

Imaging of Multiple Myeloma

Bildgebende Diagnostik des Multiplen Myeloms

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ABSTRACT

Background Multiple myeloma is a malignant hematological disease characterized by uncontrolled proliferation of monoclonal plasma cells mainly in the bone marrow. Imaging plays a crucial role in diagnosis and follow-up.

Method This literature review provides information about multiple myeloma, its precursor diseases, and available imaging techniques. Advantages and limitations as well as possible prognostic and therapeutic implications of the different imaging methods are presented in the context of the current literature.

Results and Conclusion Cross-sectional imaging has replaced conventional X-ray skeletal survey. Widely available whole-body computed tomography is routinely used to detect osteolytic lesions. Magnetic resonance imaging is the most sensitive technique to identify bone marrow infiltration and is recommended in multiple myeloma precursor diseases.

Positron emission computed tomography combines morphological and functional imaging. It is mainly used for follow-up, therapy monitoring, and response evaluation.

Key points:

- Conventional X-ray skeletal survey is obsolete.
- Whole-body CT is routinely used to detect osteolysis.
- MRI is the most sensitive modality to identify bone marrow infiltration.
- MRI is used for the workup of precursor diseases (alternatively: PET/CT).
- PET/CT is used for follow-up, therapy monitoring, and response evaluation.

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ZUSAMMENFASSUNG

Hintergrund Das Multiple Myelom ist eine maligne hämatologische Erkrankung, die sich durch die Proliferation von monoklonalen Plasmazellen vor allem im Knochenmark auszeichnet. Die Bildgebung spielt zur Diagnosestellung und Verlaufsbeurteilung eine wichtige Rolle.

Methode Dieser Übersichtsartikel informiert über das Krankheitsbild des Multiplen Myeloms samt Vorstufen und beschreibt die zur Verfügung stehenden bildgebenden Untersuchungstechniken. Diese werden samt Vor- und Nachteilen sowie möglichen prognostischen und therapeutischen Implikationen vor dem Hintergrund der aktuellen Literatur vorgestellt.

Ergebnisse und Schlussfolgerung Der konventionelle Röntgenstatus ist beim Multiple Myelom mittlerweile vollständig von Schnittbildtechniken ersetzt worden. Die breit verfügbare Ganzkörper-Computertomografie wird routinemäßig verwendet, um Osteolysen nachzuweisen. Die Magnetresonanztomografie hat die höchste Sensitivität zur Detektion von Knochenmarkbefall und wird insbesondere bei den Vorstufen des symptomatischen Multiplen Myeloms empfohlen. Die Positronen-Emissionstomografie vereint morphologische und funktionelle Bildgebung. Sie kommt vor allem bei der Verlaufsbeurteilung und Evaluation von Therapieansprechen zum Einsatz.

Introduction

Multiple myeloma (MM) is a malignant hematological disease characterized by uncontrolled proliferation of monoclonal plasma cells mainly in the bone marrow. With approx. 6500 new cases in Germany each year, MM is one of the most common hematologic neoplasias [1]. The median age of onset is 72 years in men and 74 years in women. Onset prior to the age of 45 is rare (approx. 2 % of cases). Despite therapeutic advances in recent years, the 5-year survival rate continues to be just under 50 % [1]. Bone lesions, which are associated with the most common symptoms like bone pain, fatigue, and anemia due to suppression of normal hematopoiesis, are present in over 80 % of patients at the time of initial diagnosis [2, 3].

Diagnosis is made on the basis of a "myeloma-defining event" with simultaneous biopsy-based confirmation of bone marrow infiltration $\geq 10\%$ or detection of a plasmacytoma (► Table 1). In addition to laboratory testing and processing of a bone marrow sample, imaging plays a central role: the presence of osteolysis on conventional radiography, computed tomography (CT) or positron emission tomography combined with CT (PET/CT) or the detection of more than one bone marrow lesion via magnetic resonance imaging (MRI) results in the diagnosis of a myeloma requiring treatment [4]. Modern cross-sectional imaging techniques like MRI and PET/CT can also be used to evaluate prognosis as well as to assess treatment response and disease activity in the clinical course [5–7].

The various imaging modalities are presented in the following with respect to their current importance and their advantages and disadvantages for the diagnosis and follow-up of MM and its initial stages.

Imaging for diagnosing MM

Conventional radiography

For a long time, the widely available and comparatively cost-effective conventional X-ray skeletal survey was the established method for detecting osteolytic bone lesions. Scans of the skull, cervical spine, thoracic spine, and lumbar spine on two planes as well as bilateral a. p. scans of the bony thorax, pelvis, and proximal extremities were acquired. In the past, various staging systems and diagnostic guidelines have defined conventional X-ray skeletal survey as a standard [8, 9]. However, current recommendations, e.g. by the European Myeloma Network or the European Society for Medical Oncology, are increasingly abandoning conventional radiography in favor of modern methods [10, 11]. An important weakness of conventional X-ray skeletal survey is the fact that approx. 30–50 % of trabecular bone must be destroyed to be visible as osteolysis. In the meantime, numerous studies have shown that modern cross-sectional techniques like CT, PET/CT and MRI are superior to conventional X-ray for detecting bone disease [12]. Additional disadvantages of conventional projection radiography are the lack of ability to evaluate treatment response or extraosseous involvement and the complicated examination procedure that involves the need to reposition patients who are often in

► **Table 1** Diagnostic criteria ("myeloma defining events") for multiple myeloma according to recommendations of the International Myeloma Working Group 2014 (modified after [4]).

evidence of end organ damage („CRAB“) (positive, if one or more of the following are present)

C („hypercalcaemia“)	hypercalcaemia with serum calcium $> 0.25 \text{ mmol/l}$ above upper limit of normal or $> 2.75 \text{ mmol/l}$
R („renal insufficiency“)	renal insufficiency with creatinin clearance $< 40 \text{ ml/min}$ or serum creatinine $> 177 \mu\text{mol/l}$
A („anaemia“)	haemoglobin $< 100 \text{ g/l}$ or value $> 20 \text{ g/l}$ below the lower limit of normal
B („bone lesions“)	≥ 1 osteolytic lesion ($\geq 5 \text{ mm}$) on skeletal radiography, computed tomography or positron emission tomography with computed tomography

Biomarkers of malignancy („SLiM“) (positive, if one or more of the following are present)

S („sixty percent plasma cell percentage“)	clonal plasma cell percentage in the bone marrow $\geq 60\%$
Li („light chain ratio“)	ratio of involved/uninvolved serum free light chains (κ/λ -ratio) ≥ 100
M („magnetic resonance imaging“)	more than one focal lesion ($\geq 5 \text{ mm}$) on MRI

A manifest multiple myeloma can be diagnosed, if at least one of the above-mentioned criteria is positive. CT = computed tomography, PET/CT = positron emission tomography/computed tomography, MRI = magnetic resonance imaging.

pain multiple times (► Table 2). As a result, conventional radiography has been replaced by whole-body CT as the basic imaging modality at many centers (► Fig. 1).

Whole-body CT

Due to the high intrinsic contrast of bony structures, unenhanced low-dose CT is usually performed for detecting bone involvement in MM. The arms are typically positioned in front of the body. The radiation exposure of such an examination is approx. 3–5 mSv which is two to three times that of a conventional X-ray skeletal survey [13–15]. In light of the significantly higher sensitivity and improved patient comfort in the typically older patient population, the slightly higher radiation exposure is acceptable. Moreover, it was recently able to be shown that an examination with dose values similar to those of projection radiography (around 1.5 mSv) can be achieved using modern CT techniques [16]. In addition to the high sensitivity, CT has additional advantages such as improved assessment of fracture risk, the ability to visualize extraosseous myeloma, and biopsy, surgery, and radiation planning. Moreover, clinically relevant, non-bone-related secondary diagnoses can be made on CT in approximately one-third of cases (► Table 2) [17].

In the long bones, CT additionally allows visualization of bone marrow involvement in the form of a focal or diffuse increase in bone marrow density which may be prognostically relevant

► **Table 2** Advantages and disadvantages of different imaging modalities in patients with multiple myeloma (modified after [5]).

modality	advantages	disadvantages
X-ray skeletal survey	<ul style="list-style-type: none"> ▪ low cost ▪ wide availability ▪ established by longstanding routine use 	<ul style="list-style-type: none"> ▪ poor sensitivity ▪ advanced osteodestruction necessary to visualize osteolysis ▪ time-consuming acquisition, patient discomfort ▪ summation effects e. g. in the pelvis impair assessment of lytic lesions ▪ no evaluation of non-lytic bone marrow infiltration, extramedullary disease or therapy response
whole body CT	<ul style="list-style-type: none"> ▪ high sensitivity for lytic lesions ▪ possible depiction of extramedullary disease ▪ visualization of bone marrow infiltration in the extremities ▪ wide availability ▪ short acquisition time ▪ high patient comfort ▪ relatively low cost ▪ useful for planning of surgeries, biopsies or radiation therapy 	<ul style="list-style-type: none"> ▪ no evaluation of non-lytic bone marrow infiltration in the axial skeleton ▪ higher costs and radiation dose compared to X-ray ▪ insufficient for monitoring of therapy response
ganzkörper-MRT	<ul style="list-style-type: none"> ▪ no radiation exposure ▪ high sensitivity for detection of bone marrow infiltration and extramedullary disease ▪ depiction of infiltration patterns including diffuse infiltration ▪ depiction of non-osteolytic bone marrow infiltration ▪ prognostic relevance ▪ superior assessment of spinal cord pathologies and nerve root compression ▪ possible assessment of therapy response using modern functional techniques 	<ul style="list-style-type: none"> ▪ high cost ▪ long acquisition time ▪ limited use in patients with claustrophobia or metal implants ▪ limited and delayed evaluation of therapy response using regular morphologic sequences
PET/CT	<ul style="list-style-type: none"> ▪ simultaneous morphologic and functional imaging ▪ assessment of disease activity and response to therapy ▪ pre- and post-therapeutic prognostic significance ▪ high sensitivity for extramedullary disease 	<ul style="list-style-type: none"> ▪ high cost ▪ limited availability ▪ false-positive diagnoses e. g. due to inflammatory processes ▪ limited detection of diffuse bone marrow infiltration ▪ need for further standardization

CT = computed tomography, PET/CT = positron emission tomography/computed tomography, MRI = magnetic resonance imaging.

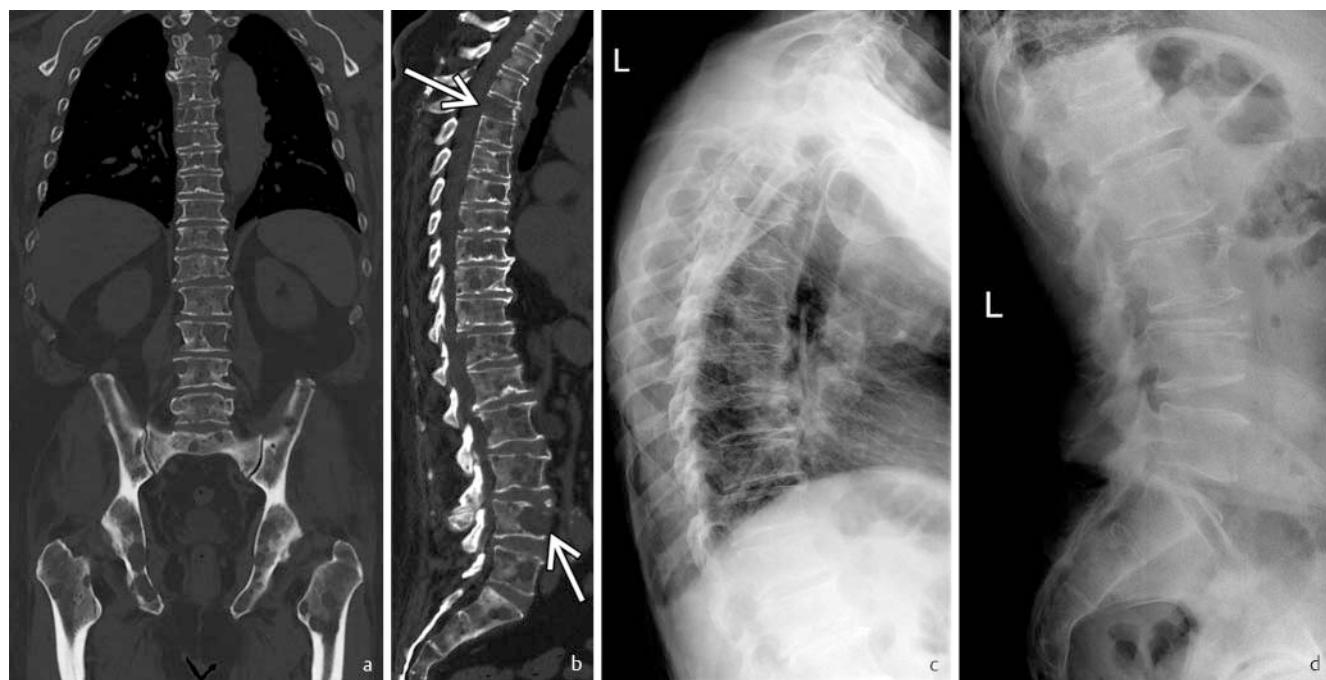
(► **Fig. 2**) [18]. However, in the spine and pelvis, visualization of diffuse or focal non-osteolytic bone marrow involvement is not possible in the case of a preserved trabecular bone structure. Only in advanced osteoporosis can an experienced examiner assess whether the axial skeleton predominantly contains healthy fatty marrow or if bone marrow infiltration is present, particularly over the clinical course. Thus, CT is particularly suitable for treatment monitoring in non-osteolytic bone marrow involvement in the long bones [19], while osteolysis caused by a lack of remineralization in the clinical course does not allow conclusions about treatment response [12]. Only the fat- or soft tissue-equivalent osteolysis "content" allows evaluation of response or determination of a relapse. MRI is the method of choice for visualizing bone marrow infiltration, particularly in the spine and pelvis [20].

MRI

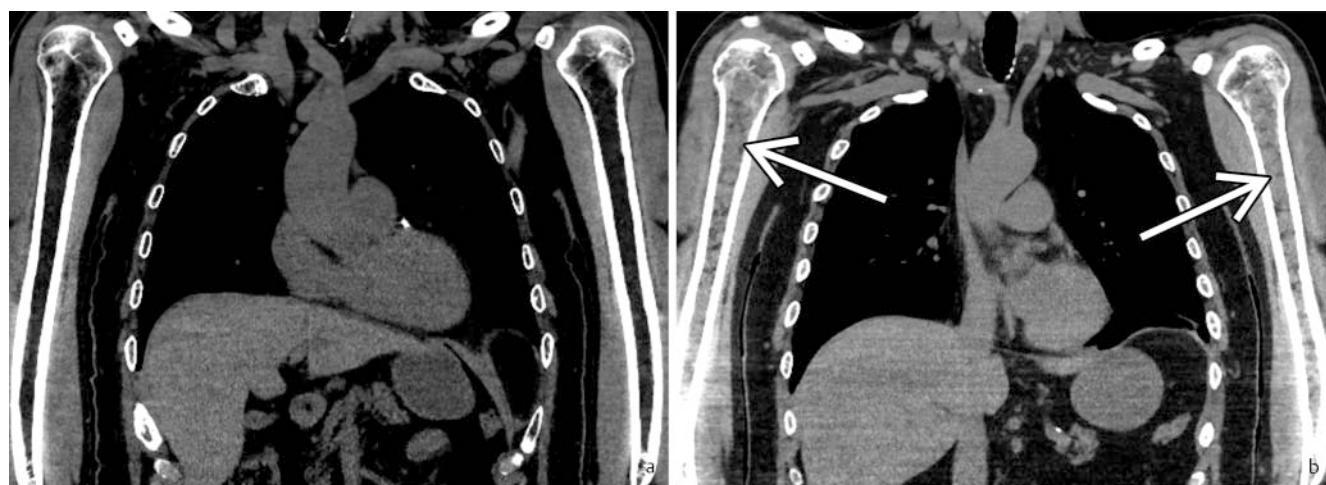
MRI is usually performed as a whole-body examination including the extremities since almost half of all patients have focal lesions outside the axial skeleton and lesions are seen exclusively in the

bones of the extremities in up to 10 % of cases [21]. Coronal and possibly sagittal T1w and T2w sequences as well as fat-saturated T2w sequences are typically used in a clinical examination protocol (► **Table 3**). When evaluating images, it is important to always take the age and medical history of the patient into account. Incomplete fatty conversion in comparatively young patients, bone marrow stimulation due to growth factors or chemotherapeutic agents, or allogeneic stem cell transplantation can in some cases only be differentiated from malignant plasma cell infiltration on a conditional basis.

Five different infiltration patterns in myeloma patients can be differentiated on MRI (► **Fig. 3, 4**): a normal appearance of the bone marrow, focal infiltration pattern (T1w hypointense lesions with a diameter of at least 5 mm), homogeneous diffuse infiltration (bone marrow on unenhanced T1 image generally more hypointense than adjacent intervertebral disc spaces without degenerative changes), mixed infiltration pattern (focal + diffuse), and the "salt and pepper" pattern (disseminated T1w hypointense lesions in front of an inhomogeneous background of T1w hyperintense



► Fig. 1 Coronal **a** and sagittal **b** computed tomography images of the spine and pelvis show multifocal osteolysis in a 60-year-old male patient with multiple myeloma. On the corresponding conventional skeletal radiography images of the thoracic **c** and lumbar **d** spine even the largest osteolytic lesion with advanced destruction of the T4 vertebral body is largely occult, while the advanced destruction of the L4 vertebral body is challenging to spot (arrows in **b**).



► Fig. 2 Coronal computed tomography images of a 64-year-old male patient with multiple myeloma in complete remission **a**, and 4 months later during relapse **b**. The humeral metaphyses show subtle osteolysis and scalloping even during remission **a**, most likely due to a treated infiltration. While the bone marrow of the humerus appears normal and fatty in **a** without any signs of cellular infiltration, a diffuse hyperdense bone marrow infiltration (arrows) can be readily seen during relapse **b**.

tense normal bone marrow) [20]. Only the plasma cell lesions in the focal or mixed infiltration pattern result in destruction of the surrounding bone substance which is expressed as osteolysis that is potentially visible on projection radiography and CT. Various studies were able to show the prognostic relevance of the MRI patterns of infiltration. A normal appearance of the bone marrow or a "salt and pepper" pattern was usually associated with an early disease stage and a better prognosis, while a diffuse infiltration

pattern or numerous focal lesions were associated with genetic high-risk constellations, an advanced disease stage, a higher tumor load, and worse progression-free survival as well as overall survival [22, 23].

The advantages of MRI are due to the fact that bone marrow infiltration can be visualized even before lytic changes occur (► Table 2). Therefore, it is not surprising that MRI is superior to conventional radiography with respect to the detection of bone

► **Table 3** Exemplary whole-body MRI protocol (1.5 T MAGNETOM Avanto fit [Siemens Healthineers, Erlangen]).

region	Sequence	TR [ms]	TE [ms]	voxel size [mm ³]	bandwidth [Hz/Pixel]
skull, neck, thorax, abdomen, extremities	T2 TIRM coronar	5240	82 (TI: 130)	0.6 × 0.6 × 5.0	303
	T1 VIBE coronar	6.4	4.8	1.5 × 1.5 × 2.5	740
	DWI axial ¹	5000	74	1.9 × 1.9 × 6.0	1628
skull	resolve DWI axial ²	3220	81/124	1.0 × 1.0 × 6.0	657
neck	DWI axial ¹	2900	87	1.7 × 1.7 × 5.0	1644

MRI = magnetic resonance imaging, TR = time to repetition, TE = time to echo, TIRM = turbo inversion recovery magnitude, TI = inversion time, VIBE = volume interpolated breathhold examination, DWI = diffusion weighted imaging.

¹ b-values: b50 and b800.

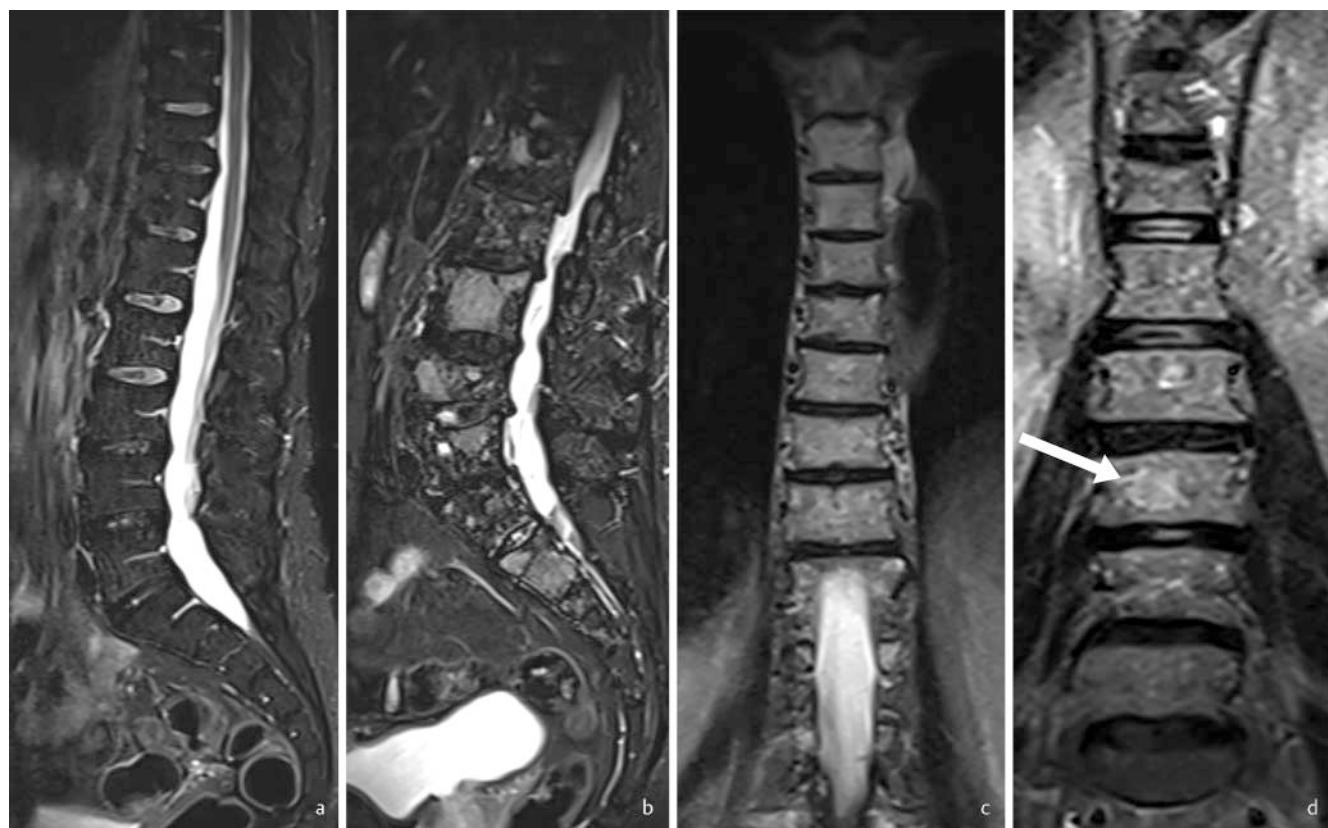
² b-values: b0 and b1000.



► **Fig. 3** Bone marrow infiltration patterns of multiple myeloma on magnetic resonance imaging using sagittal fat-saturated T1-weighted images **a–e**. Normal-appearing bone marrow shows a homogeneously T1w hyperintense distribution due to the fat content **a**. Focal lesions are visualized with a similar or lower signal intensity compared to the musculature or healthy intervertebral discs **b**, arrows with an open arrowhead point to exemplary focal lesions; pathological fractures are seen in T10 and T12 as well as L1, 4, and 5). A diffuse infiltration is indicated by a homogeneous T1w hypointense bone marrow compared to the musculature or neighboring intervertebral discs **c**. Simultaneous visualization of a generalized T1w hypointense bone marrow and additional focal lesions marks a mixed focal and diffuse infiltration **d**, arrows with a closed arrowhead point to exemplary focal lesions, that in this patient appear relatively T1w hyperintense due to high-grade diffuse T1w hypointense infiltration of the surrounding marrow). A “salt-and-pepper” pattern shows a disseminated “micronodular” T1w hypointense infiltration against a background of normal T1w hyperintense fatty bone marrow **e**, with a simultaneously normal fat-saturated T2w imaging appearance (not shown here).

involvement [12]. MRI is at least equivalent to CT and PET/CT, with individual studies showing advantages with respect to MRI [4, 12, 24, 25]. MRI is better suited than PET/CT to detect diffuse bone marrow involvement [25, 26]. A further advantage of MRI is the ability to differentiate uncomplicated osteoporotic fractures from pathological fractures based on the appearance of the bone marrow [27]. Moreover, MRI is highly suitable for visualizing extra-

medullary myeloma, which occurs in up to one-fifth of all patients and can manifest on a secondary basis (i.e., by spreading from an affected bone) or on a primary basis as an extraskeletal finding (► Fig. 5) [28]. Besides the known disadvantages of MRI in general, like limited availability, high costs, long examination time (depending on the protocol approx. 45 to ≥ 60 minutes) and only conditional applicability in patients with metal implants or claus-



► Fig. 4 Patterns of bone marrow infiltration in fat-saturated T2-weighted images a–d. Patients with a normal-appearing bone marrow and patients with a salt-and-pepper pattern show homogeneous hypointense bone marrow on T2w images a. Focal lesions appear hyperintense on fat-saturated T2w images b. A diffuse infiltration pattern is marked by homogeneously hyperintense bone marrow on fat-saturated T2w images c. In a mixed imaging pattern, circumscribed focal hyperintense lesions are visualized within homogeneous hyperintense bone marrow on fat-saturated T2w images (arrow in d).

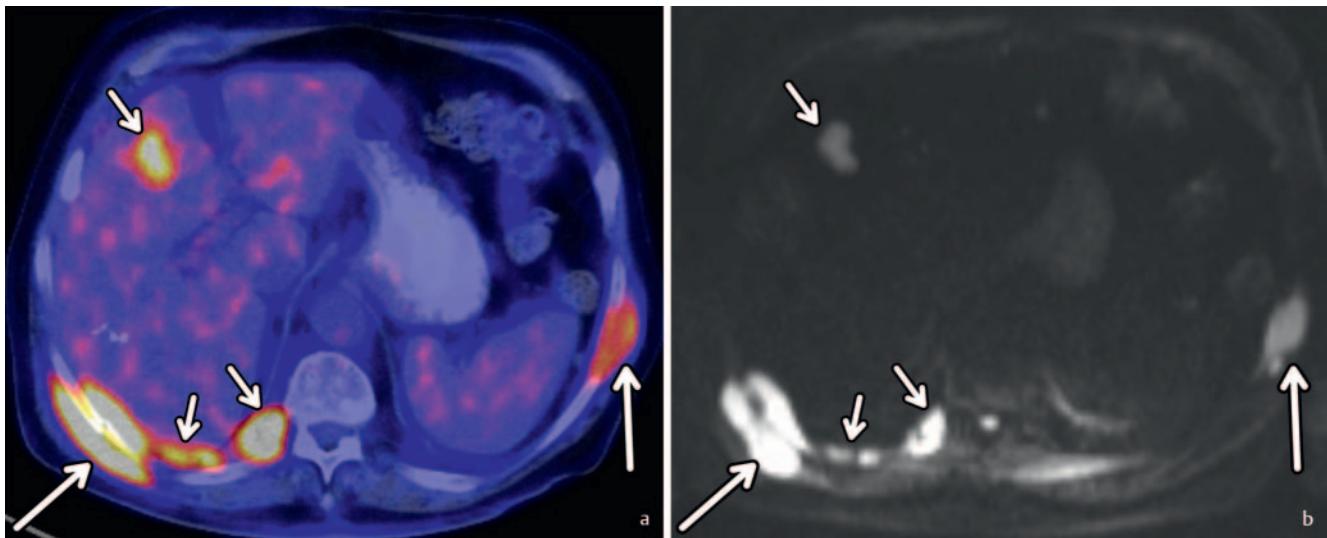
trophobia, MRI has an additional disadvantage regarding the follow-up of myeloma patients: in purely morphologic sequences it is often not possible to differentiate between vital lesions and non-vital scarring despite possible treatment response since part of the lesions disappears incompletely or only very slowly (**► Table 2**) [7, 24, 29]. Therefore, PET/CT has become established for treatment monitoring.

PET/CT

18F-fluorodeoxyglucose (FDG) PET/CT is an imaging modality that visualizes the glucose hypermetabolism of medullary and extramedullary myeloma in addition to the morphological detection of osteolysis as an additional functional component (**► Fig. 5**) [6, 12, 30]. Even though non-osteolytic lesions can also be detected on PET/CT, the persistence of at least one osteolytic lesion (≥ 5 mm) continues to be necessary according to current diagnostic guidelines for formal diagnosis of bone involvement [4]. The diagnostic performance of PET/CT for detecting focal lesions is significantly greater than that of conventional radiography and is largely comparable with MRI [12]. PET/CT is inferior to MRI only with respect to the detection of diffuse bone marrow infiltration [25, 26] since the cellular uptake rate of FDG as well as the percentage of myeloma cells in the examined volume plays a role. Given

a low cell density, e.g. in the case of low-grade diffuse involvement, the FDG uptake must also be low.

PET/CT has become established primarily for treatment monitoring. Based on the visualization of metabolic activity in myeloma lesions, a differentiation between hypermetabolism suspicious for malignancy and inactive scarring is possible, while a difference often cannot be observed on a purely morphological basis on CT or MRI [7, 29, 31, 32]. Moreover, PET/CT makes it possible to make prognostic statements both in the initial diagnosis and in the course of treatment. Therefore, for example, the detection of more than 3 hypermetabolic focal lesions at the initial diagnosis or shortly after the start of treatment is an independent predictor of a worse survival rate so that certain patients may benefit from a targeted early change of treatment [33–35]. Moreover, better treatment results were observed in patients with complete normalization of the metabolism in focal lesions after induction chemotherapy [33]. An unremarkable PET/CT examination is predictive of a long-term relapse-free survival even after autologous stem cell transplantation while the detection of active lesions is an independent predictor of a worse progression-free survival [35–37]. Despite these promising results, PET/CT is not yet established as a routine method in the clinical routine in many places due to the high costs and the limited availability (**► Table 2**).



► Fig. 5 Axial FDG PET/CT image **a** and corresponding b800 DWI image **b** of a 69-year-old male patient with multiple myeloma. Primary extramedullary disease of the pleura and of the liver in segment 4a (short arrows in **a** and **b**) as well as secondary extraosseous lesions adjacent to the ribs show a vivid hypermetabolism on PET/CT (**a**) and appear hyperintense on DWI **b**. Note: FDG = 18F-fluorodeoxyglucose, PET/CT = positron emission tomography/computed tomography, DWI = diffusion-weighted imaging.

Imaging of precursors to multiple myeloma

Monoclonal gammopathy of unclear significance (MGUS)

MGUS is an asymptomatic precursor disease of MM that does not require treatment and is usually identified incidentally after the 50th year of life on the basis of an M-gradient in routine laboratory testing and has an annual risk of progressing to myeloma requiring treatment of approx. 1% [3]. By definition, patients with monoclonal gammopathy differ from patients with "smoldering multiple myeloma" (SMM) and symptomatic MM on the basis of a lower M-protein and a plasma cell infiltration < 10% in the bone marrow biopsy. In addition, these patients may not exhibit a "myeloma-defining event" (► Table 1) [3, 4]. Although patients with MGUS per definition do not have myeloma-related osteolysis, at least one focal lesion could be detected via whole-body MRI in 23% of cases in a study including 137 patients, which proved to be an independent predictive factor for disease progression to symptomatic MM in the course of the disease [23]. To identify such cases in a timely manner and to be able to monitor them closely, MRI should be performed in the case of a diagnosis of MGUS.

"Smoldering multiple myeloma"

SMM is also an asymptomatic precursor to MM without the presence of end-organ damage. However, compared to MGUS, it has higher laboratory parameters, a plasma cell infiltration of 10–60% in the bone marrow and an annual risk of progressing to MM of 10% [3, 4]. In recent years, two studies showed that focal lesions can be detected on MRI in up to 28% of patients with SMM [38, 39]. The presence of more than one focal lesion was an independent predictor of faster progression to symptomatic MM in

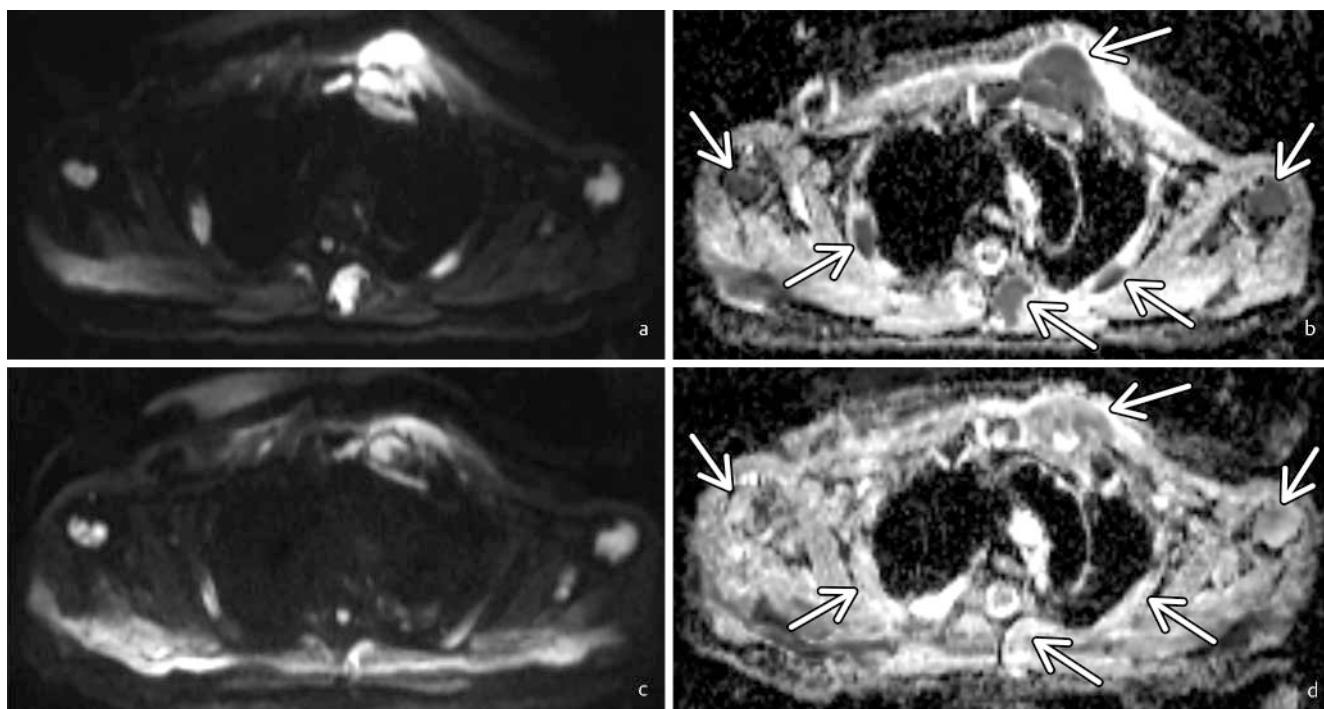
both studies. The International Myeloma Working Group (IMWG) recommends performing MRI in the case of diagnosis of SMM accordingly early in order to be able to treat high-risk patients in a timely manner. Therefore, the presence of more than one focal lesion on MRI is included in the latest version of the IMWG recommendations as a "myeloma-defining event", resulting in treatment as symptomatic myeloma [4]. In the case of unclear MRI findings, a diffuse infiltration, or the presence of only one focal lesion, a follow-up MRI should be performed at an interval of 3–6 months for better assessment of the risk of disease progression [4]. Alternatively FDG PET/CT can be performed in the case of contraindications or a lack of availability.

Solitary plasmacytoma

Solitary plasmacytoma can be divided into primary bone plasmacytoma and primary extramedullary plasmacytoma, with the primary bone plasmacytoma being associated with a higher risk of progression to MM. Besides bone marrow biopsy, the presence of osteolytic lesions in addition to the primary lesion should be ruled out on whole-body CT or PET/CT. Moreover, MRI or PET/CT, which is also suitable for visualizing extramedullary and non-osteolytic lesions and can detect additional lesions in up to one-third of all patients resulting in a change in the therapeutic approach, should be performed [4, 40].

Follow-up imaging and assessment of treatment response and minimal residual disease

Projection radiography and CT are only conditionally suitable for follow-up in patients with MM. Since remineralization of osteolytic lesions cannot be expected even after successful treatment, these



► Fig. 6 Axial b800 **a, c** and ADC **b, d** DWI images of a 69-year-old patient with multiple myeloma. The baseline exam **a, b** before initiation of therapy reveals multiple osseous and extraosseous lesions, which show restricted diffusion on the ADC-map (arrows in **b**). 10 days after VCD therapy onset, myeloma lesions become less hyperintense in the b800 images and show increasing ADC values (arrows in **d**), which can be attributed to a decline in cellularity due to early therapy response. Note: DWI = diffusion-weighted imaging, ADC = apparent diffusion coefficient, VCD = Velcade® (bortezomib), cyclophosphamide, dexamethasone.

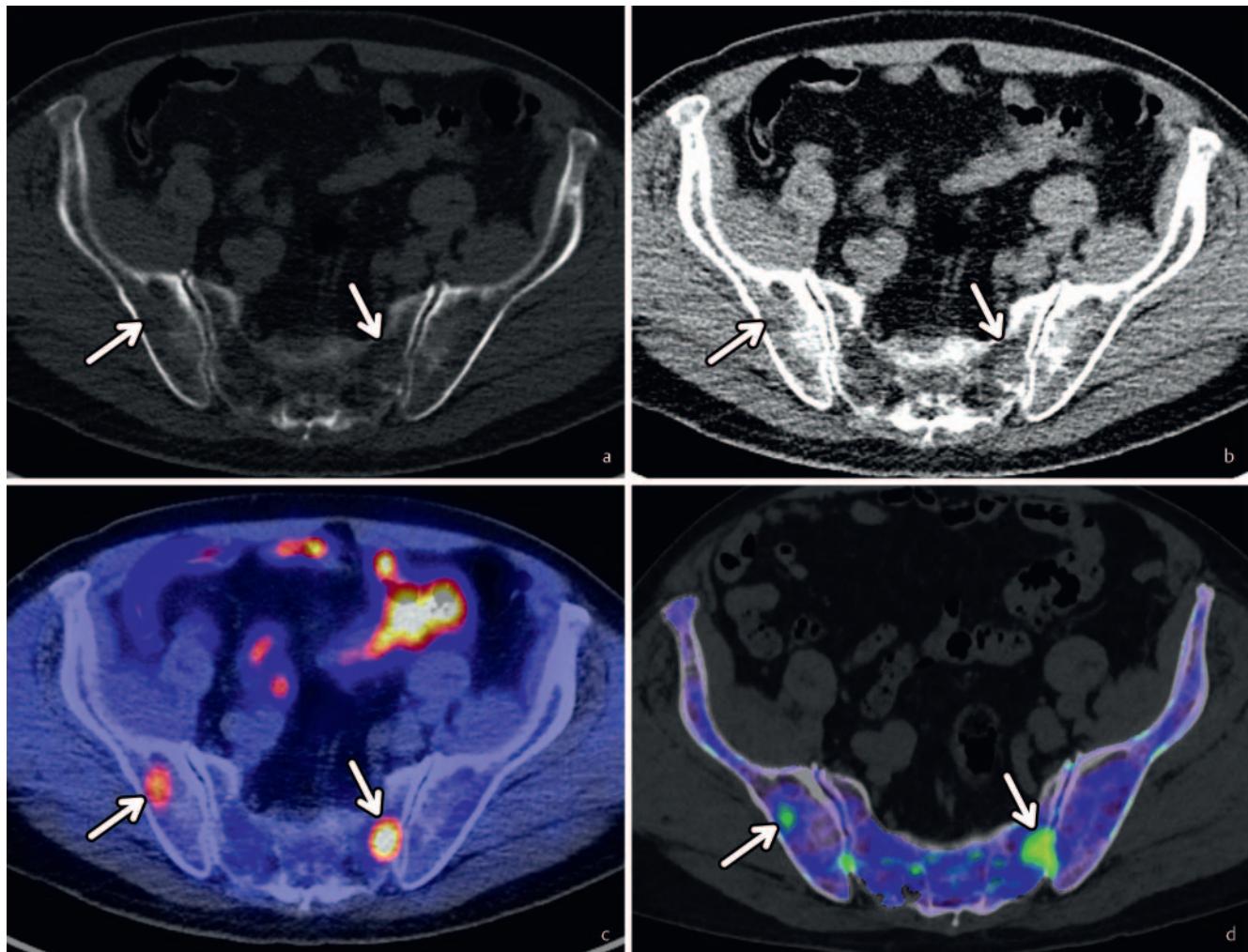
two modalities can only show disease progression with new or larger osteolytic lesions or complications like fracture of vertebral bodies [12]. Treatment response can be identified on CT only on the basis of regression of extraosseous or paraosseous soft-tissue manifestations or on the basis of regression of medullary plasma cell infiltrations in the long bones of the extremities. In the case of treatment response, increasing normalization of the bone marrow appearance or regression of focal lesions with respect to number and size can be expected on MRI. However, it cannot be assumed in all cases that focal lesions will completely disappear since non-vital scarring can continue to be visible and cannot be differentiated from plasma cell nests with residual vitality on a purely morphological basis without functional sequences [32]. In addition, MRI shows a possible treatment response only with a slight time delay of 1–3 months [24]. Response can be detected much more quickly, namely after just a few days, and with significantly higher specificity with PET/CT which is why this technique has also become established for follow-up [7, 24, 31, 32, 35].

Effective treatments have increasingly resulted in a majority of patients achieving complete remission according to the conventional definition. However, since multiple myeloma is not a uniform disease, vital plasma cell nests can continue to be visible at other locations despite response according to laboratory testing and unremarkable blind puncture of the bone marrow of the iliac crest or sternum [7, 41]. In one study including 282 patients, it was able to be shown for example that patients with complete remission according to the conventional definition and remaining vital lesions on PET/CT have a significantly shorter progression-

free survival than those without vital lesions. However, an unremarkable PET/CT after the conclusion of treatment was an independent predictor of a longer progression-free survival and overall survival [42]. Based on the increasingly clinically established treatment monitoring in lymphoma diseases, IMWG recently published criteria for the assessment of minimal residual disease using PET/CT among other things and thus highlighted the importance of functional imaging for defining remission [31]. In the future, further standardization of the criteria regarding the quantitative and visual evaluation of PET/CT examinations would be desirable.

Future developments

Since MRI with purely morphological sequences cannot differentiate vital lesions from non-vital ones with sufficient certainty, additional functional MRI techniques like dynamic contrast-enhanced (DCE) MRI and diffusion-weighted imaging (DWI) are being tested at some centers. DCE-MRI after intravenous administration of a gadolinium-containing contrast agent allows conclusions about local microcirculation in bone marrow. Correlations with disease activity, disease stage, treatment response, progression-free survival, and overall survival could be shown in studies [43, 44]. However, the fact that DCE-MRI requires dedicated software for evaluation and quantification is problematic because the software can be associated with high procurement costs and software from different providers can yield inconsistent results even using the same source data. The molecular movement of hydrogen in tissue



► Fig. 7 Axial CT of the pelvis in a 76-year-old male patient with multiple myeloma. The non-lytic lesions (arrows in **a** and **b**) can barely be seen in the bone window **a** or soft tissue window **b** settings. Both lesions show hypermetabolism on PET/CT (arrows in **c**). Using the dual-energy CT color overlay after virtual calcium removal, both lesions can readily be seen depicted in green (arrows in **d**). Note: CT = computed tomography, PET/CT = positron emission tomography/computed tomography.

can be shown on DWI-MRI allowing tissue characterization without the administration of contrast agent. Primarily cell-rich focal myeloma lesions and diffuse infiltration of bone marrow by monoclonal plasma cells have a high signal due to their diffusion restriction in the DWI sequence which is why it is highly suitable as a search sequence [45, 46]. Moreover, a correlation between quantitative DWI parameters and the degree of bone marrow infiltration as well as treatment response could be shown (**► Fig. 6**) [44, 47–49]. A general problem of DWI is its general susceptibility to interference. Both techniques are not yet widely established for routine use.

Moreover, technical advances also in morphological MRI sequences (e.g. ultrashort echo time UTE technique) could make it possible in the future to visualize even small osteolytic lesions with dedicated, high-resolution sequences, which has only been possible with CT until now. This would mean, for example, a significant reduction in radiation dose in the case of suspected SMM or MGUS where to date end-organ damage in the form of osteolytic

lesions has been ruled out via CT. However, data from prospective studies in this regard are currently lacking.

Another promising hybrid technique is PET/MRI which combines the metabolic information of PET with the excellent soft-tissue contrast of MRI. Although PET/MRI lacks the ability to visualize mineralized bone, which would seem to be a disadvantage compared, for example, to PET/CT, MRI alone has excellent sensitivity for detecting osseous, particularly intramedullary, lesions, as confirmed by the results of initial studies on the PET/MRI hybrid method, which showed comparable diagnostic performance to that of PET/CT in myeloma patients, with larger studies still lacking due in part to the low availability of such scanners [50].

Alternative tracers for PET that can be used instead of FDG provide a further development opportunity. ¹¹C-methionine is absorbed to a greater degree for example by plasma cells and can be successfully used for imaging in MM. The results of recent studies confirm that ¹¹C-methionine has a better diagnostic performance and better performance in relation to the assessment of treatment response compared to FDG [51, 52]. However,

due to the short half-life of the tracer, this technique has only been available on a limited basis to date.

There have also been further developments regarding CT in recent years. Examinations using the dual-energy technique make it possible to create virtual calcium-free datasets (► Fig. 7). Using this technique, it was able to be shown that even non-osteolytic bone marrow involvement in the axial skeleton can be detected on CT [53, 54]. Moreover, the technique can be used for the targeted biopsy of focal bone lesions that are occult on conventional CT [55]. In the future this could be relevant for MM with its highly heterogeneous intraindividual distribution, for example, for examining individual lesions in a targeted manner in addition to blind puncture of the iliac crest.

Conflict of Interest

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