Oncologic Imaging REVIEW

Imaging in multiple myeloma: Current concepts and future challenges

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ABSTRACT

Bone involvement is one of the hallmarks of multiple myeloma (MM). The large majority of patients present with osteolytic lesions, either at initial diagnosis or during the course of their disease. The definition of myeloma-related bone disease as a marker of end-organ damage requiring immediate treatment has evolved over the years, chiefly as a result of important advances in cross-sectional imaging technology and the introduction of functional and molecular imaging techniques. Conventional skeletal survey is no longer considered adequate for the work-up of myeloma patients due to its low sensitivity. Whole Body Low Dose CT (WBLDCT) is currently the imaging modality of choice for detecting osteolytic lesions in newly diagnosed MM patients. Whole Body MRI (WBMRI) with Diffusion-Weighted Imaging is the gold standard for detecting bone marrow involvement, both focal and diffuse, and is also increasingly being studied as a tool for therapy response assessment. For evaluation of response to therapy and imaging-based definition of minimal residual disease (MRD) status, ^{18}F-FDG PET/CT is currently the preferred technique. Both WBMRI and 18F-FDG PET/CT can provide valuable prognostic information and are also excellent modalities for detecting extramedullary disease. In this review we discuss the use of these advanced imaging techniques in the management of MM patients, we outline the relevant guidelines and we address the issues that need to be further investigated.

KEY WORDS: Multiple myeloma; Imaging; Whole body MRI; Whole body low dose CT; PET/CT

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Introduction

Proliferation of clonal plasma cells in the bone marrow is the cause of multiple myeloma (MM), a haematologic malignancy with an incidence of about 6/100,000 persons, only second to that of the lymphomas [1]. MM originates from a precursor, premalignant state called monoclonal gammopathy of undetermined significance (MGUS) [2]. The diagnosis of MGUS requires serum M-protein levels <3 g/dL and <10% monoclonal plasma cells in the bone marrow. The incidence of MGUS is about 3% in the population of 50 years or older, but the rate of progression to MM is only 1% per year [3]. The spectrum of plasma cell dyscrasias also includes an intermediate stage, namely smoldering MM (SMM), defined by serum M-protein levels >3 g/dL or >10% monoclonal plasma cells in the bone marrow. Risk of progression to MM for SMM patients is 10% for the first five years following diagnosis, dropping significantly thereafter [4]. Patients with SMM do not receive treatment until they develop a myeloma-defining event (i.e. they progress to MM). Patients with SMM form a very heterogeneous group, with some of them having an indolent course of disease similar to that of patients with MGUS and some progressing to symptomatic disease within two years from diagnosis (high risk SMM).

MM requires the diagnosis of end-organ damage, defined as the presence of one or more of the following: hyperCalcaemia (serum calcium level >11 mg/dL), Renal impairment (creatinine >2 mg/dL or glomerular filtration rate <40 ml/min), Anaemia (haemoglobin <10 g/dL), and myeloma-induced Bone disease, the so-called CRAB criteria; all patients with MM receive treatment upon diagnosis. In 2014, the International Myeloma Working Group (IMWG) broadened the criteria for MM in order to include a subgroup of high-risk patients with SMM who were found to benefit from early initiation of treatment; the presence of ≥60% clonal plasma cells in the bone marrow, ≥100 involved/uninvolved free light chain ratio in the serum and more than one unequivocal focal lesion greater than 5 mm on bone marrow MRI now define MM, even in the absence of other myeloma-defining criteria [5].

Novel therapies (particularly with proteasome inhibitors-PIs, and immunomodulatory drugs-IMiDs) and improved risk stratification of patients have had an important impact on the survival of patients with MM; 5-year relative survival rates for 2005-2011 rose to 49% compared to 27% for 1987-1989 [6]. Imaging, with the incorporation of significant technological advances, has contributed greatly to the more accurate stratification of patients as shown by the inclusion of MRI as one of three biomarkers defining MM in otherwise asymptomatic patients and its inclusion together with FDG/PET-CT in the Durie and Salmon PLUS staging system [5, 7].

Bone disease and imaging in multiple myeloma

Bone involvement is one of the hallmarks of MM, with osteolytic lesions occurring in up to 80% of patients at initial diagnosis and in almost all patients during the course of their disease [8]. Osteolyses increase the risk for skeletal-related events and are associated with increased morbidity and mortality. The definition of bone disease in MM has evolved over the years, mainly as a result of significant advances in cross-sectional imaging technology and the introduction of functional and molecular imaging techniques [9, 10]. For decades, bone disease in MM was defined as the presence of osteolytic lesions or the presence of osteoporosis attributed to the underlying plasma cell disorder, as determined by the conventional skeletal survey [11, 12]. Over the past few years, conventional radiographs have been increasingly replaced by cross-sectional imaging techniques, namely MRI (including Whole Body MRI - WBMRI), Whole Body Low Dose CT (WBLDCT) and 18F-FDG PET/CT. It must be noted that the whole body approach is especially important in this disease entity, because myeloma can be very heterogeneous in its distribution pattern [13]. With the introduction of these advanced techniques the role of imaging in the management of patients with plasma cell dyscrasias has greatly expanded. Apart for bone disease evaluation of newly diagnosed patients and accurate diagnosis of symptomatic myeloma requiring treatment, imaging can now also provide valuable prognostic information, both for SMM and MM patients [14, 15]. Additionally, modern imaging can identify sites of extramedullary disease and is necessary for differentiating between solitary bone plasmacytoma (SBP) and MM. Imaging may also identify and characterise myeloma-related fractures including vertebral compression fractures, provide fracture risk assessment, and identify sites of neurological complications requiring urgent local treatment. Finally, imaging plays a growing role in therapy response assessment and especially contributes to the more accurate definition of minimal residual disease. Standardisation of these sophisticated imaging techniques is crucial and ongoing,

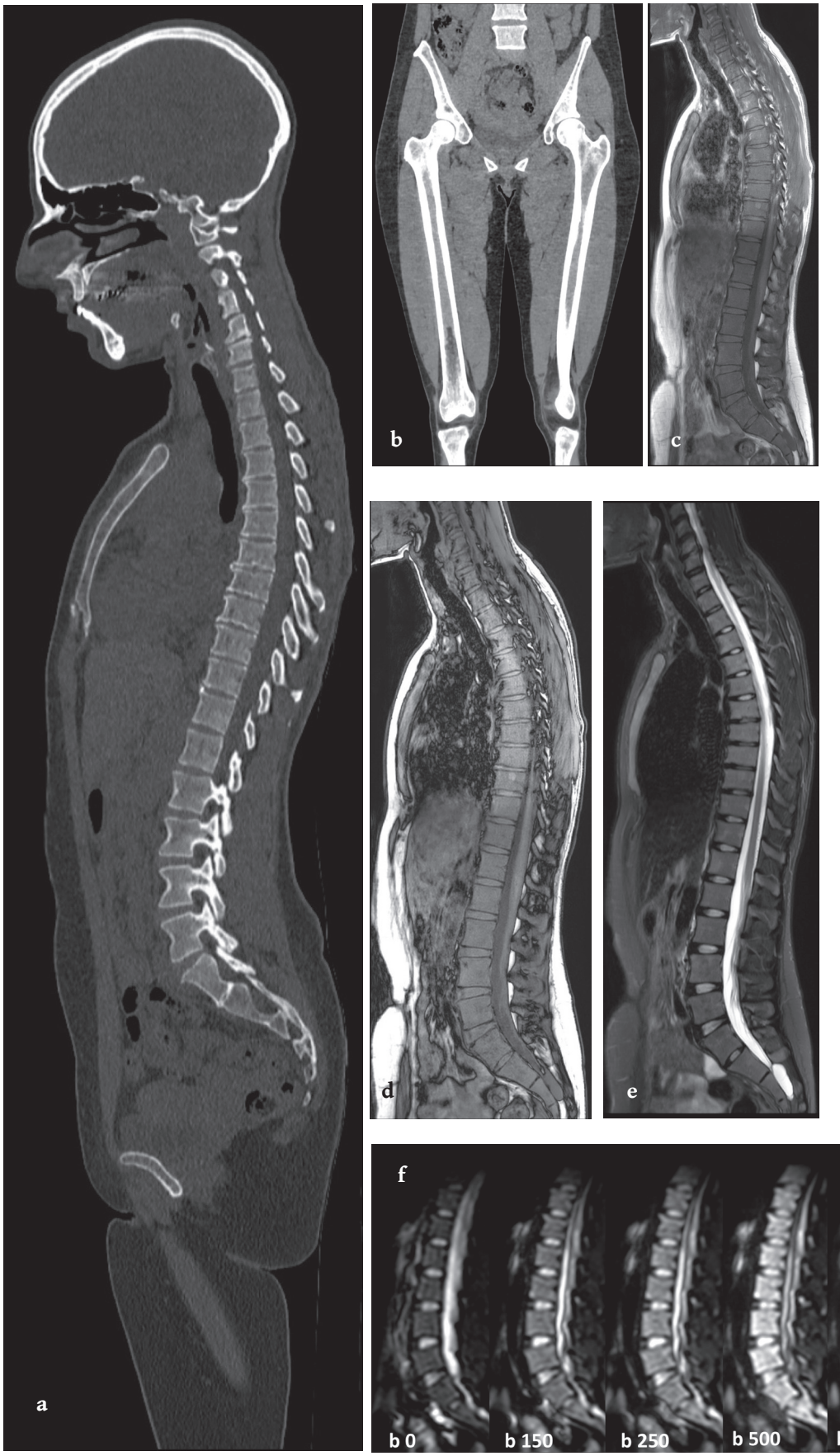

Fig. 1. *37-year-old woman with newly diagnosed multiple myeloma. WBLDCT, sagittal MPR, bone reconstruction algorithm (**a**) and coronal MPR, soft tissue reconstruction algorithm (**b**). Whole spine sagittal T1 Dixon in-phase (**c**), T1 Dixon opposed-phase (d) and STIR (**e**) MR images. DWI of the lumbosacral spine (from left to right: b values 0, 150, 250, 500, 800 s/mm^2) (**f**). No osteolyses were present on the WBLDCT study. Diffuse hyperdensities are shown filling the proximal two thirds of the medullary cavity of both femora (**b**) (mean density: 90 HU). A diffuse pattern of marrow involvement is shown on whole spine MRI performed on the same day. Note that the abnormal bone marrow is iso- to hypointense to the intervertebral discs on the T1 Dixon in-phase image (**c**) and there is no signal dropout on the opposed-phase T1 Dixon image (**d**). On DWI (**f**), the bone marrow is diffusely and markedly hyperintense on the high b-value image. Mean ADC value of the lumbar vertebral bodies was 0.812 x 10^{-3} mm^2/s.*

and consensus guidelines have recently been published with recommendations on acquisition protocols as well as on interpreting and reporting findings [9, 16-19].

Imaging multiple myeloma at diagnosis

Conventional skeletal survey

The conventional skeletal survey (CSS) consists of a series of plain radiographs of the axial skeleton and proximal limbs. It was the main imaging modality used to detect myeloma-related bone disease for decades, defined in most cases as the presence of osteolytic lesions or the presence of osteoporosis that can be attributed to myeloma [11]. The CSS suffers from very limited sensitivity compared to cross-sectional imaging techniques for the detection of osteolyses, irrespective of aetiology. Thus, it was demonstrated quite early that detection of osteolytic lesions on lateral x-rays of the lumbar spine is feasible only when between 50% and 75% of cancellous bone thickness has been replaced [20]. Furthermore, CSS is a lengthy examination and careful positioning of the patients (who are often in pain because of bone pathology) is needed for the acquisition of multiple views required to evaluate the axial skeleton and proximal long bones. The superior detection rate of CT over CSS for bone destruction was recognised early on but the high effective radiation doses prevented its routine use for myeloma patients [21]. In 2005, Horger et al first introduced a technique for performing diagnostic low dose WBCT and, since then, WBLDCT has gradually replaced CSS in many academic centers for the work-up of patients with MM [22].

Whole Body Low Dose CT

Low dose WBCT protocols, particularly with the use of iterative reconstruction algorithms to minimise image noise and artefacts, show satisfactory image quality allowing the accurate detection of myeloma-related bone destruction while maintaining low effective radiation doses, usually in the range of 4.0-7.5 mSv, about 2 to 3 times the radiation dose of a CSS (1.2-2.5 mSv) [23, 24]. Several studies have documented the increased sensitivity of WBLDCT over CSS for the demonstration of myeloma-related osteolyses [23-27]. In the largest multicenter study, which compared CSS and WBCT studies of 212 newly diagnosed SMM and MM patients, 25.5% of patients had a negative CSS but at least one osteolysis on WBCT. Moreover, in patients classified as SMM based on the CSS, the presence of osteolytic lesions on WBCT was of prognostic significance with a median time to progression to symptomatic MM of 38 months versus 82 months for those without CT-detected bone destructions [28]. In patients with symptomatic myeloma, the prognostic value of WBLDCT has not been established yet but there are ongoing studies evaluating the relationship of tumour load on WBCT images and patient survival. In 2014 the IMWG updated the criteria for the diagnosis of MM to include the presence of one or more osteolytic lesions on WBLDCT or the CT part of a ^{18}F-FDG PET/CT study as myeloma-defining events, regardless of whether they are visible on conventional radiographs [5]. The European Myeloma Network (EMN) and the European Society of Medical Oncology (ESMO) currently recommend WBLDCT as part of the initial work-up for myeloma patients [29, 30].

Apart from osteolyses, WBLDCT images reconstructed with soft-tissue convolution kernels provide information on the presence of diffuse or nodular hyperdense myelomatous infiltrates in the medullary cavities of the proximal long bones. The presence of these hyperdensities has been associated with increased tumour burden, advanced disease stage and poorer prognosis in patients with symptomatic myeloma [31, 32]. Koutoulidis et al additionally showed that diffusely increased bone marrow attenuation of the proximal limbs may actually be the only sign of myeloma-related bone disease on a WBLDCT study in about a third of patients with MM and a diffuse MRI pattern of involvement [33] (**Fig. 1**). In spite of this information, the presence of medullary hyperdensities is not currently included in the IMWG criteria for the diagnosis of MM. This is partly due to the fact that, so far, there are no clear cut-off density values between hyperdense myelomatous deposits and hyperattenuation due to red marrow reconversion, a common finding in myeloma patients who often present with anaemia. WBLDCT also provides information on the presence and characterisation of vertebral compression fractures and is very helpful for fracture risk assessment. It also allows soft-tissue evaluation for the detection of extramedullary disease (EMD), although PET/CT and WBMRI are more sensitive in this respect [34]. EMD is defined as disease outside of the bone marrow and not contiguous with a marrow lesion. It is quite rare at diagnosis (7% or less in most studies) but increases after multiple lines of treatment [35, 36].

Acknowledging the benefits of standardisation of im-

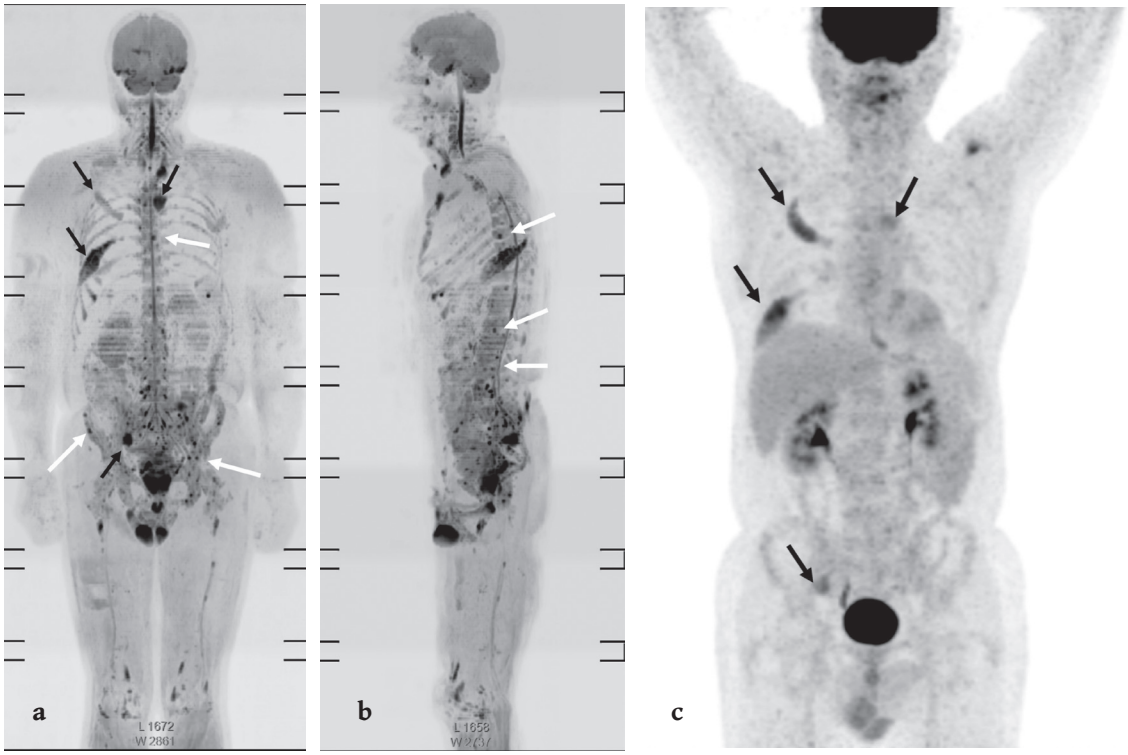

Fig. 2. *67-year-old man with newly diagnosed multiple myeloma. Whole body DWI maximum intensity projection (b value 900 s/mm², inverted greyscale) coronal (**a**) and sagittal (**b**) images. 18F FDG/PET-CT coronal image (**c**). Focal lesions (black arrows) are shown on both studies. On WBDWI multiple additional smaller foci of disease are also seen in the spine and pelvis (white arrows).*

aging techniques for better patient management, an expert panel of radiologists and haematologists recently published recommendations for the acquisition, interpretation and reporting of WBLDCT in MM and other plasma cell disorders on behalf of the IMWG Bone Working Group [9].

MRI-Whole Body MRI

MRI is superior to CSS and WBCT for assessing myeloma-related bone disease, since it directly images the bone marrow before any trabecular destruction has occurred [37-39]. With the inclusion of DWI, it shows equal or better sensitivity compared to 18FDG-PET/CT for detecting plasma cell infiltration of the bone marrow [40]. Reported MRI patterns of bone marrow infiltration in myeloma patients include normal, focal, diffuse, focal and diffuse and variegated [37, 41]. WBMRI with Diffusion Weighted Imaging (DWI) is increasingly used as a morphological and functional imaging tool for whole marrow assessment in patients with myeloma [42, 43]. When WBMRI is not available, bone marrow evaluation of myeloma patients can be performed with axial skeleton MRI which should cover the thoracolumbar spine and the pelvis and should also include a DWI sequence. DWI is an essential part of a bone marrow MRI study, and familiarity with the appearance of normal bone marrow on DWI and corresponding ADC maps is mandatory for correct interpretation. Water diffusivity is very restricted in normal marrow due to multiple factors, with the prominent presence of adipose cells probably playing a major role. Presumably, fat cells restrict the movement of water molecules as a result of augmented extracellular space tortuosity and the hydrophobic properties of fat [44, 45]. Most investigators agree that normal bone marrow ADC values are below 0.6×10^{-3} mm²/s and can be as low as 0.15×10^{-3} mm²/s, especially in elderly individuals with marked fatty marrow replacement [10, 46, 47]. Marrow infiltrating tumours, which replace fat cells and are characterised by high cellularity, show high signal on high b-value images (and low signal on inverted grayscale images) and higher ADC values than normal marrow. It has also been shown that in myeloma patients, ADC values of focal lesions are generally higher than ADC values of diffusely infiltrated marrow (1.046×10^{-3} mm²/ s versus 0.770×10^{-3} mm²/s respectively in the largest study) [48].

A WBMRI protocol can usually be completed within 45 to 60 minutes and it should always include whole body DWI with background body signal suppression (DWIBS) and Dixon-based sequences [49]. Three-dimensional maximum intensity projection (3D MIP) images extracted from high b value whole body DWI images (with b values ≥800s/mm^2) displayed with an inverted grey scale to produce PET-like images, enable visual assessment of the entire skeleton (**Fig. 2**). Source axial DWI images of the whole body should be carefully studied, and areas of abnormal diffusivity should be correlated with corresponding signal intensity changes on ADC maps and T1- or T2-weighted Dixon images to avoid misdiagnosing benign lesions (e.g. haemangiomas, normal red marrow foci) for neoplastic marrow deposits. The core protocol of a WBMRI study should also include dedicated sagittal T1-weighted and short tau inversion recovery (STIR) images of the entire spine (most common site of involvement for myeloma) to look for bone marrow lesions, impingement of neural structures requiring prompt intervention and vertebral compression fractures (VCFs). Characterisation of vertebral compression fractures is best achieved with MRI and is based on signal intensity, morphologic and quantitative features [41]. Contrast-enhanced images are not necessary with whole body MRI protocols for myeloma. Dynamic Contrast-Enhanced (DCE) MRI is usually performed as part of a spinal MRI study and it provides non-invasive assessment of the angiogenetic state of the bone marrow compartment [10, 50]. Bone marrow perfusion parameters can be extracted using either semi-quantitative or quantitative markers based on complex pharmacokinetic models. They can provide prognostic information at initial diagnosis or be used to evaluate response assessment [51-54]. Nevertheless, quantitative DCE biomarkers may suffer from low reproducibility and a widely accepted standardised DCE protocol is lacking.

MRI is the most sensitive technique for identifying myeloma-related bone marrow involvement. Early on, Moulopoulos et al showed that SMM patients with a positive spinal MRI study showed early progression to symptomatic myeloma and required treatment at a median of 16 months versus 43 months for those with normal studies [14]. More recently, the presence of more than one unequivocal focal lesion larger than 5 mm on WBMRI or axial MRI of patients with SMM, was associated with an increased risk for developing symptomatic disease within two years from diagnosis [55, 56]. Thus, the IMWG recommends that SMM patients with a negative WBLDCT should next be imaged with MRI (preferably WBMRI). If more than one unequivocal focal lesion is detected on the MRI, the patient is considered to have MM requiring immediate treatment [5]. In cases of equivocal MRI findings, the IMWG recommends a repeat study after 3-6 months, with MRI progression defining symptomatic disease that requires treatment [16]. Even though a diffuse MRI pattern is a known adverse prognostic factor for progression-free survival in SMM patients, it was not included in the updated IMWG criteria for MM. This may be partly explained by the fact that there is no uniformity in the definition of this MRI pattern among radiologists. Furthermore, because of the established association of this pattern with adverse disease features such as increased angiogenesis and high-risk cytogenetics, it is an uncommon finding in patients who do not fulfill any other criteria for the diagnosis of symptomatic myeloma [15, 55, 57-59]. Quantitative DWI is expected to increase diagnostic confidence for diffuse MRI patterns in patients with myeloma since ADC values of a diffuse bone marrow MRI pattern have been shown to be significantly higher than those of normal-appearing marrow ($0.770x10^{-3}$ mm^2/s versus $0.360x10^{-3}$ mm^2/sec respectively) [48]. WBMRI is also helpful for the diagnosis of extramedullary disease in newly diagnosed and relapsed patients.

Prognostic value of MRI at initial diagnosis

In patients with MM and a focal MRI pattern, the presence of more than 7 focal lesions on axial MRI or more than 25 focal lesions on WBMRI has been associated with inferior survival [38, 60]. A diffuse MRI pattern at diagnosis has also been associated with a negative prognostic effect on survival in some studies [57, 59]; the combination of diffuse MR imaging pattern, International Staging System (ISS) stage III, and high-risk cytogenetics has allowed identification of a subgroup of patients with very poor survival [58]. More recently, the prognostic value of focal lesion size in newly diagnosed MM patients using DWIBS images was investigated. It was shown that the presence of at least 3 large focal lesions with a product of the perpendicular diameters >5 cm^2 was associated with worse progression-free survival and overall survival [61].

In 2015, the IMWG issued a consensus statement advocating WBMRI (or axial MRI if a whole body technique

is not available) as the imaging gold standard for evaluating the bone marrow; it also recommended WBMRI as a frontline imaging examination for all patients with SMM and solitary bone plasmacytoma [16]. The British Society of Haematology (BSH) in its recently published guidelines recommends WBMRI as a first-line imaging examination for all newly-diagnosed patients with myeloma [62]. Very recently, a multidisciplinary expert panel published recommendations on the use of WBMRI in myeloma, including technical performance standards. This paper introduced the Myeloma Response Assessment and Diagnosis System (MY-RADS), designed to promote standardisation in the acquisition, interpretation, and reporting of whole-body MRI in myeloma and allow response assessment in a uniform way [19].

^{18}F-FDG PET/CT

^{18}F-FDG PET/CT combines information on glucose metabolism (PET part) and bone morphology (CT part). Use of FDG PET/CT at initial diagnosis is restricted due to several considerations including cost, limited availability and increased radiation dose delivered to the patient. Nevertheless, PET/CT has been found to be more sensitive than CSS for the detection of osteolysis in newly diagnosed patients with myeloma with sensitivity and specificity values in the range of 80%-100% [63-65]. It performs almost as well as MRI for detecting focal disease, although small, <1 cm focal lesions may be beyond the resolution of PET/CT. Moreover, MRI is superior in detecting diffuse myeloma patterns [40, 66]. PET/CT was recently shown to be falsely negative in 11% of 227 newly-diagnosed patients with MM who had positive WBMRI-DWI studies, most of them with diffuse patterns of marrow involvement. The authors found an association between PET negativity and expression of hexokinase-2, an important enzyme for the cycle of glycolysis; lower levels of this enzyme result in lower levels of the radiotracer trapped within malignant cells and, therefore, less activity [67].

Prognostic value of ^{18}F-FDG PET/CT at initial diagnosis

^{18}F-FDG PET/CT performed at diagnosis is an important prognostic tool for patients with MM; the presence of 3 or more focal lesions or EMD at baseline PET/CT is associated with inferior progression-free and overall survival [68-70]. A baseline standardised uptake value (SUV) greater than 4.2 has also been associated with inferior progression-free survival but the evidence is not as robust, and this criterion is not currently included in the IMWG adverse PET/CT prognosticators for MM [17, 69]. Several new PET/CT radiotracers such as 18F-fluorocholine (FCH), 11C-methionine (MET), and 68Ga-Pentixafor that targets chemokine receptor-4 (CXCR4), have been tried in several studies with very encouraging results [65, 71].

In 2017 the IMWG issued a consensus statement on technique, standardisation of interpretation criteria, and optimal use of ^{18}F-FDG PET/CT at diagnosis and after treatment. The consensus statement concludes that ^{18}F-FDG PET/CT may be used for the distinction of smoldering from symptomatic myeloma at initial diagnosis if WBMRI is not available [17]. Performing ^{18}F-FDG PET/CT at baseline also allows comparison of pre-treatment and post-treatment images, in order to identify patients with imaging minimal residual disease (MRD) negativity [34].

Imaging diagnostic criteria of myeloma-defining bone disease according to the latest IMWG criteria as well as still unresolved issues are summarised in **Table 1**.

Imaging multiple myeloma after therapy

Since the advent of novel therapeutic agents for MM, the majority of treated patients achieve good responses to induction therapy. Frustratingly though, most patients ultimately relapse, presumably because of undetected by conventional means MRD in the bone marrow or at extraskeletal sites. For this reason, cell-based and molecular-based techniques which increase the sensitivity of MRD detection in the bone marrow are now widely used. These techniques however examine a specific bone marrow sample and MM is a disease with known heterogeneity in its distribution pattern and a propensity for extramedullary spread that increases with multiple relapses. With advanced imaging techniques, large volumes of bone marrow as well as extraskeletal sites, which may also harbour clonal plasma cells, can be examined. Furthermore, since many of the novel anti-myeloma agents require long term treatment schedules and may have complicated toxicity profiles, it is very important to develop means that can identify poor responders early during the course of treatment.

For these reasons, in 2016, the IMWG defined new response categories of MRD negativity for patients with MM. MRD negativity requires the absence of clonal plasma cells in the bone marrow assessed by sensitive cell-

Table 1. Imaging diagnosis of myeloma-defining bone disease

Modality	*IMWG guidelines for diagnosis*	*Unresolved issues*
WBLDCT	One or more osteolytic lesions ≥5 mm in size	• Role of diffuse or nodular hyperdensities in the medullary cavities of femora and humeri for myeloma-defining bone disease in the absence of osteolytic lesions
WBMRI	More than one focal lesion ≥5 mm in size	• Role of a diffuse MRI pattern for myeloma-defining bone disease in the absence of focal lesions
18F-FDG PET/CT	One or more hypermetabolic osteolytic lesions ≥5 mm in size	• Role of focally increased FDG uptake for myeloma-defining bone disease in the absence of underlying osteolysis (considered positive in Ref. 17) • Role of diffusely increased FDG uptake for myeloma-defining bone disease in the absence of osteolytic lesions

IMWG: International Myeloma Working Group

based (flow MRD-negative) or molecular (sequencing MRD-negative) techniques. A major development in the new IMWG response criteria was the inclusion of a third, imaging-based, category of MRD negativity (imaging plus MRD-negative) which incorporates imaging with ^{18}F-FDG PET/CT because of its currently validated superiority to other imaging modalities in the post-therapy assessment of myeloma patients. Imaging plus MRD-negative status requires resolution of all foci of increased tracer activity at baseline or preceding PET/CT or decrease of metabolic activity to less than that of the mediastinal blood pool or surrounding normal tissues [13].

Several studies have evaluated the role of ^{18}F-FDG PET/CT in the post-therapy assessment of myeloma patients. Normalisation of PET/CT obtained at different time points after initiation of therapy was predictive of improved survival [72, 73]. For those patients who achieve flow or sequencing MRD-negativity, a normalised PET/CT study before maintenance therapy is associated with significantly higher progression-free survival [74]. In addition, a SUV >4.2 after first line treatment has been shown to independently predict progression [72]. Based on this information, the 2017 IMWG consensus statement recommended functional imaging with ^{18}F-FDG PET/CT for monitoring and assessing the effect of therapy for MM [17]. It must be stressed again that when systematic MRD assessment (including imaging MRD) is being applied, for example in the context of clinical trials, patients should be imaged with ^{18}F-FDG PET/CT at initial diagnosis to create a baseline for future response assessment [34].

WBLDCT is not recommended for the post-therapy assessment of MM since healing signs of osteolysis appear late after initiation of treatment and it is difficult to accurately distinguish active from inactive disease. CT signs of response to therapy include replacement of the soft-tissue density at sites of osteolyses by fat and development of perilesional and intralesional sclerosis [9]. Sclerosis is more common in patients treated with bortezomib-based regimens [75].

On conventional MRI, morphological changes of myelomatous marrow are not sensitive markers of response. It is well known that MRI abnormalities may not resolve completely even in patients who achieve a complete response to myeloma therapy or may do so with considerable delay. Focal MRI lesions in responding patients may resolve, decrease in size, show less enhancement or become brighter on STIR images of the bone marrow. Diffuse MRI patterns, on the other hand, may revert to focal or variegated patterns or may show a gradual increase in T1 signal intensity as normal fatty marrow is reinstituted in the axial skeleton [76]. Conventional MRI is, therefore, inferior to ^{18}F-FDG PET/CT for the evaluation of the effect of anti-myeloma therapy. However, with the application of functional MRI techniques, such as DWI

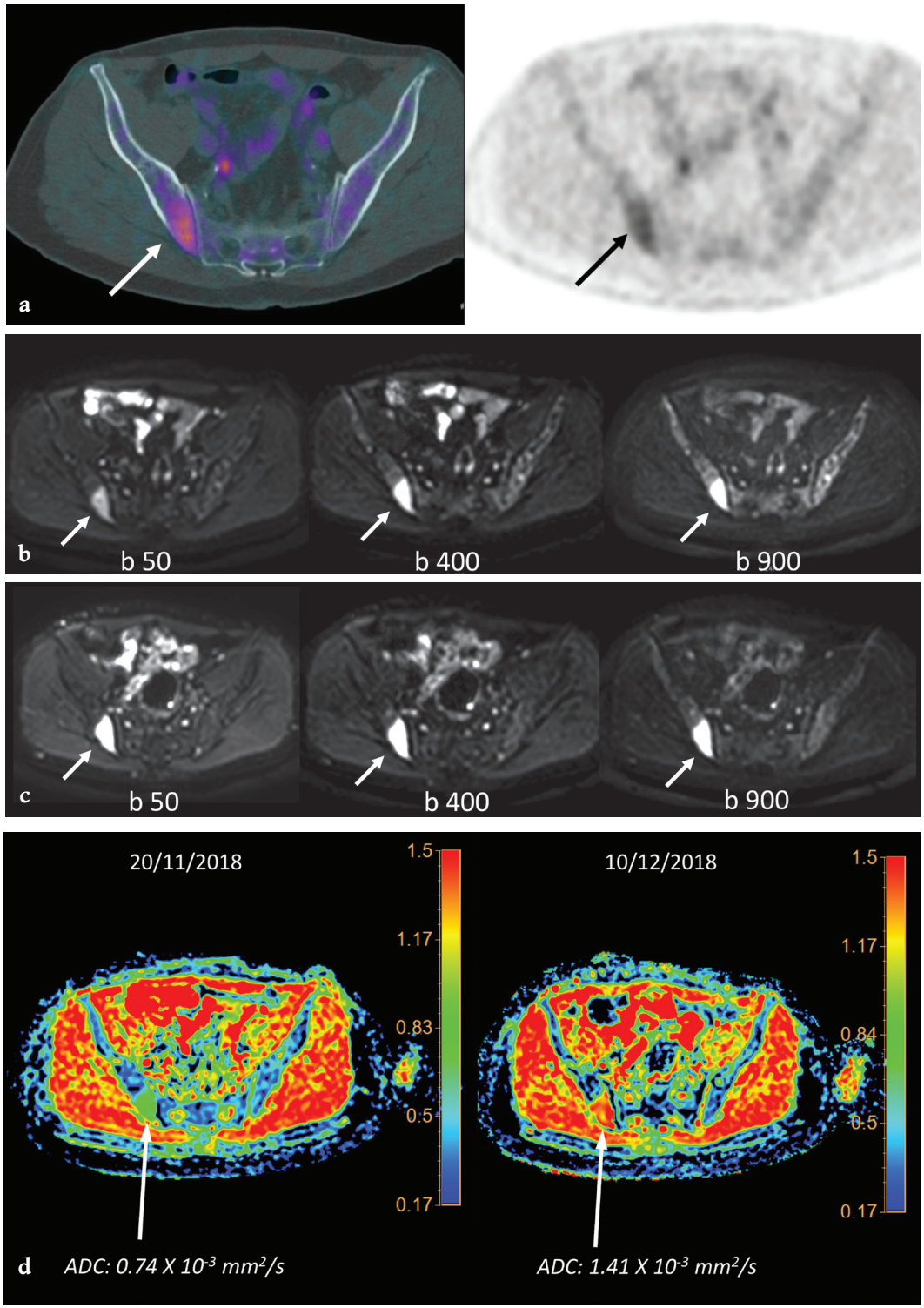

Fig. 3. *Same patient as in* ***Fig. 2.*** *Pre-treatment axial 18F FDG/PET-CT image of the pelvis (**a**). Axial DWI of the pelvis (b values 50, 400, 900 s/mm²) acquired before initiation of treatment (**b**), and three weeks later, after one cycle of VRD (bortezomib, lenalidomide, dexamethasone) (**c**), with corresponding colour-coded ADC maps (**d**). The patient achieved very good response to treatment at the time of best response assessment. An area of increased metabolic activity in the right iliac bone (arrow) is shown on 18F FDG/PET-CT (**a**). On pre-treatment DW images (**b**) there is restricted diffusivity of the right iliac bone lesion. On post-treatment DW images (**c**) the signal intensity of the right iliac bone lesion has increased. ADC value of the lesion has risen from 0.74x10⁻³ mm²/s to 1.41x10⁻³ mm²/s after treatment (**d**).*

Table 2. Imaging-based response assessment and MRD definition in myeloma

Modality	*Imaging findings of response*	*IMWG Guidelines for response assessment*
WBLDCT	**Morphological+** • Partial or complete fatty replacement of osteolytic lesions • Decrease in number and size of osteolytic lesions • Sclerosis of osteolytic lesions • Decrease in number and size of medullary hyperdensities	• Not recommended for response assessment
WBMRI	**Morphological++** • Return of normal fat containing marrow in areas previously infiltrated by focal or diffuse disease • Decrease in number and size of focal lesions • Conversion of a diffuse pattern into discrete focal lesions **Functional++** • Previously evident lesion shows increase in ADC from <1400 x10^{-3} mm^2/s to ≥1400 x10^{-3} mm^2/s • >40% increase in ADC from baseline with corresponding decrease in normalised high b-value signal intensity • Increase in lesional signal fat fraction based on Dixon techniques	• Promising, but not currently recommended for Imaging MRD assessement due to limited data • Prospective comparison of functional MRI techniques and PET/CT after therapy needed
^{18}F-FDG PET/CT	**Functional+++** • Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less than mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue	• Defines the Imaging MRD-negative response category

MRD: Minimal Residual Disease, IMWG: International Myeloma Working Group, ADC: Apparent Diffusion Coefficient
**Ref. 9, **Ref. 19, ***Ref. 17*

and Dixon-based fat fraction calculation for therapy assessment, there is increasing evidence for the potential of these techniques as imaging biomarkers of response in myeloma patients. The majority of such MRI studies have focused on DWI techniques; ADCs of responding focal lesions have been shown to increase as early as 4 to 6 weeks after treatment initiation as a result of increased diffusivity due to necrosis of marrow cells and increased water motion [77]. Later on, around week 20, ADC values appear to decrease as the number of hydrophobic fat cells in the marrow increases. There is published evidence that ADC values of focal lesions >1400 x 10^{-3} mm^2/s are indicative of very good response to therapy [19, 46] (**Fig. 3**). WBMRI offers the advantage of studying the entire bone marrow compartment with segmentation techniques. Giles et al studied ADC histograms of the entire bone marrow extracted with a semi-automated technique from WBDWI studies and found an increase in mean ADC values in the vast majority of responding myeloma patients at a median of 13 weeks after therapy [78]. Latifoltojar et al reported an increase in both ADC values and fat fractions of focal marrow lesions in responding myeloma patients after two cycles of chemotherapy; they concluded that signal fat fraction may prove to be a very reliable indicator of response [79]. Both these techniques need to be validated in larger patient populations and a consensus must be reached on optimal time of imaging after therapy. Prospective studies in patients receiving treatment for MM will evaluate the potential of functional quantitative MRI techniques as an alternative to ^{18}F-FDG PET/CT for definition of imaging MRD. WBMRI is an attractive alternative in this

context due to its lack of ionising radiation. If at least its non-inferiority to PET/CT for imaging MRD definition could be established, it could be used both at baseline assessment and at various time-points during the course of treatments for response assessment.

Imaging findings of response on WBLDCT, WBMRI and 18F-FDG PET/CT, as well as current IMWG guidelines for imaging-based response assessment and MRD definition are summarised in **Table 2**.

Conclusions

Conventional skeletal survey has been substituted by WBLDCT for the evaluation of bone disease in newly diagnosed patients with MM. WBMRI or ^{18}F-FDG PET/CT may also be used in the same setting and should be part of the work-up for patients with SMM or solitary bone plasmacytoma. For assessment of response to therapy and MRD imaging definition, PET/CT is currently the imaging modality of choice. However, WBMRI remains the gold standard for the detection of bone marrow involvement, while at the same time it provides important prognostic information and may identify the presence of EMD. If future studies with WBMRI including functional techniques, show that it may be applied for the assessment of MRD-negative status alongside with cell-based and molecular-based techniques, then WBMRI could be used as a single examination throughout the course of multiple myeloma, avoiding the ionising radiation and high cost of PET/CT. **R**

Conflict of interest

The authors declared no conflicts of interest.

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