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Whole body MRI and PET/CT in haematological malignancies

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Abstract

The usefulness of whole body magnetic resonance imaging (MRI) and positron emission tomography (PET)/computed tomography (CT) in haematological malignancies is reviewed. PET/CT combining functional and anatomical information is currently a valuable tool in the management of patients with lymphoma, especially in the assessment of early treatment response. MRI is advantageous in evaluating bone marrow involvement and therefore plays an important role in clinical decision making for patients with myeloma. The development of whole body functional MR studies is underway and can potentially complement the PET/CT for better patient care.

Keywords: *Whole body; MRI; PET/CT; functional imaging; treatment response.*

Introduction

Therapeutic strategies as well as patients' prognoses strongly depend on initial accurate diagnosis and tumour staging as well as therapeutic response monitoring, especially in haematological malignancies where extensive disease involvement is common. Therefore, development of an imaging modality which can encompass the entire body is of great importance. Whole body (WB) imaging can be achieved with positron emission tomography (PET) by providing functional information on tumour metabolism. The introduction of combined PET/computed tomography (CT) has produced even more promising results for oncological imaging[1]. Magnetic resonance imaging (MRI) provides excellent tissue contrast, detailed morphological information and lack of ionizing radiation. Moreover, the rapidly evolving technique with multi-channel phased array surface coils and parallel imaging acquisition has enabled a high-spatial-resolution WB MR exam within a reasonable time. Functional information, either focused dynamic contrast-enhanced study or WB diffusion-weighted imaging (DWI), can currently be combined with anatomic coverage[2,3]. The objective of this paper is to review the usefulness of WB MRI and PET/CT in the management of haematological malignancies.

PET/CT

Lymphoma

Imaging with [^{18}F]fluorodeoxyglucose (FDG) PET is increasingly recognized as a valuable tool for lymphoma management. The advantage of PET over conventional imaging techniques, such as CT or MRI, is that PET increases the ability to distinguish between viable tumour and necrosis or fibrosis in residual masses after treatment. Recently, the International Working Group (IWG) response criteria have been revised by incorporating PET information which allows the elimination of the complete remission/unconfirmed (CRu) category[4].

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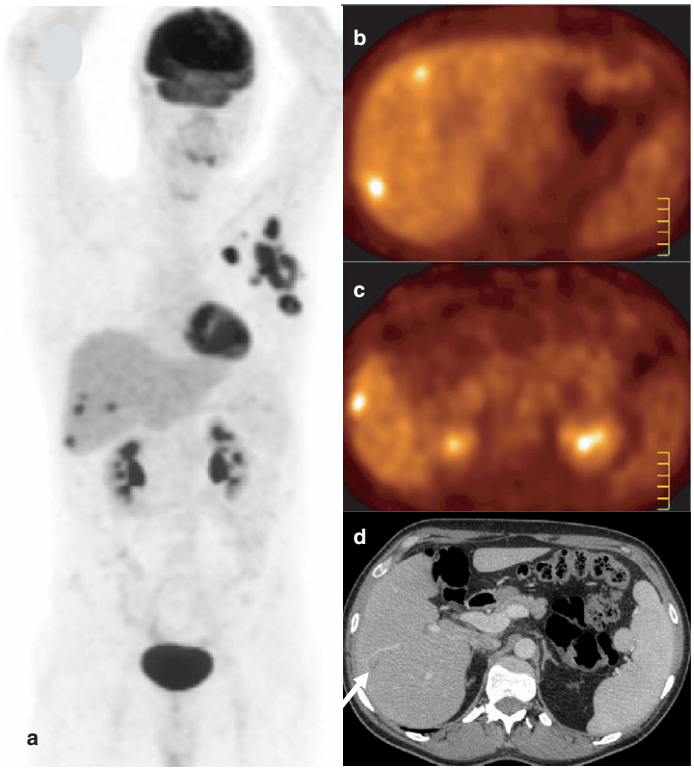

Figure 1 **A 36-year-old patient with aggressive non-Hodgkin's lymphoma who initially presented with a huge left axillary mass and partial response at completion of first-line chemotherapy. At re-staging 10 months later (a–c), PET/CT with FDG demonstrates, in addition to local residual disease over the left axillary region, at least four occult hepatic lesions (fused-CT images not shown). Only one of the lesions (arrow) can be retrospectively identified on the contrast-enhanced abdominal CT performed 9 days earlier (d). The patient's condition deteriorated rapidly after the PET/CT exam.**

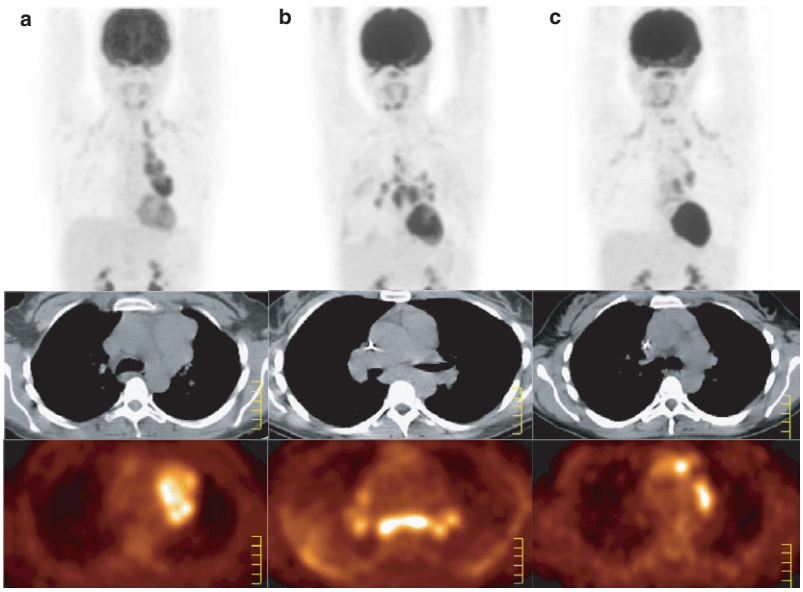

Figure 2 **A 31-year-old patient presented with Hodgkin's lymphoma. (a, left column) Baseline PET/CT shows left anterior mediastinal mass with associated lymph nodes over left lower neck. (b, middle column) PET/CT at the end of treatment demonstrates abnormal FDG uptake, mainly in the subcarinal and bilateral hilar areas, which was proven by mediastinoscopic lymph node biopsy to be related to sarcoidosis instead of disease progression. (c, right column) PET/CT performed 6 months later, lymphoma relapse over the anterior mediastinum is noted while the activity of sarcoidosis regresses. Note: faint bilateral neck and axillary uptake corresponds to physiologic brown fat activity.**

Staging

Compared with CT which relies on size criteria, FDG PET alone is more sensitive for occult splenic disease and improves the detection of bone lesions and small tumour foci for instance lymph nodes <1 to 1.5 cm) (Fig. 1). Tatsumi *et al.*[5] have shown in a series of 53 patients with lymphoma (20 Hodgkin and 33 non-Hodgkin) using a combined PET/CT scanner that out of 48 discordant sites, PET was correct in 40 (83%) while false-negative CT findings were mostly attributable to small lesion size. PET provided accurate staging in an incremental nine (17%, upstaging in four and downstaging in five) while CT provided correct upstaging in two patients. PET/CT, combining both functional and precise anatomical/attenuation correction information, allows more reliable lymphoma staging[6]. Metabolic imaging is particularly important in distinguishing disseminated disease from localized disease that might be amenable to irradiation. However, PET is weak in detecting central nervous system (CNS) involvement, and PET complements but cannot replace bone marrow biopsy; in addition, physiologic uptake by the bowel, muscles or even brown fat should be carefully identified on co-registered CT images.

Response monitoring/prognosis stratification

The role of PET or PET/CT in monitoring response to treatment in lymphoma cannot be overemphasized. Not only has it been integrated into the revised IWG criteria at completion of first-line therapy, the mid-therapy (interim) exam has also emerged as a powerful prognostic tool and is more informative than established prognostic indices and proposed immunohistophenotyping[7–9]. PET is strongly recommended at baseline and for post-treatment assessment of diffuse large B-cell lymphoma (DLBCL) and Hodgkin's lymphoma since a complete response after 4–6 treatment cycles is required for a curative outcome. However, PET is not routinely recommended in other incurable histologies—only if they were PET positive before therapy[4].

Regarding the early response assessment (mostly after only two cycles of chemotherapy), several studies have demonstrated that a negative interim PET is highly predictive of either event or progression-free as well as overall survival[7,8,10]. Of particular clinical significance is that most patients who respond rapidly to first-line therapy will more probably achieve durable remission. To the contrary, those who have persistent abnormal FDG uptake at mid-therapy PET might potentially benefit from more toxic treatments.

However, interpretation of PET relies mainly on qualitative visual analysis, i.e. positive or negative; therefore, the reproducibility of the response designation may be compromised especially when only minimal residual uptake is present. Moreover, some interim PET-positive patients still have a good outcome[7]. Semiquantitative measures such as the standardized uptake value is clinically feasible and has been recently proven helpful in patient risk stratification, both in Hodgkin's and non-Hodgkin's lymphoma[8,11]. Finally, in the post-therapeutic setting, some false-positive findings of FDG-PET caused by infections or the inflammatory process, more difficult to recognize, require rigorous imaging and clinical correlation for patient management (Fig. 2). Patients with complete IWG response still require further regular CT follow-up as disease relapse can happen even if the post-therapeutic PET at completion of first-line therapy is negative.

Myeloma

In contrast to the well established application in lymphoma, PET studies focusing on the management of myeloma are relatively limited. The role of imaging includes an assessment of the extent of intramedullary disease, detection of extramedullary foci, severity of disease at presentation and later follow-up, and the identification of complications[12]. FDG-PET has been shown to be valuable in detecting extramedullary disease and provide important prognostic information[13]. Along with MRI, PET information has been recently integrated in the Durie/Salmon PLUS staging system, guiding clinical decision making[14]. In one study, FDG PET/CT was found to lead to management changes in 9/16 patients but is less sensitive than MRI of the spine in the detection of diffuse bone marrow infiltration[15]. Another PET/CT study using [^{11}C]methionine also demonstrated the potential to image active myeloma lesions[16].

WB MRI

Currently WB MRI is not yet uniformly accepted as an imaging modality, either for staging or for treatment follow-up, because of the lack of wide availability and inadequate clinical-based evidence. However, rapidly evolving technique and continuous development of functional studies has shown its potential.

Lymphoma

In a study on eight children with lymphoma, WB MRI using short tau inversion recovery (STIR) has been proven more sensitive than conventional imaging (CT, gallium-67 scintigraphy, bone scintigraphy) in detecting bone marrow involvement at initial staging while detection of nodal and visceral involvement correlated well[17]. However, until now PET/CT remains the most accurate modality in lymph node staging[3,18]. Recent development of WB MR diffusion-weighted imaging (DWI) can provide functional information on lesions related to motion of water molecules over very small distances[2]. Lesions with higher cellularity and

water motion restriction such as lymphoma foci show a higher signal. Ballon *et al*.[19] have demonstrated in a patient with acute myelogenous leukaemia that this rapid WB MRI technique can feasibly monitor the therapeutic response of bone marrow disease. The clinical potential of WB DWI in haematological malignancy should be evaluated on the basis of larger patient cohorts.

Myeloma

Morphological study

WB MRI has been recognized as the only imaging technique that allows direct visualization of bone marrow and its components with high spatial resolution compared to X-rays, CT and scintigraphy[20]. State-of-the-art sequences consist of a combination of spin-echo T1-weighted and T2-weighted images (T2WI) with fat saturation (Fig. 3). It is more sensitive and specific than radiological skeletal survey and reveals bone marrow disease and extensive disease more reliably[21]. Several studies demonstrated that X-rays often yield false negative results, especially in the spine and pelvis, where anatomical structures are complex and overlaid by bowels or ribs[22]. WB MRI also helps in detecting occult bone marrow infiltration in solitary plasmacytoma and allowing tumour mass assessment with hypo- or non-secretory disease. Moreover, the number of MRI-detected focal lesions has been shown to independently affect survival in a prospective study with 611 newly diagnosed patients[23]. When considering treatment response

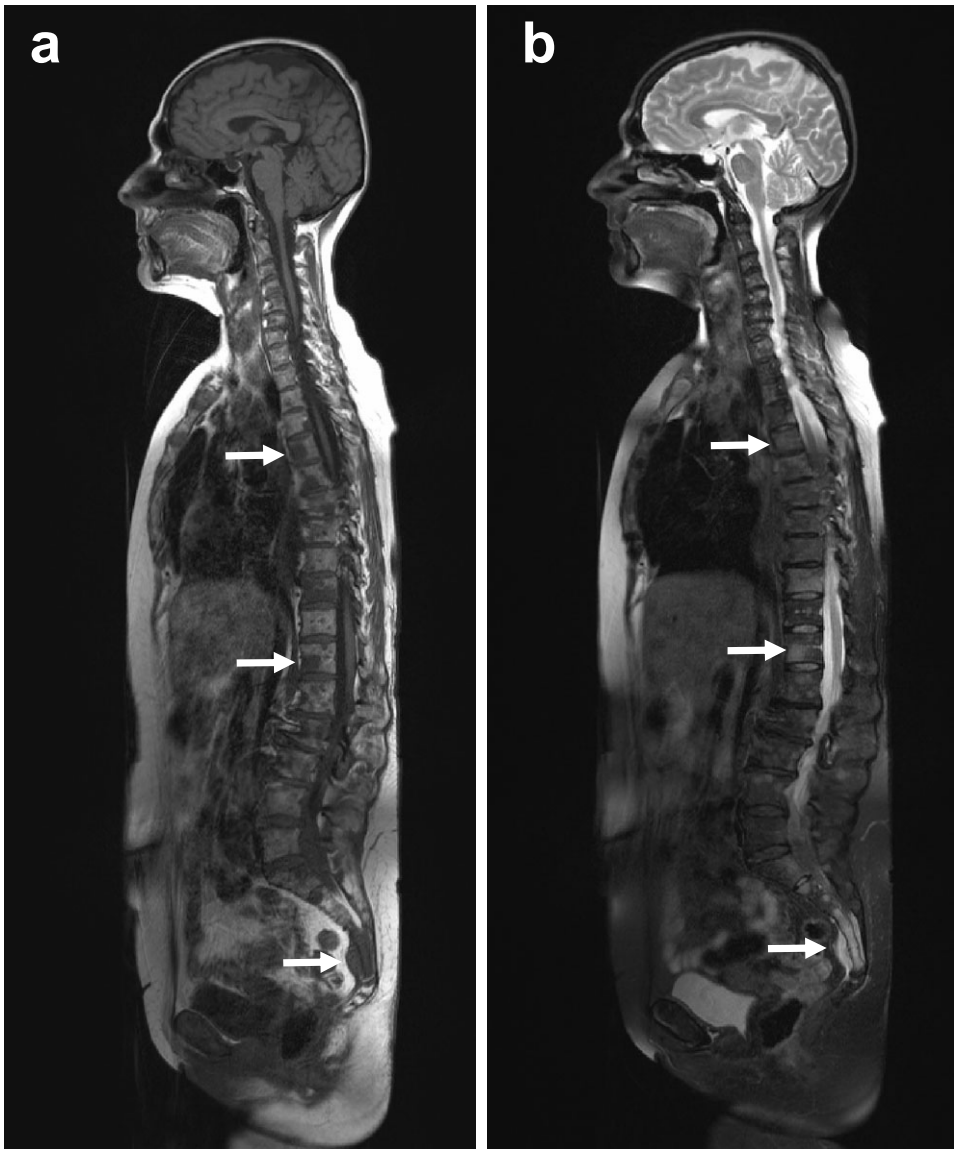

Figure 3 **A 51-year-old patient with multiple myeloma in relapse. (a) T1-weighted spin echo (TR/TE 400/10 ms), (b) T2-weighted (TR/TE 3800/70 ms) fat-saturated turbo spin echo (echo train length = 21) sagittal images show multiple focal lesions within the bone marrow and a sacral mass (arrows). Lesions present with low signal on T1WI surrounded by high signal normal marrow and high signal on T2WI with fat saturation.**

monitoring, T2 signal changes and/or decreased size of focal myeloma lesions or a normalization of bone marrow signal in diffuse infiltration can be noted following successful therapy[24,25]. MRI is also valuable in the identification of complications such as epidural involvement.

Functional study

Angiogenesis plays an important role in the clinical outcome of multiple myeloma[26]. MRI with administration of gadolinium is capable of reflecting neovascularization and grade of infiltration of bone marrow in patients with diffuse multiple myeloma[27]. In our previous experience using dynamic gadolinium-enhanced study in nine myeloma patients showed that contrast enhancement decreased in all six patients who responded to treatment but not in two of three who did not[28]. Recently in progressive multiple myeloma, Hillengass *et al*.[29] also demonstrated that the maximal amplitude of lumbar bone marrow enhancement from dynamic contrast-enhanced MRI is a predictor of event-free survival. However, these functional studies were limited mostly to the MRI of spine only. In our own preliminary experience using 3D gradient-echo sequence with a rolling table platform, parallel imaging technique and multi-channel phased array surface coil devices, WB dynamic gadolinium-enhanced imaging with 152 images

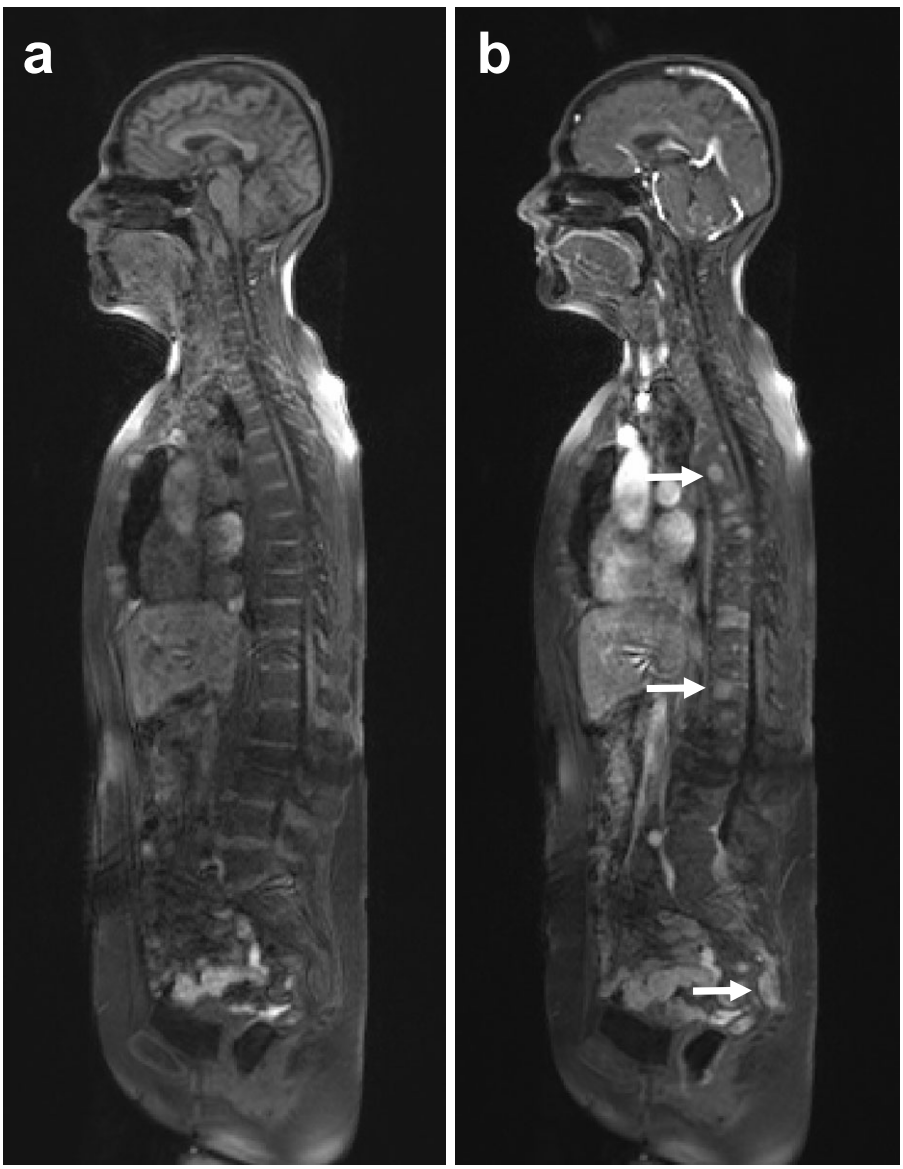

Figure 4 **The same patient as in Fig. 3 with gadolinium-enhanced dynamic study using 3D gradient-echo sequence (TR/TE 3.7/1.3 ms). Sagittal images before (a) and immediately (b) after automated injection of gadolinium show arterial enhancement of lesions (arrows) including the sacral mass, in contrast to the surrounding normal bone marrow.**

(in-plane resolution 2.6×2 mm) encompassing almost the entire bone marrow space is feasible within 60 s (Fig. 4). A significant difference exists regarding the maximal enhancement between normal bone marrow and diffuse or focal myeloma involvement (unpublished data). This functional information can be combined with high-resolution T1- and T2-weighted WB morphological study in about 30 min. Future implications for patient management will be a thorough baseline staging and assessment of disease activity, therapy response monitoring and prognosis prediction.

Conclusion

Both MRI and PET/CT provide whole body imaging, which is of paramount importance in the appreciation of disease extension in haematological malignancies. They offer the advantage of combining functional and anatomical information, which can help in evaluating disease aggressiveness, treatment response and prognosis stratification. PET/CT remains more accurate in lymph node staging; MRI is the modality of choice in assessing bone marrow and CNS involvement.

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