Multiple Myeloma Guidelines and Their Recent Updates: Implications for Imaging

Leitlinien zum multiplen Myelom und ihre aktuellen Anpassungen: Konsequenzen für die Bildgebung

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ABSTRACT

Background In 2014, the diagnostic criteria for multiple myeloma were updated, leading to revised recommendations for imaging modalities and definition of therapy response. This review provides an overview of the current definitions of monoclonal plasma cell disease, diagnostic options, and changes relevant to radiologists.

Method A pubmed search regarding the multiple myeloma guidelines was conducted, and results were filtered considering publications of international associations and expert reviews. Recommendations by the International Myeloma Working Group (IMWG), the National Comprehensive Cancer Network (NCCN, USA), the European Society for Medical Oncology (ESMO), and the European Myeloma Network are acknowledged.

Results and Conclusion Conventional skeletal survey is to be replaced by cross-sectional imaging techniques. For initial diagnostics of bone lesions or bone marrow involvement defining multiple myeloma, whole-body low-dose CT and whole-body MRI are recommended. Two or more focal bone marrow lesions suspicious for myeloma on MRI will now define symptomatic disease even in the case of intact mineralized bone. Follow-up imaging is not clearly specified so far. New guidelines concerning the definitions of minimal residual disease include the assessment of focal lesions before and after treatment using ^{18}F-FDG-PET/CT, with the potential to redefine the role of PET/CT in the diagnostics of multiple myeloma.

Key points:

- Whole-body low-dose CT is recommended by international reference organizations for detecting lytic bone lesions.
- Focal myeloma lesions detected on whole-body MRI will indicate symptomatic multiple myeloma requiring therapy, even in the absence of damage to mineralized bone.
- The IMWG recommends using cross-sectional imaging in the initial work-up: whole-body low-dose CT, MRI, or PET/CT, depending on availability and resources.
- The diagnostic potential of ^{18}F-FDG-PET/CT is highlighted by its inclusion in the definition of minimal residual disease after therapy; implementation in Germany is uncertain due to limited access in the daily routine.

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ZUSAMMENFASSUNG

Hintergrund Seit 2014 haben sich die diagnostischen Kriterien für das multiple Myelom und seine nicht therapiepflichtigen Vorstufen geändert. Zudem wurden neue Empfehlungen zur Modalität der Bildgebung und zum Therapieansprechen vorgeschlagen. Dieser Übersichtsartikel soll einen Überblick über aktuelle Definitionen, diagnostische Optionen und neue, für den Radiologen relevante Empfehlungen zum Vorgehen bei Plasmazellerkrankungen bieten.

Methode Eine Pubmed-Suche bezüglich Leitlinien zum multiplen Myelom wurde durchgeführt und hinsichtlich der aktuellsten Veröffentlichungen internationaler Fachgesellschaften und Expertenreviews gefiltert. Die Empfehlungen der „International Myeloma Working Group“ (IMWG), des „National Comprehensive Cancer Networks“ (NCCN, USA),

der Europäischen Gesellschaft für Medizinische Onkologie (ESMO) sowie des Europäischen Myelom-Netzwerks (EMN) wurden zusammengefasst.

Ergebnisse und Schlussfolgerung Der konventionelle Skelettstatus nach dem „Pariser Schema“ sollte zunehmend durch die Schnittbildgebung ersetzt werden. Zur Differenzierung eines durch Osteolysen oder Knochenmarkbeteiligung therapiepflichtigen multiplen Myeloms von seinen Vorstufen wird eine initiale Diagnostik mittels Ganzkörper-Niedrigdosis-CT und ggf. Ganzkörper-MRT empfohlen. 2 oder mehr fokale Myelom-verdächtige Herdbefunde zeigen nun auch bei intaktem mineralisiertem Knochen ein symptomatisches Myelom an. Zur Verlaufsbeurteilung gibt es bisher keine klare Empfehlung. Die Beurteilung eines fokalen Befalls vor und nach Therapie mittels ^{18}F-FDG-PET/CT ist Bestandteil der neuen Guidelines zur Detektion einer minimalen Resterkrankung, die somit die Rolle der PET/CT neu definieren könnten.

Introduction

Imaging plays an important role in the diagnosis and follow-up of multiple myeloma. The implementation, technical improvements, and increasing availability of cross-sectional imaging has resulted in a shift in paradigm in recent years. The advantages of “modern” imaging methods, primarily their higher sensitivity and specificity compared to conventional skeletal survey, have also resulted in changes to the guidelines.

This review summarizes the current recommendations regarding imaging in plasma cell diseases and provides radiologists with an overview of multiple myeloma and its precurser states.

Background of multiple myeloma

Multiple myeloma is characterized by the proliferation of atypical plasma cells and can result in a measurable immunoglobulin peak or pathological light chains in the serum or urine as a diagnostic feature [1]. Chromosomal aberrations result in altered expression of transcription factors regulating proliferation, proangiogenesis, and bone metabolism as well as cell survival. Over the course of the disease, the changes in the microenvironment result in disruption of normal bone metabolism with increased activity of the osteoclasts and inhibition of the osteoblasts [2]. The increase in bone resorption and the suppression of the normal hematopoietic bone marrow result in the following classic symptoms: anemia, hypercalcemia, and osteolysis. The production of paraproteins also results in renal insufficiency (CRAB criteria) [1].

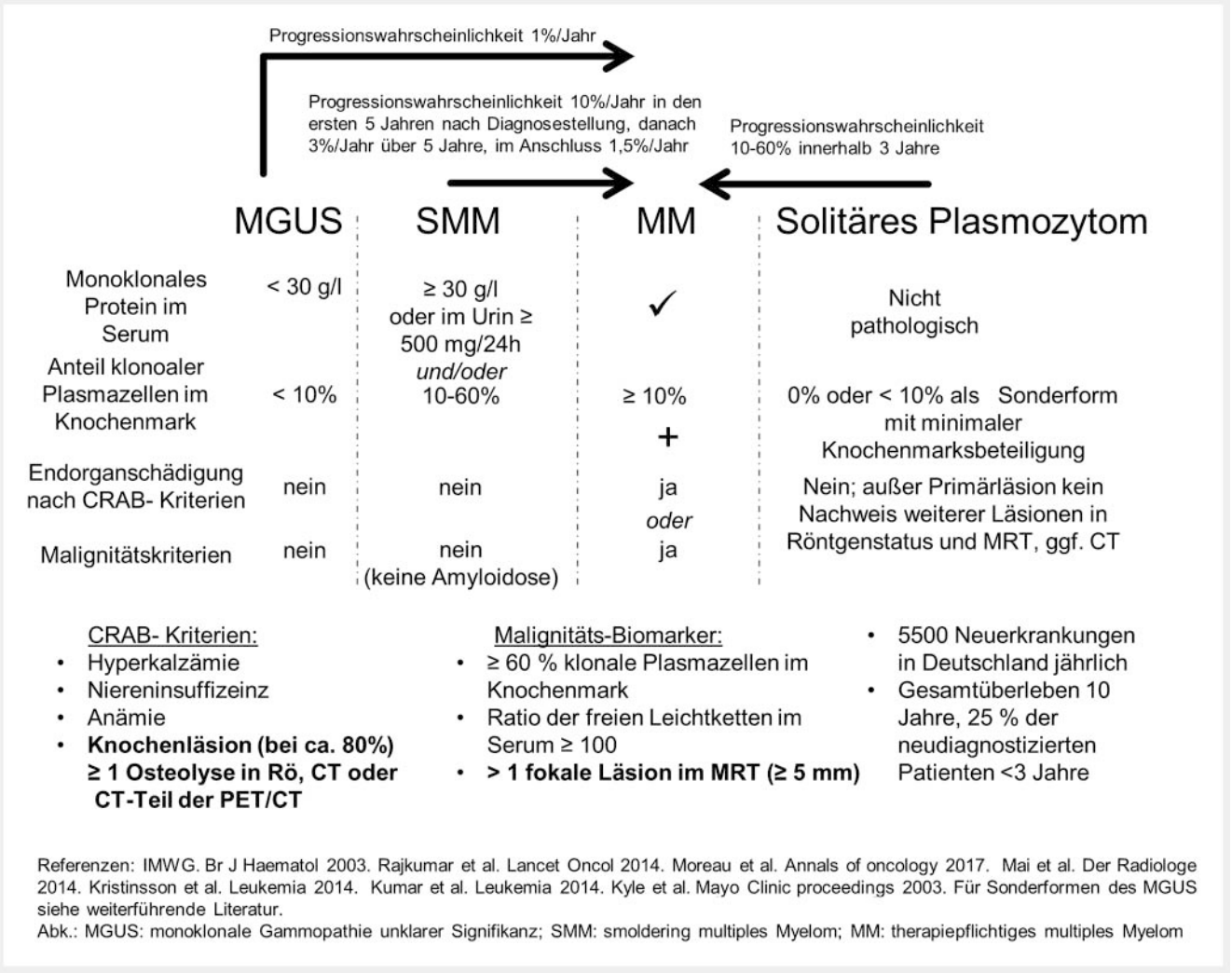
However, the differentiation between asymptomatic and symptomatic stages is essential for clinical decisions in patients newly diagnosed with a plasma cell disease. The criteria of the International Myeloma Working Group published in 2014 (Rajkumar 2014, [3]) are valid now. Asymptomatic preliminary stages like monoclonal gammopathy of unclear significance (MGUS) and smoldering or indolent multiple myeloma (SMM) can evolve to a stage requiring treatment, while MGUS differs from SMM with respect to the level of monoclonal proteins in the serum and the percentage of atypical plasma cells in the bone marrow biopsy [1, 4]. MGUS is common in the clinically healthy population with the prevalence increasing with age (3 % among people ≥ 50 years and 5 % among people ≥ 70 years [5]). Statistically, the progression rate in symptomatic MM is 1 %/year in MGUS and 10 %/year in SMM, but the individual time to progression is highly variable in both groups [6]. Approximately 5500 people are diagnosed with multiple myeloma each year in Germany [7].

Importance of imaging in the diagnosis of MM

▶ **Fig. 1** provides a summary of the current diagnostic criteria of the International Myeloma Working Group (IMWG). Damage to mineralized bone that can be diagnosed as osteolysis on conventional radiography, computed tomography (CT) or on the CT part of positron emission computed tomography (PET/CT) is relevant for radiologists. Newly implemented here is the definition of malignancy criteria for the first time as more than one focal myeloma-typical lesion on magnetic resonance imaging (MRI) even in the case of intact mineralized bone. These lesions are characterized by circumscribed hyperintensity in T2w fat-suppressed sequences such as TIRM (turbo inversion recovery magnitude) with corresponding focal T1w signal attenuation (▶ **Fig. 2a**) [8, 9]. In 2010, Hillengass et al. were able to show that focal involvement and particularly more than one focal lesion on MRI in patients not requiring treatment are relevant for progression-free survival. In the meantime, numerous studies have been able to examine and confirm the prognostic significance of these findings in the bone marrow so that the guidelines were updated and the importance of MRI has been recognized [10 – 13]. A differentiation cannot be made between MGUS and smoldering myeloma on CT, PET/CT, or MRI. This requires serological and biopsy data.

Current staging system

In 1975, Durie and Salmon created a staging system based on Hb and serum calcium levels, bone lesions, M-gradient, and renal function to reflect the tumor burden and found a correlation with treatment response and survival. According to the definition, not more than one osteolytic lesion is present on imaging in stage I while multiple osteolytic lesions are present in stage III [14]. In 2003, the “Durie & Salmon Plus” staging system was presented, proposing stages from minor to severe diffuse disease based on the number of focal lesions using whole-body MRI or PET/CT measurements (IA: single plasmocytoma, IB: < 5 focal lesions, II: 5 – 20 focal lesions, III: > 20 focal lesions) [15]. It must be noted that particularly the number of lesions used to define the individual stages is not supported by empirical studies and is the result of

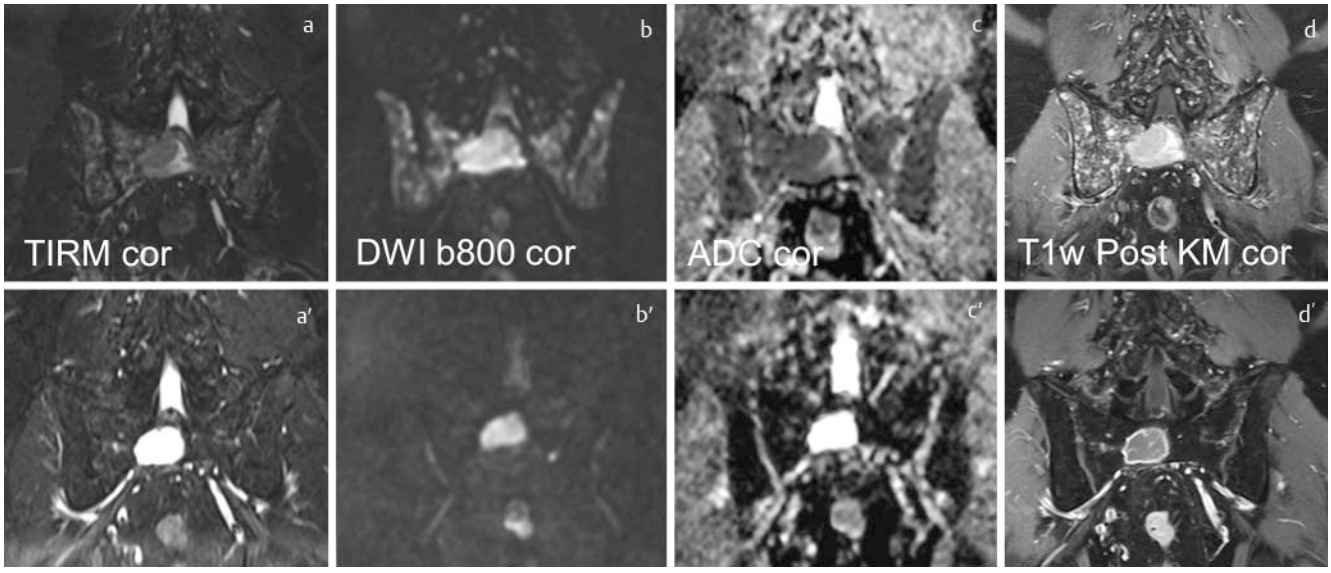


▶ **Fig. 1** Summary of current diagnostic criteria of the International Myeloma Working Group: The monoclonal protein level in the serum or urine, the percentage of malignant plasma cells in the bone marrow and the presence of end organ damage or malignancy criteria can be used to differentiate between multiple myeloma requiring treatment and its preliminary stages that do not require treatment. End organ damage can manifest as hypercalcemia, renal insufficiency, anemia, and bone lesions. These are referred to as the CRAB criteria. The task of radiological diagnostics is the detection of osteolytic lesions or focal bone marrow lesions caused by myeloma as a biomarker of malignancy (in bold). Solitary plasmacytoma as a disease with no or minimal systemic components represents a special form. The probability of progression to a systemic disease requiring treatment is provided in each case.

a rather arbitrary definition. Moreover, additional clinical or laboratory parameters are not taken into consideration in contrast to the "classic" Durie & Salmon classification. Accordingly, this system is rarely applied at least in Germany. Since 2005, the recognized international staging system (ISS) has classified the disease based on β2-microglobulin and albumin in serum in 3 stages (I: β2 < 3.5 mg/dl, albumin > 35 g/l; III: β2 > 5.5 mg/l; II: neither I nor III) with decreasing overall survival [4, 16]. Visible morphological parameters are not included in the ISS. In their current guidelines, the European Society for Medical Oncology (ESMO) presents an addition to the staging system for improved risk stratification (revised (R)-ISS). The revised system includes additional information regarding cytogenetics from fluorescence in-situ hybridization and lactate dehydrogenase [4].

Shift in paradigm: Clear recommendation for low-dose CT

Conventional skeletal survey was state-of-the-art in the radiological diagnosis of multiple myeloma for a long time [17]. However, according to the new IMWG guidelines, detection of one or more osteolytic lesions (> 5 mm) on CT (possibly using the low-dose technique or as part of a PET/CT examination) is sufficient for diagnosis regardless of whether a corresponding lesion is detected on conventional radiography (see ▶ **Fig. 3**). In contrast, increased ^{18}F-FDG uptake alone as well as osteoporosis or compression fracture without detection of osteolysis is not indicative. The elimination of osteoporosis as a defining criterion is the result of the age- and menopause-based frequency in the normal population. In all unclear cases, short-term follow-up is indicated [3]. Numerous



▶ **Fig. 2** Definition of the focal involvement on MRI in coronal (cor) view of a large lesion in the os sacrum as an example: Typical signal increase in the TIRM sequence **a**, significantly impaired diffusion on the b800 image **b** with ADC decrease **c** and significant contrast enhancement **d**. After treatment, shrinking of the lesion with a fluid-isointense signal **a'** with T2-shine-through **b', c'** and significant decrease in contrast enhancement **d'**. Regression of the diffuse involvement is also seen.

studies comparing the available imaging modalities have been published in recent years and confirm the increased sensitivity of cross-sectional imaging compared to conventional skeletal survey [18 – 21]. A study by the International Myeloma Working Group published in 2017 was able to show that one-fourth of examined myeloma patients had an unremarkable conventional skeletal survey but additional osteolytic lesions were visible on low-dose CT (▶ **Fig. 3d**). It was reported in the same publication that 22 % of SMM patients with unremarkable X-ray findings already had osteolytic lesions therefore requiring treatment [22]. The guidelines of the ESMO and EMN (European Myeloma Network) therefore advocate the use of whole-body low-dose CT as the new standard for detecting relevant osteolytic lesions. Conventional skeletal survey can continue to be used where CT is not available [4, 23]. However, since myeloma patients are treated at specialized centers or practices, this should already be the exception. Multiple lesions < 5 mm are difficult to differentiate from a patchy bone structure as seen in osteopenic bone. A standardized interpretation in these cases has not yet been defined.

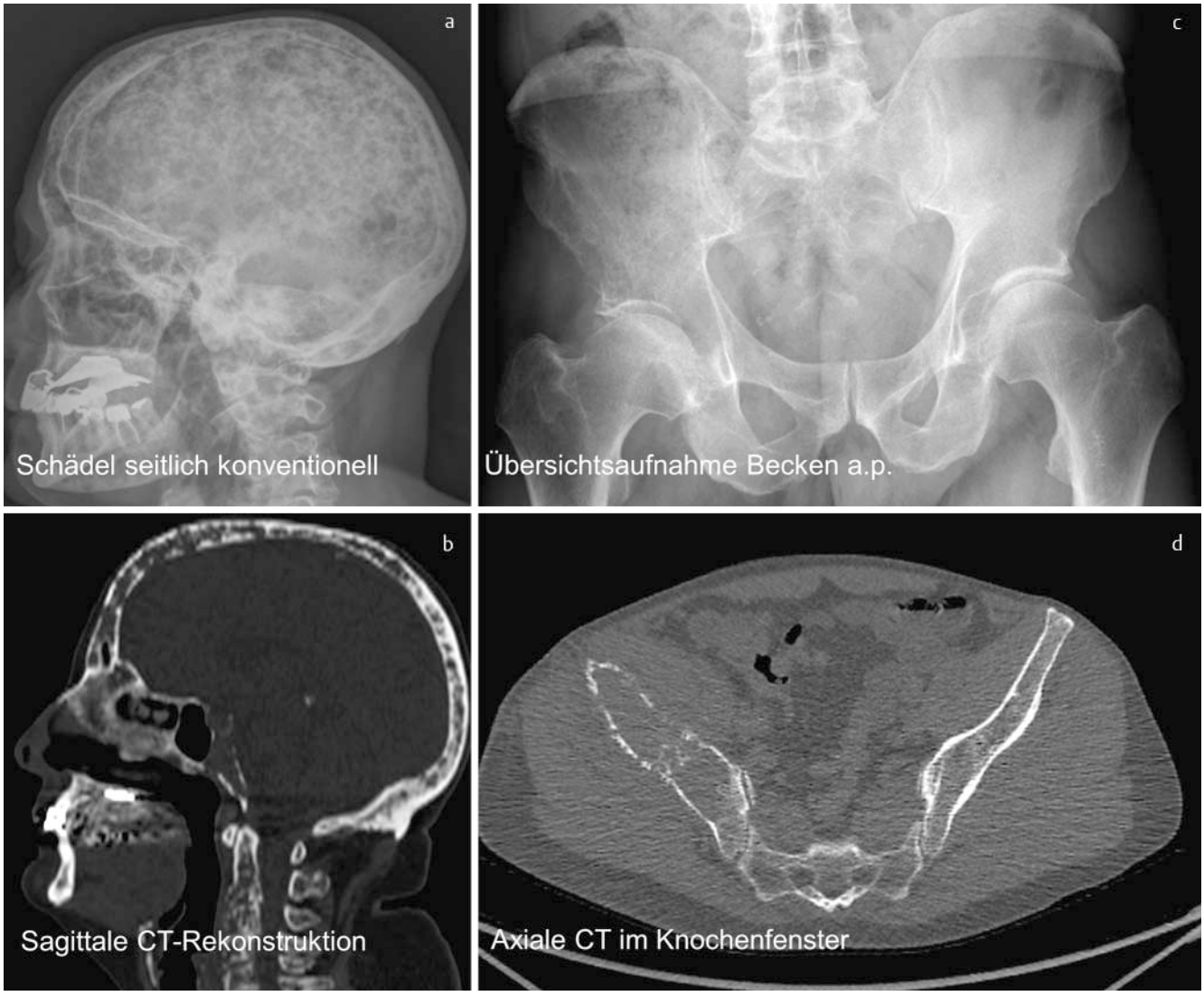
At our institute, patients with suspicion of plasma cell disease undergo a whole-body low-dose CT examination (45 mAs, 100 kV, Sn140) with the patient in a basic position with the arms placed in front of the body with the hands holding, for example, a cloth or a plastic pillow. This prevents the arms and spine from being on the same plane resulting in beam-hardening artifacts that complicate evaluation of the spine. The source images (1 mm) are used to generate axial series in both the bone and the soft-tissue kernel for evaluation of the bone marrow. In addition, coronal and sagittal reconstructions are calculated for better evaluation of the medullary cavities of the long bones and the structural stability of the spinal column.

The experts of the NCCN ("National Comprehensive Cancer Network", USA) recommend using conventional skeletal survey or low-dose CT for diagnosis. Under certain circumstances, e. g. in the case of symptoms or when conventional skeletal survey and CT do not provide a definitive finding, whole-body MRI or PET/CT is indicated [24]. PET/CT has prognostic significance after treatment [25]. It should be mentioned that these statements and the status of PET/CT in the USA are a result of the unique health care situation in the United States and this information does not relate to Germany.

Together with the Association of the Scientific Medical Societies in Germany, German guidelines were announced and work began in May 2018. We have high hopes regarding the assessment of MRI, particularly with respect to the future regulation of reimbursement by the health insurance funds.

Status of MRI

Focal and diffuse infiltration patterns of multiple myeloma can be detected on MRI (▶ **Fig. 4**) that provide information about the tumor mass and can be associated with cytogenetic risk factors [26, 27]. A salt & pepper pattern (▶ **Fig. 4b**), moderate involvement (▶ **Fig. 4c**) and extensive involvement (▶ **Fig. 4d**) are differentiated from normal bone marrow (▶ **Fig. 4a**) with increasing diffuse infiltration via T1w and T2 TIRM signal alterations. The damage to mineralized bone often does not correlate with the extent of bone marrow involvement visible on MRI. As already discussed above, the available studies indicate the prognostic relevance of focal involvement so that patients with a proven higher risk profile now can be treated earlier. MRI is therefore recommended by experts in the initial diagnosis work-up of smoldering myeloma [28]. When possible, whole-body MRI should be given preference over spinal MRI for complete staging so that relevant extraaxial lesions are not missed [29]. We recommend the acqui-



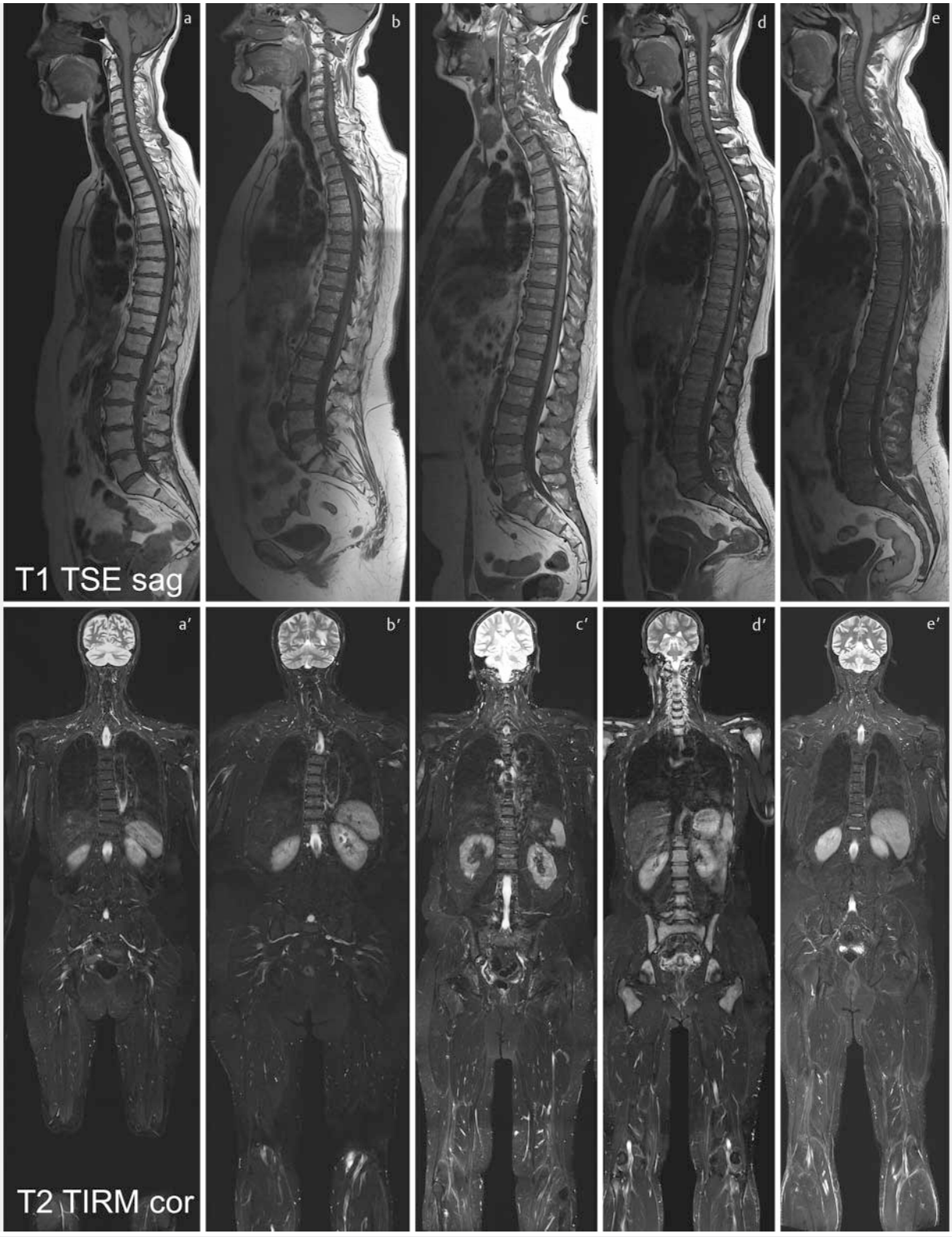
▶ **Fig. 3** Multifocal patchy involvement of the skull: Classic "raindrop skull" appearance of calvarial multiple myeloma, well-defined lytic lesions" on lateral X-ray **a** with corresponding osteolytic lesions on CT (sagittal reconstruction, **b**). Increased sensitivity of CT: Osteolysis in the right os ilium and ischium was not detected on the initial pelvic X-ray a. p. **c**; but axial CT shows the destruction of the cortical bone **d**.

sition of coronal T1w and coronal T2 TIRM/STIR sequences from the head to below the knee that are acquired in an overlapping manner in six blocks, for example, depending on the size of the patient and are then merged (composed). In addition, a sagittal T1w sequence of the spine should be included in the protocol. Diffusion-weighted imaging can support evaluation particularly over the course of the disease and has already been established for many years at our institute (b = 50 and b = 800 s/mm^2). Protocol recommendations including sequence parameters are available under www.dkfz.de/en/radiologie/research/Imaging_in_monoclonal_plasma_cell_disorders. In the case of suspicion of intraspinal involvement or a risk to the bone marrow, additional sequences in axial scan orientation are recommended.

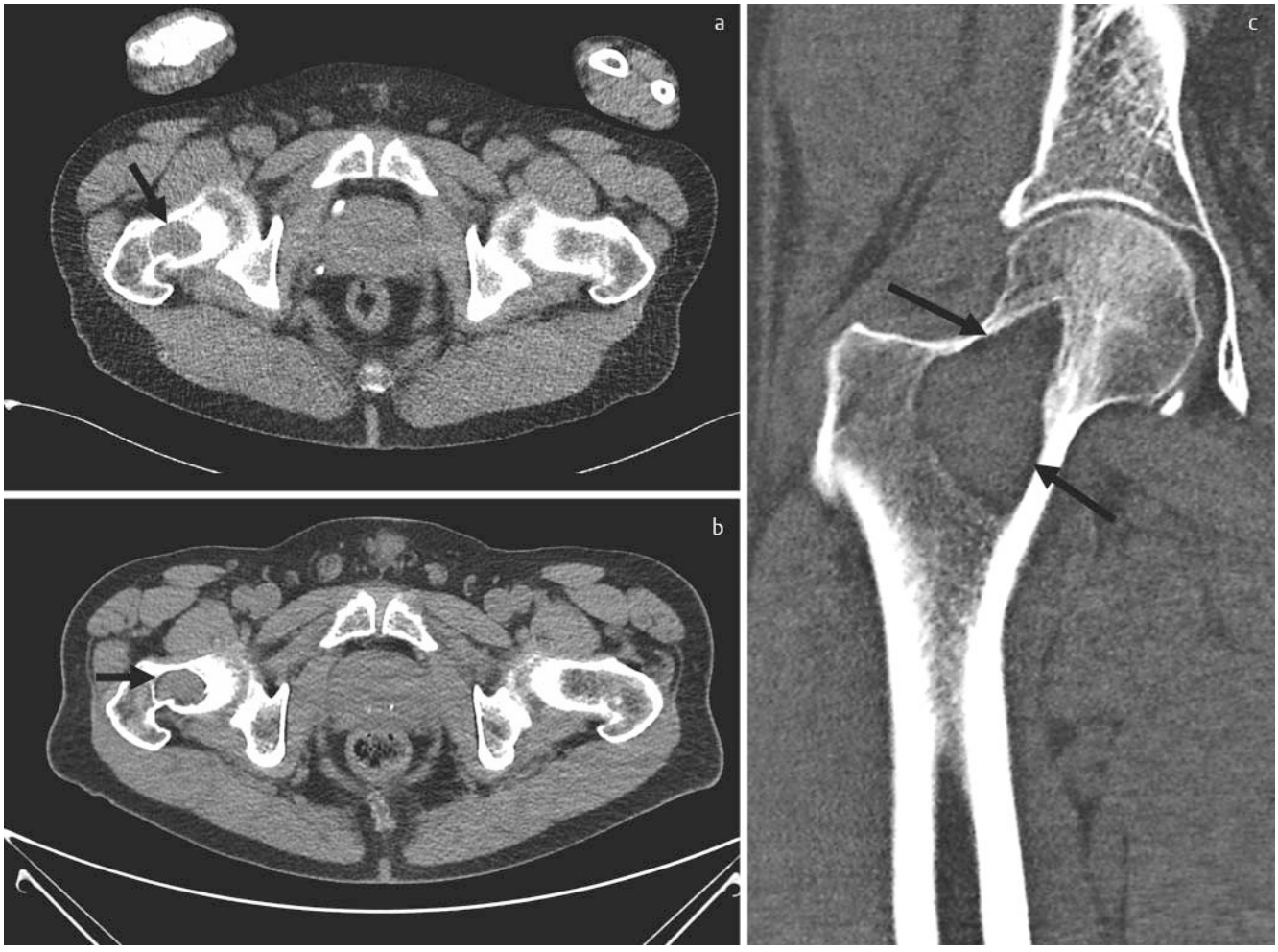
However, the EMN recommends performing MRI only in asymptomatic patients without the detection of an osteolytic lesion on CT. Depending on availability and financing options, ^{18}F-FDG-PET/CT can also be used to evaluate bone lesions [4].

Diffuse bone marrow involvement without additional focal lesions indicates an increased risk of progression but for the time being is not an independent indication for treatment. However, short-term follow-up after three to six months is recommended in the case of a diffuse pattern of involvement, a solitary focal lesion, or unclear findings [3, 30, 31]. In the case of progression on MRI, the patient is considered symptomatic. In patients with suspicion of solitary plasmocytoma, additional involvement at other locations must be ruled out using all available methods including MRI [32].

Standardized systematic reporting is still being developed and would help to improve comparability. Given the wide range of patterns of involvement, the morphology of individual lesions and possible complications, this is an ambitious undertaking. It will require the use of interactive software.



▶ **Fig. 4** Pattern of involvement on MRI in the case of diffuse infiltration of the bone marrow according to Baur et al. (Röfo, 1996 [33]) based on sections of the sagittal (sag) T1w TSE sequence of the spine and the coronal (cor) T2 TIRM sequence (head to proximal lower leg): **a** normal bone marrow signal; **b** salt and pepper pattern with patchy signal inhomogeneities in the T1w sequence without significant signal increase in the T2 TIRM sequence **b'** as a possible correlate of minimal involvement; **c** extensive T1w signal decrease but still hyperintense with respect to the intervertebral disc with signal increase in the TIRM sequence defines moderate diffuse involvement **c'**; **d** extensive involvement (severe) is seen as T1w signal decrease and significant signal increase in the TIRM sequence **d'**. The T1w signal decrease **e** without signal increase in the TIRM sequence **e'** is a morphological correlate of a patient with hypercellular bone marrow in myelodysplastic syndrome in this case.



▶ **Fig. 5** 5 months after the end of treatment, a large osteolytic lesion in the right femoral neck (arrow, **a** axial CT) shows a "halo phenomenon", a fat margin after retraction of the soft-tissue content of the lesion inside the sclerotic zone as a sign of treatment response (arrows **b**), enlargement in coronal view **c**.

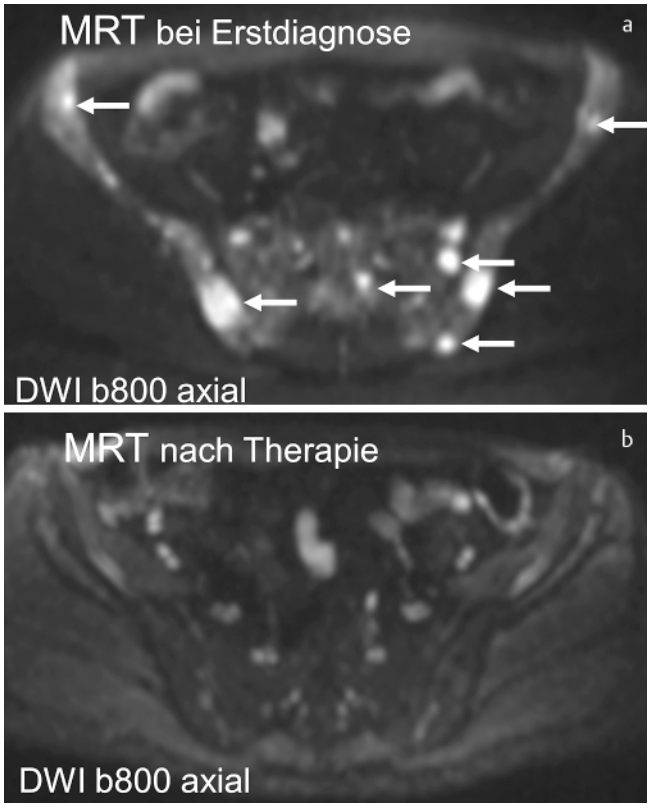
Or perhaps PET/CT?

The major advantage of PET/CT is the combined anatomical and functional information. The use of ^{18}F-FDG as a radioactively labeled tracer is currently established clinically and in studies. The sensitivity of the examination is significantly better than that of conventional skeletal survey [33]. The proponents of the method argue, with a certain degree of justification, that ^{18}F-FDG-PET primarily detects lesions with high activity and cell density and thus significant clinical relevance. However, it is questionable whether it should be performed in place of rather than in addition to CT or MRI because of its low sensitivity with respect to diffuse infiltration pattern. The CT component of PET/CT should be performed with a diagnostic whole-body skeletal protocol (including the necessary multiplanar reconstructions) so that an additional skeletal CT examination is not necessary.

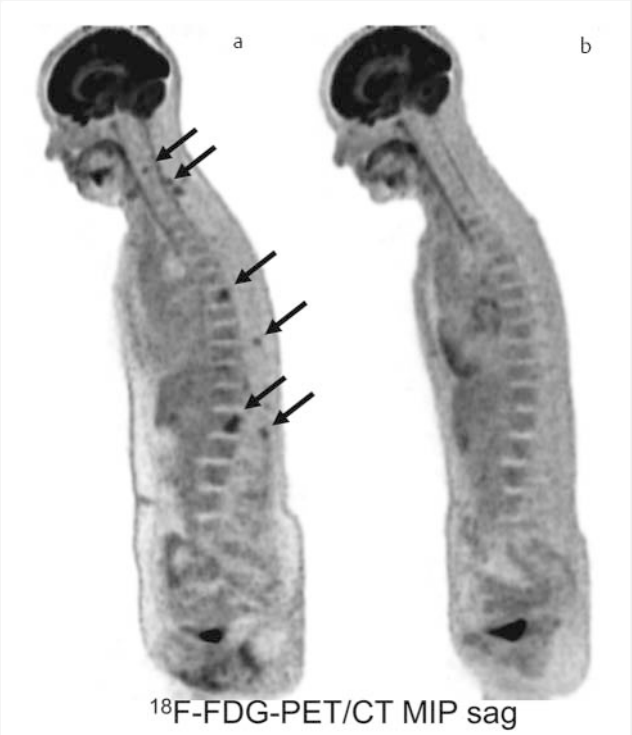
A systematic review of the currently available studies for comparing whole-body MRI and PET/CT shows that MRI is more sensitive but less specific regarding the detection of lesions [34]. However, response to treatment can be detected earlier with PET/CT than MRI. In the case of the latter, persistent lesions can be difficult to evaluate, particularly since successfully treated lesions with a constant size can show a significant increase in signal intensity on T2w and diffusion-weighted images [35, 36]. Multiple studies highlight the prognostic significance of PET-positive lesions both in the initial diagnosis and in relapse [37, 38]. However, routine use of PET/CT in all newly diagnosed patients is not established and is also currently not approved for follow-up in Germany. However, the additional diagnostic information can be useful, for example, in the case of extramedullary involvement and forms of the disease with hyposecretion or asecretion, in which treatment monitoring using serological parameters cannot be ensured [39, 40]. The IMWG recommends PET/CT when the skeletal survey is negative and MRI is not available [41].

Evaluation of treatment response

There are no clearly defined procedures for follow-up and treatment evaluation so far. Relapse in the form of new lesions or enlargement of existing lesions can be detected via skeletal survey, MRI or (PET/)CT [42]. Serial whole-body low-dose CT examina-



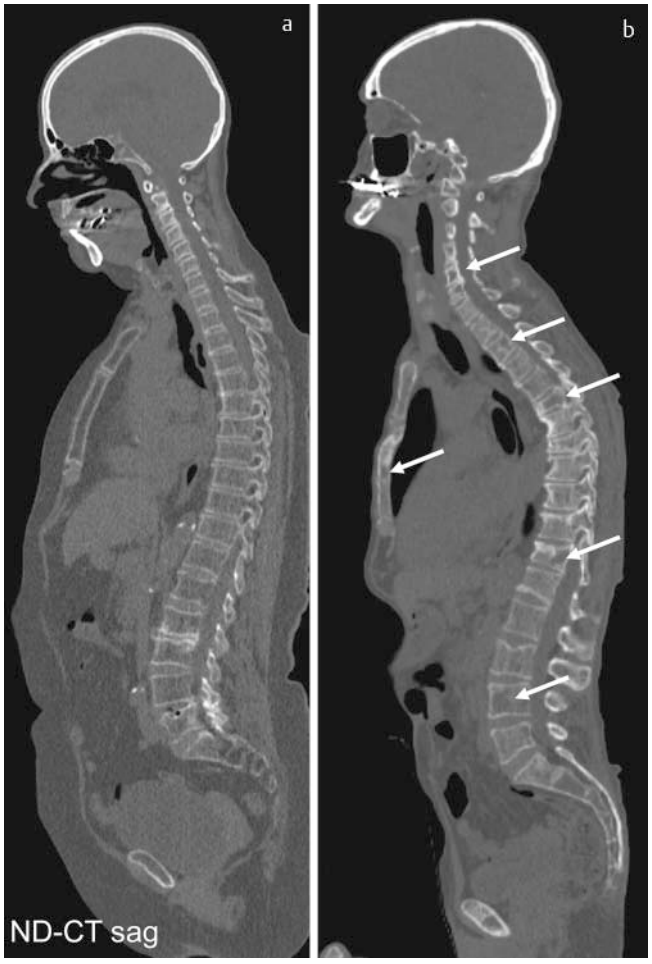
▶ **Fig. 6** Evaluation of response via diffusion-weighted MRI: Image of multiple suspicious hyperintense lesions in the pelvis on b800 image in axial view **a** with resolution after treatment **b**.



▶ **Fig. 7** Evaluation of response via PET: Maximum intensity projection of ^{18}F-FDG-PET/CT examination in sagittal reconstruction with detection of multiple lesions (arrows) prior to treatment **a**, visible treatment response 3 months after autologous stem cell transplantation and prior to maintenance therapy **b**.

tions are suitable for follow-up in the case of focal involvement [43]. When available, native whole-body MRI can be used for the evaluation of treatment response [39] even if the IMWG has been rather reserved with its recommendations to date due to a considerable quantity of false-positive findings [32]. The morphological changes in the case of response to treatment differ fundamentally from those in bone metastases of solid tumors. Therefore, osseous consolidation of an osteolytic lesion is an exception even after successful treatment. Instead a sharper border or marginal sclerosis that appears hypoechoic on MRI is seen. Initially, typically muscle-isodense contents of an osteolytic lesion will decrease measurably in HU as a result of treatment and assume water-equivalent or even fat-equivalent density values. In large osteolytic lesions, a so-called "halo phenomenon" is often seen (▶ **Fig. 5**): A retraction of the soft-tissue component of the lesion with the formation of a fat-equivalent margin between it and the newly formed sclerotic margin. MRI can either demonstrate an adjustment of the signal intensity with respect to the surrounding bone marrow or a significant increase in signal in T2w STIR/TIRM or diffusion-weighted sequences, possibly accompanied by an increase in the diffusion coefficient ADC (▶ **Fig. 2b, c**). In ambiguous cases, lesion vitality can only be clarified with the help of Gd-containing contrast agents that are otherwise not routinely used in the diagnosis of myeloma (▶ **Fig. 2d**). The use of dynamic contrast-enhanced sequences can provide additional information regarding vitality and treatment response with qualitative curve analysis and the determination and comparison of quantitative parameters [44]. Particularly in light of the current debate regarding necessity and possible risks, the use of Gd-containing MR contrast agents outside of studies must be individually discussed nun redundant. Considering this, diffusion weighted imagin renders a high potential. Signal differences between healthy and diseased bone marrow (▶ **Fig. 6a**) can further improve the sensitivity of MRI without the administration of contrast agents [44]. Signal normalization in case of treatment response can support interpretation of follow-up exams (▶ **Fig. 6b**) [39, 45, 46]. The evaluation of diffuse involvement of the medullary cavity with preserved spongiosa or in lesions in the fatty medullary cavities of the long bones is ultimately easiest. The signal intensity in T1w, STIR/TIRM and diffusion-weighted sequences normalizes in the first case and in the latter case a decrease in size or complete regression is seen. Signs of a lack of response or progression are the absence of one of the described reactions and an increase in density or size or an ill-defined margin. Quantitative ADC maps can be used to better display diffuse infiltration, and they have also contributed to a better understanding of treatment-induced changes [47].

Due to new treatment options, the response criteria were also updated by the IMWG. A stage of minimal residual disease (MRD) was added to the existing criteria based on the detection of monoclonal protein and aberrant plasma cells which are CR (complete remission), VGPR (very good partial response), PR (partial



▶ **Fig. 8** Differentiation between osteoporosis and multiple myeloma: Low-dose whole-body CT in sagittal reconstruction with **a** osteopenic bone structure in senile osteoporosis and **b** rarefaction of the bone structure with multiple osteolytic lesions presumably caused by myeloma (arrows indicate lesions of the spine and sternum).

▶ **Table 1** Checklist for interpreting CT and MRI findings in patients with multiple myeloma.

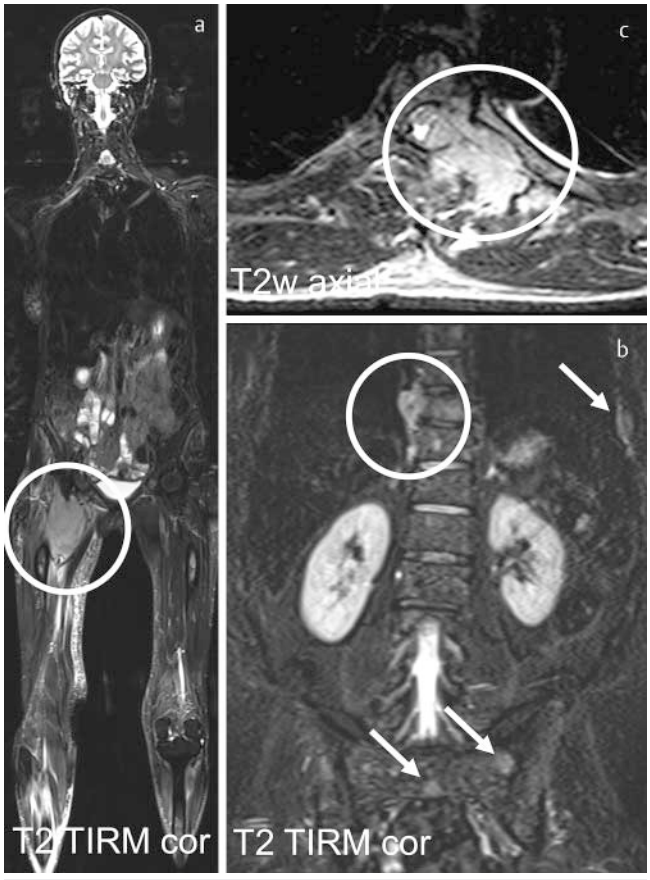
CT	MRI
evaluation of bone microstructure (▶ **Fig. 3, 5, 8**) ▪ osteolysis ▪ osteopenia ▪ (pathological) fracture check implanted foreign objects (osteosynthesis, stabilization, etc.); signs of loosening?	focal infiltration pattern (▶ **Fig. 2**) ▪ > 1 focal T1w hypointense and T2 TIRM hyperintense lesion in bone marrow ▪ Involvement of the medullary cavity of the long bones → Differentiation between myeloma requiring treatment and its precursors MGUS/SMM ▪ unifocality versus multifocality → determination whether local therapy would be useful (solitary plasmacytoma) ▪ spinal involvement (▶ **Fig. 9c**) → emergency treatment (radiation therapy) depending on symptoms
	evaluation of diffuse involvement (▶ **Fig. 4**) ▪ normal bone marrow signal ▪ salt and pepper pattern ▪ moderate involvement ▪ extensive involvement (severe)
extraosseous involvement ▪ soft-tissue lesions ▪ lymphoma	extraosseous involvement (▶ **Fig. 9a, b**) → prognostically unfavorable
stability at risk? (▶ **Fig. 5**) → orthopedic consultation if necessary	focal lesion in contact with cortical bone or suspicion of risk to stability? → CT using full-dose protocol for evaluating corresponding osteolytic lesions
morphological signs of response after treatment (▶ **Fig. 5**)	morphological signs of response after treatment (▶ **Fig. 2**)

response) and PD (progress). New technical methods like next-generation flow cytometry and next-generation sequencing are used for this purpose. Thus one category describes for example the combination of negative imaging, in this case PET/CT, with an MRD-negative finding either in flow cytometry or sequencing (imaging + MRD-negative). All lesions with initially increased tracer uptake should disappear or the measurable SUV (standardized uptake value) should be smaller than the value of the mediastinal blood pool or the surrounding tissue (▶ **Fig. 7**) [48, 49]. Based on the currently available studies, the IMWG recommends follow-up exams using ^{18}F-FDG-PET/CT because monitoring of disease activity based on the change in FDG uptake as in response assessment in lymphoma is easier than based on the morphology of the osteolytic lesions (see above) [49, 50]. Due to the health care situation in Germany, this update is currently still problematic since baseline examinations are not available in most cases but it has the potential to reform diagnostics since ^{18}F-FDG-PET/CT will play a greater role in the management of multiple myeloma in the future. To date, the information regarding MRD does not have an effect on treatment decision but it is being examined in clinical studies [4].

Borderline cases and pitfalls

Evaluation and diagnosis can be complicated in some cases. Osteoporosis with accompanying fracture is no longer disease-defining but an inhomogeneous “patchy” manifestation of osteoporosis can simulate small osteolytic lesions (▶ **Fig. 8**). Imaging often cannot assess whether osteopenia is caused by myeloma. However, soft-tissue density infiltration of normal fatty bone marrow can be detected on CT through wide-meshed trabecular structures. Differentiation, for example, between degenerative cysts and osteolytic lesions is also important. The comparison with previous imaging and the presence of a sclerotic margin in cysts can support differentiation.

Hypercellular bone marrow can resemble a manifestation of myeloma as well as physiological hematopoietic bone marrow in younger patients (< 50 years). CT can confirm infiltration of the medullary cavity and may show erosion of the inner cortical



▶ **Fig. 9** Extraosseous lesions and myeloma manifestation with cortical destruction: In the T2w-TIRM sequence in coronal view, hyperintense soft-tissue mass of the right upper leg **a** and paravertebral right **b** additional focal lesions in the pelvis and one rib (arrows). Spinal emergency situation in because of infiltration of the spinal canal and as well as affection of the spinal cord and nerve root (left thoracic) (**c**, T2w axial).

bone (scalloping) which would indicate a malignant cause. The same problem can be seen after treatment in the form of a rebound with repopulation of red bone marrow, particularly when growth factors are used. Since an indication for treatment is not based solely on imaging, the findings must be evaluated in conjunction with clinical and serological parameters. Therefore, it is helpful to acquire sufficient information regarding comorbidities (e. g. myelodysplastic syndrome, ▶ **Fig. 4e**) or treatment in all cases.

Additional, so far evaluation of lesions after treatment and the time period for healing still need to be defined more clearly. A T2 shine-through effect with a significant increase in T2 signal intensity is often seen on diffusion MRI in the case of treated lesions (see above ▶ **Fig. 2**).

▶ **Table 1** provides a checklist of the questions to be answered by the radiologist after CT or MRI examination of a patient with multiple myeloma.

Summary of the international guidelines

- Whole-body low-dose CT is recommended by the ESMO and EMN instead of conventional skeletal survey as a new standard for the initial detection of osteolytic lesions.
- According to experts, the detection of focal lesions in the case of intact mineralized bone on native whole-body MRI is decisive for treatment (indication in guidelines currently only under certain conditions, e. g. in negative CT findings, depending on availability).
- ^{18}F-FDG-PET/CT will play a greater role in the case of minimal residual disease after therapy.
- The German guidelines currently under development are highly anticipated. Since whole-body MRI and PET-CT are not routine examinations outside study centers in Germany, reimbursement must be targeted to allow routine use.

Conflict of Interest

The authors declare that they have no conflict of interest.

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