From multislice CT to whole-body biomarker imaging in lymphoma patients

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Abstract Until recently, only nuclear medicine techniques allowed combining whole-body anatomical and functional information. Now, diffusion-weighted imaging seeks to compete with these techniques in the field of oncology, providing assessment of tumour spread, characterizing lesions and evaluating therapeutic response. The first issue has been widely evaluated since the first published whole-body diffusion-weighted images looking like scintigraphy. Optimal background suppression and diffusion weighting highlighted tumours with restricted diffusion. For the two latter issues, ADC seems to represent the key element; it should allow differentiation between benign and malignant tissue, and active from inactive lesions after treatment. This is of paramount importance for the monitoring of lymphomas treated with chemotherapy alone, or for solid tumors treated by neoadjuvant therapies. However, imaging protocols still differ between studies, and there is considerable overlap in ADC values between healthy and neoplastic tissues. Despite this difficulty to identify a clinically reliable threshold for malignancy, there is no doubt that ADC will represent as a reliable biomarker in the future for some malignancies, and lymphomas represent a helpful model for this purpose.

Keywords Diffusion · Lymphoma · Whole-body imaging · Drug therapy · MRI

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Magnetic resonance imaging (MRI) has been established for years as a versatile morphological imaging modality, combining high spatial resolution and tissue contrast. More recently, it also has been developed to a method that can be used to get functional or even metabolic information. These developments are driven by the need of a better staging of diseases (particularly tumours), characterization of disease subtypes or by applications in the field of treatment monitoring.

Indeed, imaging techniques play more than ever a prominent role in the management of the care of the patient who has suspected or known malignancy. Images are needed at every step of patients' support: diagnosis, staging, re-evaluation and follow-up. The ideal examination for this purpose would therefore combine extensive anatomical coverage, high spatial resolution and contrast, good reproducibility with minimal radiation exposure and acceptable duration and cost. Recently, Lin et al compared whole-body diffusion-weighted MRI (DWI) with FDG-PET in patients with aggressive lymphomas [1]. This article illustrates the potential role of DWI as an alternative to FDG-PET in staging spread of disease and in assessing total tumour burden. Not only does DWI findings match PET/CT in 94% of lymph node regions and 100% of extranodal lesions, but also the images shown are remarkable in terms of contrast and spatial resolution. Additionally, the use of carefully selected b values allows image analysis of good quality ADC maps. FDG-avid lesions at PET/CT exhibit restricted diffusion in 89% of cases. Interestingly, some PET-positive lymph node regions that showed high signal on ADC maps had low SUV values. Therefore, DWI, which reflects cellularity and tissue architecture, tends to correlate with FDG-PET, which indicates glucose metabolic activity and disease aggressiveness. Kwee et al have assessed the value of whole-body magnetic resonance

imaging (MRI), including diffusion-weighted imaging (DWI), for the initial staging of malignant lymphoma, compared with computed tomography (CT). Their results suggest that in the initial staging of malignant lymphoma, whole-body MRI (with and without DWI) provides similar results in the majority of patients to staging using CT. Indeed whole-body MRI never understaged relative to CT and usually correctly overstaged relative to CT, with a possible advantage of using DWI [2].

There is no doubt that MRI will have an enormous impact in cancer patients in the future. Controlling table movements and matching the centre of the region of interest to the centre of the bore of the magnet have now overcome the limitation of anatomical coverage for staging (Fig. 1). The limitation of reliable biomarker indices for tumour characterization is being currently widely investigated. Spectroscopy, perfusion or diffusion have now also found their place in many MR protocols for various organs such as brain, breast, liver or prostate, providing multifunctional mapping. However, diffusion is probably the most promising one to date, as it remains compatible with whole-body examinations while maintaining a reasonable duration (30–45 min.), making it usable on a routine clinical basis. This is enabled by multi-channel RF coil arrays coupled with parallel imaging reconstruction techniques. With DWI in cancer patients, we are currently at the very beginning of the story, as was FDG-PET 10 years ago. However, despite continuous technical improvements, one cannot consider DWI as an artefact-free technique. Apart from the usual contraindications to MRI, metal implants or simply regions that are prone to magnetic field heterogeneity such as shoulders may preclude lesions' detection and characterization.

The next challenge will be the assessment of therapeutic response, especially in high-grade lymphoma. Currently, it is based on the International Working Group Criteria, which were elaborated in 1999 and modified in 2007. In non FDG-avid lymphomas, bidimensional measurements of lesions representative of tumour burden on contrast-enhanced CT remain the cornerstone of patients' evaluation. In FDG-avid lymphomas, integrated PET/CT has become the problem solver in case of residual masses, eliminating the concept of uncertain complete response; however, it should be interpreted preferably in comparison with a baseline PET/CT. If DWI should become an efficient tool for both staging and follow-up, ADC should prove to be biomarker at least as reliable as the SUV in PET/CT. This obviously deserves further studies in larger series of patients. Hence, Huang et al. have evaluated the feasibility of T2-weighted MRI and DWI for in vivo detection of response of human diffuse large B-cell lymphoma xenografts in severe combined immunodeficient mice to

multi-agent chemotherapy. DWI revealed a significant ($P<0.03$) increase in the mean apparent diffusion coefficient treated tumours as early as 1 week after initiation of treatment. However, a significant ($P<0.03$) decrease in mean T2 was observed only after two cycles. The therapeutic response of the treated tumours detected by MRI was accompanied by changes in tumour cell density, proliferation and apoptosis revealed by histological studies performed upon completion of the longitudinal study [3]. In solid tumours, many recent papers investigate the role of DWI in the monitoring of neoadjuvant chemotherapy. Therapy-induced changes in ADCs of lymph node metastases address the same issues as the management of lymphomas. Two recent papers investigate the changes in ADCs after chemoradiation of locally advanced rectal cancer [4, 5]. Kim et al measured ADCs in rectal cancer before and after neoadjuvant chemoradiation. They show that post-chemoradiation ADC alone can reliably differentiate a pathologically complete response (pCR) from a non-pCR in locally advanced rectal cancer [4]. Conversely, Lambregts et al show that DWI as a stand alone technique is not reliable, and recommend using preferably T2-weighted images to assess pCR [5]. The main gain from the addition of DWI would be an increase in the number of detected nodes and an improved PPV for identification of metastatic nodes.

DWI could be considered an important supportive tool for the diagnosis of enlarged cervical lymph nodes. A threshold value of $1.03 \times 10^{-3} \text{ mm}^2/\text{s}$, could help to distinguish benign from malignant nodes with a sensitivity of 100% and a specificity of 92.9% [6]. Holzapfel et al, have reported similar results using a threshold ADC value of $1.02 \times 10^{-3} \text{ mm}^2/\text{s}$ [7]. Also, Sumi et al demonstrated recently that MRI allows differentiation between lymphoma and squamous cell carcinoma on the basis of ADCs in cervical lymph nodes [8]. However, Lambregts et al found a significant difference of ADCs between malignant and benign lymph nodes in patients with rectal cancer, but a considerable overlap in values made it difficult to identify a clinically reliable threshold for malignancy [5]. Kwee et al suggest that ADC measurements may not always be sufficiently reproducible to discriminate malignant from non-malignant lymph nodes in free breathing conditions. They found that mean ADC of normal lymph nodes varied between 1.15 and $1.18 \times 10^{-3} \text{ mm}^2/\text{s}$. However, in their study, limits of agreement for inter or intra-observer could reach $\pm 30\%$ [9]. This low reproducibility could be explained by a slice position mismatch between different b values in free breathing condition. Because of the allowance of respiratory motion in DWIBS, slice levels of images obtained with different b-values may not be identical. Consequently, ADC measurements of moving organs in DWIBS may be less accurate, less reproducible,

Fig. 1 Pre (left) and post (right) treatment whole-body DWI in a patient with diffuse large B-cell lymphoma who responded well to chemotherapy. Targets lesions are left cervical lymph nodes (arrows).

After treatment the lymph nodes exhibit a marked decrease in their size and an increase in their signal on the ADC map

and different from breath hold or respiratory triggered DWI [10]. The individual ADCs in DWIBS are more scattered than those in respiratory-triggered DWI. In their study, Lin et al recommend for ADC mapping a respiratory-gated acquisition [1]. However, data acquisition time for respiratory triggered DWI is approximately 2 to 3 times longer [10]. In addition, mean reading times for staging assessment on whole-body DW images are 30% shorter than those on whole-body MR images obtained with DW imaging and integrated FDG PET/CT images [11]. More in-vivo research is needed to determine the accuracy and reproducibility of ADC measurements in DWIBS.

Lastly, the ultimate aim would be to improve the management of patients with lymphoma by identifying those patients who can be cured with minimal treatment and equally those for whom conventional treatment is doomed to failure and in whom more intensive strategies should be employed from the outset. ADC as an index of tumour aggressiveness deserves also further investigations. Hence, ADC measurements within contrast-enhancing regions of primary central nervous system lymphoma tumours may provide non-invasive insight into clinical outcome. ADC

measurements less than the median value of $0.7 \times 10^{-3} \text{ mm}^2/\text{s}$ could be associated with shorter progression-free and overall survival [12].

In summary, MRI is now a multifunctional imaging technique, which allows detecting biophysical or metabolic parameters that can be used as biomarker for the assessment of underlying biological processes in a wide variety of tissues and diseases. The number of recent papers on DWI in various malignant conditions clearly predicts a success story. However, it has taken years for DWI to find its place in neuroimaging, and just as many years for FDG-PET in oncology. Now things are clearer in these two fields. For DWI in cancer patients, there is no standardized protocol for DWI in terms of b values, and no clear threshold of ADCs between benign and malignant conditions. Also, there is still a debate on the need to combine functional maps with morphological images, and on the need to perform pre and post-therapy evaluations. A consensus has to be found in imaging protocols to make DWI a reliable cancer biomarker [13]. As often stated, further studies are deserved before DWI comes to maturity, despite very promising initial results.

References

1. Lin C, Luciani A, Itti E et al (2010) Whole-body diffusion-weighted magnetic resonance imaging with apparent diffusion coefficient mapping for staging patients with diffuse large B-cell lymphoma. *Eur Radiol* 20:2027–2038
2. Kwee TC, van Ufford HM, Beek FJ et al (2009) Whole-body MRI, including diffusion-weighted imaging, for the initial staging of malignant lymphoma: comparison to computed tomography. *Invest Radiol* 44:683–690
3. Huang MQ, Pickup S, Nelson DS et al (2008) Monitoring response to chemotherapy of non-Hodgkin's lymphoma xenografts by T(2)-weighted and diffusion-weighted MRI. *NMR Biomed* 21:1021–1029
4. Kim SH, Lee JY, Lee JM, Han JK, Choi BI (2010) Apparent diffusion coefficient for evaluating tumour response to neoadjuvant chemoradiation therapy for locally advanced rectal cancer. *Eur Radiol*. doi:10.1007/s00330-010-1989-y
5. Lambregts DM, Maas M, Riedl RG et al (2010) Value of ADC measurements for nodal staging after chemoradiation in locally advanced rectal cancer—a per lesion validation study. *Eur Radiol*. doi:10.1007/s00330-010-1937-x
6. Perrone A, Guerrisi P, Izzo L et al (2009) Diffusion-weighted MRI in cervical lymph nodes: differentiation between benign and malignant lesions. *Eur J Radiol*. doi:10.1016/j.ejrad.2009.07.039
7. Holzapfel K, Duetsch S, Fauser C, Eiber M, Rummeny EJ, Gaa J (2009) Value of diffusion-weighted MR imaging in the differentiation between benign and malignant cervical lymph nodes. *Eur J Radiol* 72:381–387
8. Sumi M, Nakamura T (2009) Diagnostic importance of focal defects in the apparent diffusion coefficient-based differentiation between lymphoma and squamous cell carcinoma nodes in the neck. *Eur Radiol* 19:975–981
9. Kwee TC, Takahara T, Luijten PR, Nieuvelstein RA (2009) ADC measurements of lymph nodes: inter- and intra-observer reproducibility study and an overview of the literature. *Eur J Radiol* 75:215–220
10. Nasu K, Kuroki Y, Sekiguchi R, Nawano S (2006) The effect of simultaneous use of respiratory triggering in diffusion-weighted imaging of the liver. *Magn Reson Med Sci* 5:129–136
11. Ohno Y, Koyama H, Onishi Y et al (2008) Non-small cell lung cancer: whole-body MR examination for M-stage assessment—utility for whole-body diffusion-weighted imaging compared with integrated FDG PET/CT. *Radiology* 248:643–654
12. Barajas RF Jr., Rubenstein JL, Chang JS, Hwang J, Cha S (2010) Diffusion-weighted MR imaging derived apparent diffusion coefficient is predictive of clinical outcome in primary central nervous system lymphoma. *AJNR Am J Neuroradiol* 31:60–66
13. Padhani AR, Liu G, Mu-Koh D et al (2009) Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. *Neoplasia* 11:102–125