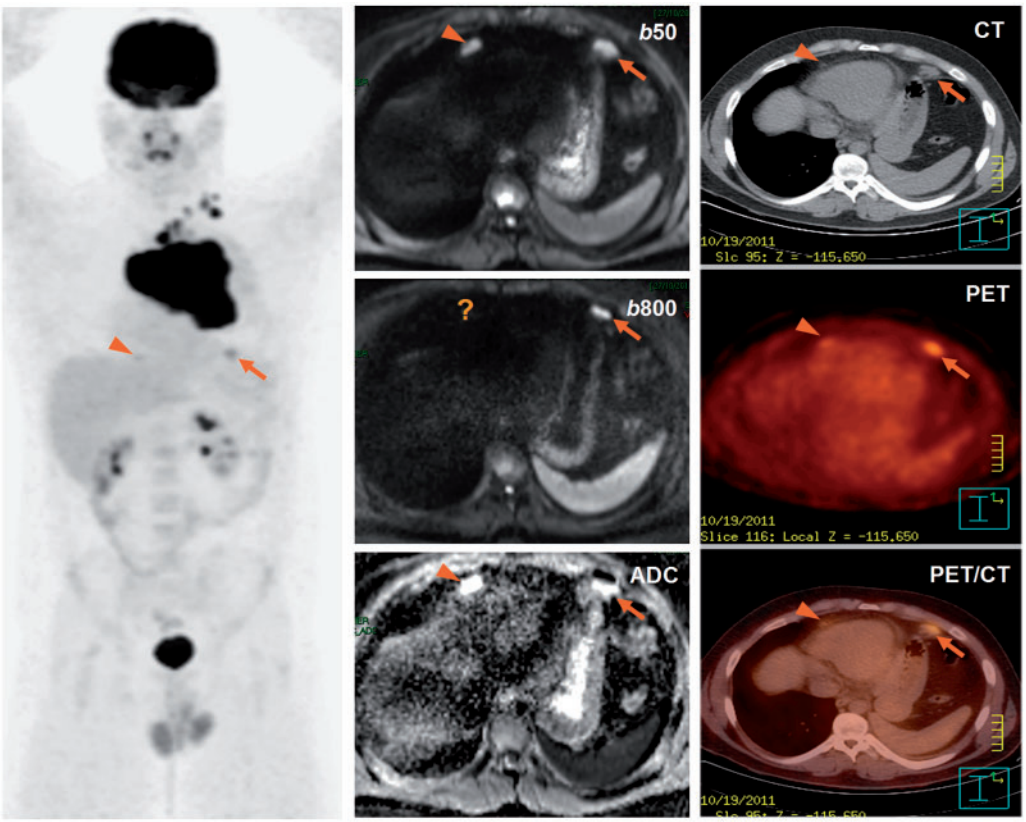

Figure 3 **Whole-body FDG-PET image in maximum-intensity projection, axial 3-T diffusion-weighted images (*b*50 and *b*800) including the ADC map, and FDG-PET/CT images in a 19-year-old patient with primary mediastinal B-cell lymphoma. Although the diffusion-weighted images were acquired under respiratory gating, the bilateral FDG-avid diaphragmatic nodes (arrowhead and arrow) appear completely white on the corresponding ADC map, probably related to cardiac motion and/or lung susceptibility artefacts.**

Extranodal involvement

Because of excellent soft-tissue contrast, whole-body diffusion MRI helped to identify additional lesions in comparison with FDG-PET/CT, in particular extranodal involvement in the liver, spleen, and kidneys[10,11] (Fig. 4). Similar to nodal lesions, extranodal lymphoma involvement frequently shows restricted diffusion. Therefore, diffusion MRI is not able to depict "diffuse" spleen involvement as FDG-PET does, and bone marrow lesions can sometimes be overlooked because normal spleen and bone marrow already show restricted diffusion. However, small focal splenic lesions can still be clearly delineated on the respiratory-gated diffusion MRI[10]. The detection of lung lesions is still challenging owing to susceptibility artefacts, and are better assessed with "qualitative" analysis because the validity of their ADC values is unknown, in particular in small lesions.

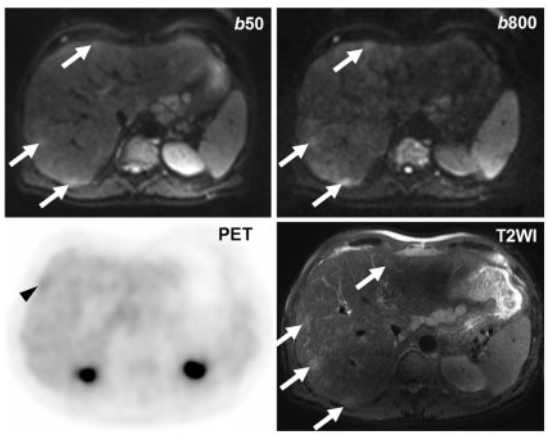

Figure 4 **1.5-T diffusion-weighted images (*b*50 and *b*800) and FDG-PET image in a 57-year-old patient with histologically proven concomitant diffuse large B-cell lymphoma and follicular lymphoma. Diffusion MRI helped to detect miliary hepatic lesions (arrows) while FDG-PET shows only equivocal focal increased uptake (arrowhead). Hepatic involvement was confirmed on the dedicated hepatic T2-weighted images (T2WI) (arrows).**

Response assessment

While size criteria alone may be sufficient for the initial lymph node staging, bio-physiological information

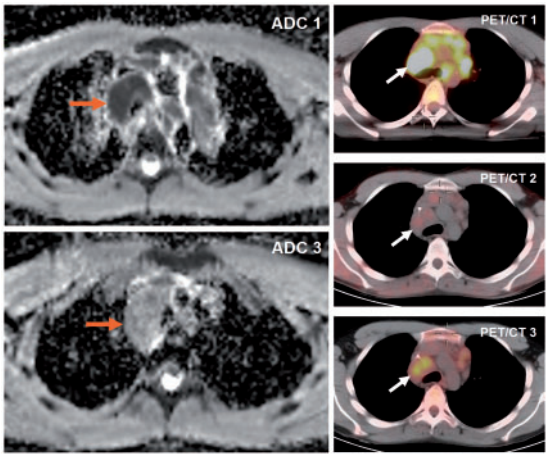

Figure 5 **Serial 3-T ADC maps and FDG-PET/CT images (no. 1 at baseline, no. 2 after two cycles, and no. 3 after four cycles of chemotherapy) for the same patient with Hodgkin lymphoma as in Fig. 1. The ADC of the right paratracheal nodal mass (arrow) increased from 0.606×10^{-3} mm^2/s at baseline to 1.554×10^{-3} mm^2/s after four cycles, indicating a good response to treatment while stable disease was issued based on Cheson's CT criteria. Low residual FDG uptake was noted after two cycles, which increased in intensity after four cycles of chemotherapy. Mediastinoscopic biopsy directly after the third PET/CT scan revealed no evidence of residual disease.**

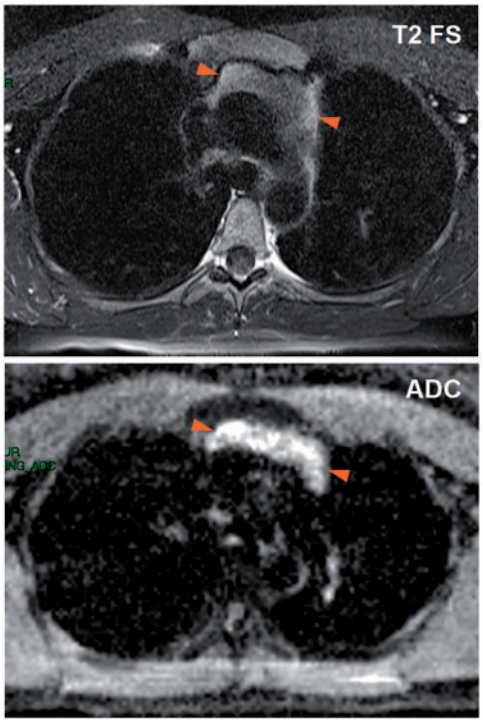

Figure 6 **A 30-year-old patient with cervico-mediastinal Hodgkin lymphoma was considered in complete remission on CT and FDG-PET/CT at the end of treatment. An anterior mediastinal mass (arrowheads) was identified during the 6-month post-treatment CT follow-up. The mass lesion shows no restricted diffusion on the ADC map, and is therefore more in favour of a benign thymic hyperplasia. T2 FS, T2-weighted fat-saturated MR image. Signal drop on opposition phased T1-weighted images confirmed fat content (images not shown).**

provided by diffusion MRI regarding the change of cellularity, tissue composition and architecture after treatment will potentially be helpful in response assessment as compared with diagnostic CT or conventional MR examinations (Fig. 5). Our previous results in DLBCL patients also showed that post-treatment ADC values of residual masses (lymph node regions and organs) on whole-body diffusion MRI increased significantly compared with baseline[16]. Combining ADC analysis would have decreased substantially the false-positive interpretation, both for the nodal and extranodal residual lymphoma involvement[16]. Future studies are required to establish the role of ADC in characterizing lymphoma residual tumours. Recently we noticed in one patient at the end of therapy that the post-treatment inflammatory process may result in false-positive findings on diffusion MRI and FDG-PET/CT owing to macrophage proliferation. Diffusion MRI may also help in differentiating anterior mediastinal residual or recurrent tumour from benign thymic rebound, which is common in both children and young adults after chemotherapy[23] (Fig. 6).

Conclusion

Whole-body diffusion MRI seems a feasible and promising technique for both initial staging and response assessment in patients with lymphoma. Investigators should be familiar with the caveats when interpreting ADC maps. In addition, there is still no agreement concerning the *b* values applied, which may compromise the reproducibility of the results among different study series. It should also be noted that thus far most of the studies have included mixed histological subtypes of lymphoma patients. Larger-scaled prospective studies with long-term follow-up are necessary to confirm its usefulness in the management of lymphoma patients.

Conflict of interest

The authors have no conflicts of interest to declare.

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