

REVIEW

International myeloma working group consensus statement and guidelines regarding the current role of imaging techniques in the diagnosis and monitoring of multiple Myeloma

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Several imaging technologies are used for the diagnosis and management of patients with multiple myeloma (MM). Conventional radiography, computed tomography (CT), magnetic resonance imaging (MRI) and nuclear medicine imaging are all used in an attempt to better clarify the extent of bone disease and soft tissue disease in MM. This review summarizes all available data in the literature and provides recommendations for the use of each of the technologies. Conventional radiography still remains the 'gold standard' of the staging procedure of newly diagnosed and relapsed myeloma patients. MRI gives information complementary to skeletal survey and is recommended in MM patients with normal conventional radiography and in all patients with an apparently solitary plasmacytoma of bone. Urgent MRI or CT (if MRI is not available) is the diagnostic procedure of choice to assess suspected cord compression. Bone scintigraphy has no place in the routine staging of myeloma, whereas sequential dual-energy X-ray absorptiometry scans are not recommended. Positron emission tomography/CT or MIBI imaging are also not recommended for routine use in the management of myeloma patients, although both techniques may be useful in selected cases that warrant clarification of previous imaging findings, but such an approach should ideally be made within the context of a clinical trial.

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Introduction

Multiple myeloma (MM) is a plasma-cell malignancy and is characterized by the presence of lytic bone disease causing severe bone pain, pathological fractures, spinal cord compression and hypercalcemia. Up to 90% of myeloma patients develop osteolytic lesions during the course of their disease.¹ These lesions occur predominantly in the axial skeleton, that is, skull, spine, rib cage and pelvis, as well as the proximal areas of

the arms and legs.² Furthermore, almost 10% of the patients present with diffuse osteopenia or osteoporosis at diagnosis.³ Myeloma bone destruction represents a major cause of morbidity and mortality. Progression of skeletal disease is often not affected by chemotherapy even in responding patients.⁴ The mechanisms of bone destruction are related to increased osteoclastic bone resorption, which is accompanied by an exhausted osteoblast function and reduced bone formation.^{5–7} Thus, a characteristic feature of myeloma bone disease is that the lesions rarely heal even when the patients are in complete remission.^{3,8} This finding is in keeping with the observation that bone scans are often negative in myeloma patients who have extensive lytic lesions, and offer very little in the follow-up of bone disease in these patients.⁹ Appropriate use of imaging techniques is essential in the identification and characterization of the skeletal complications resulting from MM and in determination of the extent of intramedullary bone disease. Imaging also is critical for detection of extramedullary foci, identification and characterization of infectious and other complications and evaluation of progression of the disease. However, we lack a consensual and standardized imaging protocol for both newly diagnosed myeloma patients or for following patients in the course of treatment and disease progression.¹⁰

Lytic lesions are generally diagnosed by radiographic analysis. One weakness of radiographic detection is that it may reveal lytic disease only when over 30% of the trabecular bone has been lost.¹¹ This results in suboptimal assessment of generalized osteopenia, which affects MM patients and correlates with an increased risk of early vertebral collapse.¹² The morbidity of vertebral collapse is significant. Chronic pain, functional limitations and respiratory compromise, which increase the risk of pulmonary infections are typical clinical sequelae of vertebral compression fractures. Due to the limitations of standard radiographic analysis, computed tomography (CT) or magnetic resonance imaging (MRI) have been used to increase the sensitivity and specificity of early detection of myeloma-associated bone destruction. CT and MRI also allow discrimination of malignant and benign compression fractures, visualization of soft tissue involvement and spinal cord and/or nerve root compression or jeopardy.

In recent years, positron emission tomography (PET) has also been used in MM imaging. 18F-fluorodeoxyglucose (FDG) is taken up by metabolically active cells, which can then be imaged using PET. High uptake by tumor cells is visible on PET

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imaging, as they have increased metabolic rates. This review summarizes all available data for the role of imaging in MM and aims to provide practical information for the usage of these techniques by clinicians who manage myeloma patients.

Conventional radiology

Since 1903, when Weber first observed that myeloma lesions are evident on radiographs, X-rays have been extensively used to identify myeloma-related bone lesions both at diagnosis and during disease course. Lytic lesions on plain X-rays are typically holes – that is, punched-out lesions with absent reactive sclerosis of the surrounding bone – in the flat bones of the skull and pelvis.¹³ In the long bones, there is a range of appearances from endosteal scalloping, to discrete small (<1 cm) lytic lesions, to mottled areas of multiple small lesions, to large destructive lesions.¹⁴ These lesions correspond to nodular replacement of marrow by plasma cells with entire bone destruction.¹⁵ Conventional radiography may also reveal diffuse osteoporosis, which is best recognized in the spine.¹⁶

The presence of lytic lesions is a criterion for myeloma diagnosis, whereas the extent of lytic disease is included in Durie–Salmon staging system.¹⁷ Therefore, it is important to include in a ‘complete skeletal survey’ all areas of possible myeloma involvement, such as the cervical, thoracic and lumbar spine, skull, chest, pelvis, humeri and femora. Almost 80% of patients with myeloma will have radiological evidence of skeletal involvement on the skeletal survey, most commonly affecting the following sites: vertebrae in 65% of patients, ribs in 45%, skull in 40%, shoulders in 40%, pelvis in 30% and long bones in 25%. However, radiologically detectable lesions distal to the elbows and knees are exceptional.¹⁸ Patients who are asymptomatic but have radiological evidence of bone disease (at least one lytic lesion) are at high risk of progression with a median time to progression of 8 months.^{19,20} The importance of the presence of lytic lesions is further supported by the notion that in the International Myeloma Working Group Classification for plasma cell dyscrasias, patients with bone disease are classified as ‘symptomatic’ and require treatment even in the absence of clinical symptoms.²¹

However, even with complete radiographic surveys 10–20% of the patients have normal results.¹⁸ This may be due to some important disadvantages of conventional radiology, as suggested in Table 1. In plain X-rays some areas are not well visualized; for this reason both lateral and anteroposterior views of the spine are needed for the better visualization of the vertebral bodies. Furthermore, conventional X-rays have limited sensitivity as they cannot detect early lytic lesions and limited specificity as they fail to distinguish myeloma-related osteoporosis from osteoporosis due to other reasons, such as steroid-induced or postmenopausal osteoporosis.¹⁸ The observer and technology dependence of conventional X-rays have also the risk of underdiagnosis of lytic disease. It has also reported that the

reproducibility of the results is very low between different centers and in a recent study an expert radiological review of skeletal surveys was able to detect additional abnormalities in 23% of the studied cases.²² A major disadvantage of conventional X-rays is that almost 20 separate films/exposures are needed, requiring a lengthy period on the radiographic table. The patient’s ability to tolerate the standard bone survey is an important issue because myeloma patients can experience severe pain when they are rotated and positioned for multiple individual radiographic exposures. To override this problem, some centers have introduced a whole-body conventional radiographic skeletal survey, the low-dose whole-body radiographic system (Statscan) for the detection of focal metastatic deposits in cancer and myeloma patients, which can give a high quality imaging of the bones in less than 5 min.²³ In a study of 30 patients with solid tumors metastatic to the skeleton and MM, the whole-body radiography was found as effective as CT or MRI in revealing focal lesions,²³ a result that has not yet been confirmed by others.¹⁰ Furthermore, plain X-rays cannot be used for the assessment of response to therapy as the lytic bone lesions seldom show evidence of healing,⁸ whereas new compression vertebral fractures do not always indicate disease progression and may occur due to ongoing bone loss or reduction of tumor mass that supports the bony cortex.²⁴ For all these reasons, although conventional X-rays are considered as a ‘gold standard’ for the determination of the extent of myeloma bone disease at diagnosis, further imaging is needed during follow-up mainly in the absence of the detection of lytic lesions or the presence of diffuse osteoporosis only.

Computed tomography

CT scanning allows the detection of small osteolytic lesions in MM, which are not revealed by plain radiography. CT imaging is much faster than standard radiographic procedures and allows excellent 3D reconstruction of images. In a few institutions, CT scanning has replaced conventional radiography as the initial imaging tool used in patients with trauma to the spine²⁵ or pelvis.²⁶ Furthermore, CT can accurately depict the extent of associated soft tissue masses and can direct needle biopsy for histological diagnosis.²⁷ The advantages of CT vs conventional X-rays: (1) the duration of the examination is practically three times less than that necessary to perform standard radiography; therefore, there is significant economy in the work time of technicians; (2) CT scanning allows the complete diagnostic evaluation in a single examination without having to reposition the patients, a procedure that is necessary in conventional studies; this is certainly an important point to consider when examining a patient in pain; (3) the diagnostic sensitivity of CT imaging is superior to that of standard radiography and reveals more lesions as compared with conventional radiology, mainly in areas that cannot be accurately visualized by plain radiography, for example, scapulae, rib or sternum;^{28,29} (4) CT has proven to be superior in estimating fracture risk and instability;^{30,31} (5) CT scanning can demonstrate other unsuspected pathological processes, especially those involving the lungs, although the percentage is not significant;³² (6) it is superior in planning the radiation therapy or the surgical intervention as it depicts the anatomic area very accurately (Table 2). Furthermore, a novel CT technique, the multidetector row computed tomography (MDCT) was found to be very sensitive in detecting small osteolytic lesions (<5 mm) in the spine, as compared with MRI and PET.³³

Table 1 Conventional radiology: limitations

- Some areas not well visualized
- Limited sensitivity: 10–20% of lesions/abnormalities missed
- Reduced specificity vs benign causes of osteopenia (e.g., steroids/postmenopausal)
- Observer dependent
- Time/tolerance for standard survey not ideal
- Usual fail to show response to treatment

Table 2 Advantages of computed tomography (CT)

- Detects small osteolytic lesions
- Faster than standard radiographic survey
- Provides 3D reconstruction of images
- Shows associated soft tissue disease
- Greater sensitivity and specificity versus standard radiography
- Allows estimation of fracture risk
- Excellent for radiotherapy planning and for surgical intervention

One of the negative points advanced against CT scanning is the radiation dose delivered to patients. The amount of radiation is 1.3–3 times higher than that delivered during standard radiography.^{31,34} In summary, conventional or low-dose CT scanning of the spine is considered to be a realistic alternative to standard radiography in MM patients presenting with painful symptoms because it allows for obtaining an exhaustive evaluation of the skeletal lesions in a short period. Furthermore, CT is helpful as a basis for radiation therapy planning, for the preparation for surgical intervention to delineate the anatomic architecture as precisely as possible and for a CT-guided needle biopsy. Finally, CT may identify lesions that are negative on plain radiography, and should be considered in patients who remain symptomatic despite having no evidence of osteolysis on the skeletal survey.

Magnetic resonance imaging

MRI has been widely available for the evaluation of MM during the last two decades and is used by several myeloma centers of excellence for the management of myeloma patients. MRI allows visualization of the medullary cavity and a direct assessment of the degree of MM cell infiltration before bone destruction becomes visible on plain radiographs, in the absence of radiation exposure.^{35,36} Furthermore, in the event of suspected cord compression, MRI is the technique of choice.³⁷ It provides an accurate assessment of the level and extent of cord or nerve root compression, the size of the tumor mass and the degree to which it has extended into the epidural space. MRI can also be used to predict the risk for vertebral fracture. Patients with advanced myeloma who had more than 10 lesions on spinal MRI had a 6- to 10-fold higher risk of fracture than patients who had normal appearance or fewer than 10 lesions on MRI.³⁸ However, MRI does not predict the risk of fracture by level.³⁹

MRI can assist in the distinction between benign from malignant compression fractures. A benign osteoporotic fracture is suggested when a retropulsed bone fragment is seen, when fat signal is preserved on T1-weighted images throughout the body and there is no high signal on T2-weighted images, when there is only a thin (<1 cm) surrounding soft tissue component and when horizontal band-like areas representing the fracture plane are seen following gadolinium administration. A malignant etiology of collapse is suggested when the posterior cortex is convex toward the spinal canal, epidural mass is seen, when the entire vertebral body or pedicles are replaced by low signal on T1-weighted images, and high or heterogeneous signal is seen within the body following gadolinium injection or on T2-weighted images.¹⁰ MRI can be also used for the accurate illustration of the vertebral fractures or the percentage loss of vertebral height before the performance of percutaneous vertebroplasty and kyphoplasty.^{40,41}

MR imaging is the most sensitive and specific imaging modality for the diagnosis of avascular necrosis of the femoral

Table 3 Role of magnetic resonance imaging (MRI)

- More sensitive than standard radiography
- Excellent imaging of axial skeleton
- Discriminates myeloma vs normal marrow
- Excellent diagnostic discrimination for spinal cord/nerve compression issues, as well as soft tissue disease
- Can detect avascular necrosis of the femoral head
- Can detect amyloid/light chain deposits in the heart and other sites
- Can be used to assess disease status in monoclonal gammopathy of undetermined significance (MGUS), asymptomatic myeloma and for solitary plasmacytoma of bone
- Can be used to monitor response (although improvements can be delayed)

head that may result from high-dose steroid therapy or radiotherapy, and is demonstrated by the presence of the characteristic double-line sign on T2-weighted MR images.⁴² Early recognition of avascular necrosis before the development of a subchondral fracture is extremely important for the success of conservative management.

In general, the advantages of MRI over conventional radiography and CT scan include: (1) the excellent imaging of the axial skeleton due to the greater sensitivity of the method, (2) the discrimination of myeloma from normal marrow, (3) the accurate illustration of spinal cord and/or nerve root compression, soft tissue extension, head and neck plasmacytomas, avascular necrosis of the femoral head and (4) better evaluation of cardiac amyloidosis and/or soft tissue amyloid deposits (see Table 3).

MRI sequences in myeloma

Several MRI techniques have been developed to aid in the assessment of the bone marrow in hematological malignancies.⁴³ The MRI sequences that are most informative are the T1-weighted, the T2-weighted with fat suppression, the short time inversion recovery (STIR) and the gadolinium T1-weighted with fat suppression. Typical myeloma lesions have a low signal intensity on T1-weighted images and a high signal intensity on T2-weighted and STIR images⁴⁴ and generally show enhancement on gadolinium enhanced images. In a recent study, three MRI sequences were evaluated to reveal the method which provides the highest confidence level in depicting the MM lesions.⁴⁵ The authors compared a precontrast T1w-TSE sequence (TR: 700 ms, TE: 10 ms), a T2w-TIRM sequence (TR: 8000 ms, TE: 80 ms) and a contrast-enhanced T1w-TSE sequence with fat saturation (TR: 700 ms, TE: 10 ms). The turbo inversion recovery magnitude (TIRM) sequence is a turbo spin-echo sequence (TSE) with an inversion recovery pulse (IR) in combination with the calculation of the magnitude signal intensity (M). Studying 59 MRI examinations of 23 consecutive patients, the authors found that the T2w-TIRM sequences achieved the highest level of sensitivity and best reliability. However, they suggest that for an exact staging and grading the examination protocol should encompass unenhanced and enhanced T1w-MRI sequences, in addition to T2w-TIRM.⁴⁵

MRI patterns in myeloma

Five MR imaging patterns of marrow involvement in myeloma have been recognized: (1) normal appearance of bone marrow despite minor microscopic plasma cell infiltration, (2) focal involvement, (3) homogeneous diffuse infiltration, (4) combined

diffuse and focal infiltration, (5) 'salt-and-pepper'-pattern with inhomogeneous bone marrow with interposition of fat islands.^{35,46} In almost 30% of MM patients a normal-looking bone marrow signal is found in all sequences with high signal on T1-weighted and intermediate signal intensity on T2-weighted spin-echo images as well as low signal in fat-saturated sequences, such as STIR.³⁵ More specifically, a normal marrow appearance is present at diagnosis in 50–75% of untreated Durie–Salmon stage I myeloma and in 20% of untreated Durie–Salmon stage III disease.^{47,48} In histology, this corresponds to a slight interstitial plasma cell infiltration (<20 vol% in bone marrow biopsy).

The focal pattern consists of localized areas of abnormal marrow and is found in approximately 30% of myeloma cases. On T1-weighted images, focal lesions are darker than yellow marrow and slightly darker or isointense to red marrow. On T2-weighted images they are brighter than both red and yellow marrow, and on enhanced T1-weighted images they enhance to various degrees depending on the vascularity of the underlying myeloma. STIR and fat-saturation T2-weighted images provide contrast between focal lesions and uninvolved marrow.^{35,47}

In the diffuse MR pattern of abnormal marrow, the normal bone marrow is completely replaced by the abnormal process. The intervertebral discs appear brighter or isointense to the diseased marrow. On T1-weighted images, there is a diffuse decrease in the signal intensity of the marrow. On T2-weighted images, a variable increase in the signal intensity of the abnormal marrow is observed. After the administration of intravenous contrast, the abnormal marrow enhances. The intervertebral discs appear darker than the enhanced spine.^{35,47}

A combined focal and diffuse infiltration pattern can be found in about 10% of myeloma patients. On T1-weighted SE images the bone marrow signal intensity is diffusely decreased with additional foci interspersed. Those foci are often better demarcated on fat-saturated or gradient-echo images.

Finally in about 3–5% of the patients the so-called 'salt-and-pepper'-pattern can be found. On T1-weighted SE images, and also on gradient-echo and T2-weighted SE sequences, the bone marrow presents a very inhomogeneous patchy pattern. However, no hyperintense areas are demarcated in fat-saturated sequences. This imaging corresponds to bone marrow with circumscribed fat islands beside normal bone marrow with a minor infiltration of plasma cells (<20%).^{35,47}

Low tumor burden is usually associated with a normal MRI pattern, but a high tumor burden is usually suspected when there is diffuse hypointense change on T1-weighted images, diffuse hyperintensity on T2-weighted images and enhancement with gadolinium injection. In general, patients with normal or 'salt-and-pepper' MRI pattern tend to have signs of lower tumor burden than those with diffuse or focal marrow involvement patterns.^{47–49} Furthermore, a significant correlation between diffuse and focal MRI patterns of marrow involvement with low serum hemoglobin values and high percentage of marrow plasmacytosis has been reported, supporting that diffuse or focal marrow involvement patterns correlate with high tumor burden.⁴⁷

The main methodological consideration with MRI imaging is the lack of specificity of the findings. Focal or diffuse changes may exist at diagnosis, may be variations of the normal, or reflect an alternative pathological or physiological process such as iron loading,⁵⁰ amyloid deposition⁵¹ or reactive marrow hyperplasia.

MRI vs conventional radiography and CT

MRI is more sensitive than conventional radiography in detecting lytic lesions in the skeleton. Ludwig *et al* showed that

41 foci with abnormal signal intensity were detected by MRI in 192 thoracic and lumbar vertebrae from 18 myeloma patients, compared to X-ray films that showed osteolytic lesions in 4 vertebral bodies and bone scanning, which was positive in 2 cases only.⁵² Ghanem *et al* reported that the whole-body MRI detected bone marrow infiltration in 20% of myeloma patients (10/54) who had negative skeletal X-rays. Furthermore, MRI revealed bone involvement more extensively than conventional radiography in 90% (27/30) of patients with concordant positive imaging findings.⁵³ MRI was found to be superior to radiographs for the detection of osteolytic lesions in the pelvis (75% vs 46% of patients) and the spine (76% vs 42% of patients),⁵⁴ especially in the lumbar spine.⁵⁵ A recent study in 41 newly diagnosed MM showed that whole-body MRI is also superior to whole-body MDCT, a very sensitive CT methodology, in detecting bone lesions in the skeleton.⁵⁶ In the largest series of patients published to date, Walker *et al* compared MRI and conventional radiography in 611 patients who were treated uniformly with a tandem autologous transplantation. MRI and conventional radiography detected focal lesions in 74 and 56% of imaged anatomic sites, respectively. Furthermore, 52% of 267 patients with normal skeletal survey had focal lesions on MRI. More specifically, significantly higher proportions of patients had focal lesions on MRI than on conventional radiography in spine (78 vs 16%; $P < 0.001$), pelvis (64 vs 28%; $P < 0.001$) and sternum (24 vs 3%; $P < 0.001$); similar percentages were noted with both techniques in skull and shoulders, and lower fractions were seen on MRI than on conventional radiography in ribs (10 vs 43%; $P < 0.001$) and long bones (that is, humeri and femora; 37 vs 48%; $P = 0.006$).⁵⁷

MRI findings in MGUS

Monoclonal gammopathy of undetermined significance (MGUS) is defined by a monoclonal immunoglobulin concentration in serum of 3 g/100 ml or less, the absence of lytic bone lesions, anemia, hypercalcemia and renal insufficiency related to the proliferation of monoclonal plasma cells, and a proportion of plasma cells in the bone marrow of 10% or less. In large referral centers, half the patients with a monoclonal gammopathy have MGUS, whereas only 15% to 20% have MM.⁵⁸ Although, lytic lesions are not found in MGUS by definition, osteoporosis is a common finding among MGUS patients who have a higher incidence of vertebral fractures compared to normal population.⁵⁹ Therefore, sometimes it is difficult to differentiate MGUS from early myeloma. MRI studies have been performed in patients with MGUS. Bellaiche *et al* found that the MRI of the thoracolumbar spine was normal in all tested patients with MGUS ($n = 24$) compared with only 6 out of 44 (13.6%) with newly diagnosed MM.⁶⁰ In another study, bone marrow abnormalities were detected with MRI imaging in 7 out of 37 patients (19%) with MGUS or monoclonal gammopathy of borderline significance (all MGUS criteria but plasma cell infiltration of between 10 and 30%). All patients with a normal MRI investigation had not required treatment after a median follow-up of 30 months, whereas time to progression to MM was significantly higher for patients with abnormal MRI.⁶¹

MRI and solitary plasmacytoma of the bone

Approximately 2% of patients with plasma cell dyscrasias have solitary bone plasmacytoma (SBP). The diagnosis of SBP requires a solitary bone lesion, a biopsy of which shows infiltration by plasma cells, negative results on a skeletal survey, absence of clonal plasma cells in a random sample of bone marrow and no

evidence of anemia, hypercalcemia or renal involvement suggesting systemic myeloma. Although definitive radiotherapy usually eradicates the local disease, the majority of patients will develop MM because of the growth of previously occult lesions which have not been detected by conventional radiography.⁶² MRI imaging is the preferred imaging modality for the initial assessment and for the follow-up of the osseous and extraosseous extent of an SBP. Mouloupoulos *et al* showed that MRI of the thoracic and lumbosacral spine showed additional foci of marrow replacement in four of 12 patients with SBP; thus some patients who have an SBP diagnosed by standard criteria may be understaged if an MRI is not performed. After treatment with definitive radiotherapy to the painful lesion, three patients developed systemic disease within 18 months from diagnosis.⁶³ Furthermore, Liebross *et al* reported that among SBP patients with thoracolumbar spine disease, seven of eight staged with plain radiographs alone developed MM in comparison with only one of seven patients who also had MRI studies of the spine.⁶⁴ These results suggest that MRI should be part of the staging procedures in patients with SBP, to better assess both the extent of the local tumor and the revealing of occult lesions elsewhere. Coronal images of the central skeleton may increase the incidence of unsuspected lesions.

MRI in smoldering multiple myeloma

Asymptomatic patients with paraprotein level in the serum of ≥ 30 g/l and/or bone marrow clonal plasma cells of $\geq 10\%$, and no myeloma-related organ or tissue impairment, are considered to have smoldering multiple myeloma (SMM), according to the International Myeloma Working Group.²¹ These patients account for about 15–20% of myeloma patients, and have a median time to disease progression of 2–3 years. According to current practice, patients with SMM may remain stable for years without therapy and thus should be followed without treatment until there is evidence of imminent disease progression.^{65,66} Asymptomatic patients with at least one lytic lesion in conventional X-rays have a median time to progression of 10 months; therefore, they should be treated at diagnosis.⁶⁷ MRI reveals abnormal marrow appearance in 30–50% of the patients.^{35,47} Mouloupoulos *et al* reported that patients with abnormal MRI studies required therapy after a median of 16 months vs 43 months for those with normal MRI studies ($P < 0.01$).⁶⁸ Moreover, Mariette *et al* showed that during a median follow-up of 25 months, 10 out of 53 SMM patients developed disease progression; of those, 8 out of 17 had abnormal MRI and 2 out of 38 patients had normal MRI. In that study, abnormal MRI independently predicted for time to progression.⁶⁹ This result has not been confirmed by other studies. However, MRI may be particularly useful in patients with asymptomatic myeloma who have an intermediate risk for disease progression.⁷⁰

MRI and assessment of response

MRI can be used to assess the effects of antimyeloma therapy, although the response rates to conventional chemotherapy are similar among patients with different MRI patterns⁴⁶ and the time to complete response (CR) is similar among patients with different number of focal lesions on MRI (>7 vs ≤ 7).⁵⁷ A change in MRI pattern may correlate with response to therapy. Mouloupoulos *et al* reported that CR is characterized by complete resolution of the preceding marrow abnormality, and partial response is demonstrated by conversion of a diffuse to a variegated or focal pattern.⁷¹ Features suggestive of an objective

response to treatment include a reduction in signal intensity on T2-weighted spin-echo images and the absence of contrast-induced rim-enhancement that was previously present.³⁵ Focal lesions may shrink or remain unchanged in size after effective antimyeloma therapy⁷² or they may remain hyperintense in both responders and nonresponders to treatment due to treatment-induced necrosis and inflammation.⁷³ Therefore, post-antimyeloma therapy MRI of the bone marrow may provide important information for patients with equivocal clinical and laboratory results as well as for patients with nonsecretory myeloma. In a study by the Arkansas group, focal lesions were present on MRI in 27 of 30 patients with nonsecretory MM. After treatment, bone marrow-defined CR occurred in 22 (81%) of these 27 patients, and MRI-CR was documented in 41% of patients at 36 months.⁵⁷

Autologous stem cell transplantation (ASCT) is considered the treatment of choice for younger myeloma patients. Lecouvet *et al* developed an index for the assessment of changes occurring in the spine after transplant.⁷⁴ The index numerically combines findings related to the number of lesions, lesion size, contrast enhancement and marrow background. A score of 0, 1 or 2 is given for each parameter depending on whether there is improvement, stability or worsening. Patients with an index below 4 had a better treatment response than those with an index of 4 or more. In this point, it is crucial to mention that MRI evaluation post-ASCT has to be performed at least 1 month after G-CSF administration. There can be diffuse or focal marrow changes after treatment with G-CSF that cannot be easily distinguished by active disease.⁷⁵

MRI findings and prognosis in symptomatic myeloma

The prognostic value of MRI findings in symptomatic myeloma has been evaluated in different studies. Patients with a single lytic lesion on plain radiography, who are found to have further lesions on MRI have a shorter time to progression and shorter time to starting therapy compared to those with a normal MRI study.^{20,68,70,76} Patients with advanced disease who have normal MR findings and receive conventional dose chemotherapy have a longer survival compared to those with diffuse or focal abnormalities on MR imaging.⁷⁷ The pattern of MR bone marrow involvement in myeloma also has prognostic significance, with both focal and diffuse patterns being associated with a higher tumor burden.^{47–49,77} In 142 symptomatic myeloma patients, Mouloupoulos *et al* showed that the median survival was 24 months for patients with the diffuse pattern, 51 months for those with the focal pattern, 52 months for those with the variegated pattern and 56 months for patients with the normal pattern ($P = 0.001$). The presence or absence of a diffuse MRI pattern separated patients with ISS stages I and II into two subgroups with significantly different survival times of 28 months and 61 months, respectively ($P = 0.01$). Furthermore, a diffuse MRI pattern predicted inferior outcome regardless of whether or not patients had received high-dose therapy with ASCT.⁴⁶

The largest study in the literature, which reported on the prognostic value of MRI in myeloma patients was published by the Arkansas group. In 611 myeloma patients who were treated uniformly with a tandem autologous transplantation-based protocol, MRI, but not conventional radiography, defined that focal lesions independently affected survival. In particular, cytogenetic abnormalities and more than seven focal lesions on MRI distinguished three risk groups: 5-year survival was 76% in the absence of both more than seven focal lesions on MRI and cytogenetic abnormality ($n = 276$), 61% in the presence of one

of these adverse features ($n=262$) and 37% in the presence of both unfavorable parameters ($n=67$). High number of MRI focal lesions (>7) correlated with low albumin and elevated levels of C-reactive protein, lactate dehydrogenase and creatinine, but did not correlate with age, β 2-microglobulin and cytogenetic abnormalities. Resolution of the focal lesions on MRI post-antimyeloma therapy that occurred in 60% of the patients identified a subgroup with superior survival. Furthermore, at disease progression after CR, according to clinical criteria, MRI focal lesions were present in 70% of the patients, including 26% with new focal lesions outside of the areas of initial involvement, 28% focal lesions that were larger than the original lesions and 15% with both an increase in original size and new MRI focal lesions.⁵⁷

Nuclear medicine imaging

Traditional technetium bone scintigraphy has high sensitivity for the detection of solid tumors metastatic to the skeleton but its sensitivity in MM and solitary plasmacytoma is very low. Technetium bone scintigraphy scanning may detect lytic lesions in 35–60% of MM patients, but its specificity and sensitivity at the time of the initial diagnosis, in follow-up studies and in the evaluation of bone pain is lower compared to conventional radiography.^{78–80} In myeloma patients, the skull, the extremities, the iliac and pubic bones are better assessed with plain radiography, whereas for new vertebral lesions and for lesions in the ribs and sternum, bone scintigraphy seems to be superior and for sacrum both methods are equal.⁸¹ The inferiority of bone scans vs conventional radiography is primarily due to the osteoblast dysfunction in myeloma,^{1,6,7} as skeletal uptake of ^{99m}Tc-diphosphonate is related mainly to osteoblastic process. Therefore, newer techniques have been developed in an effort to improve the sensitivity of detection of myeloma bone disease.

^{99m}Tc-sestamibi

^{99m}Tc-labeled hexakis-2-methoxyisobutylisonitrile (^{99m}Tc-sestamibi) is a lipophilic cationic γ -emitting radiopharmaceutical originally introduced as a myocardial perfusion imaging tracer. Because of its biochemical characteristics, which favor accumulation in tissues with high cell density and mitochondrial activation, ^{99m}Tc-sestamibi (MIBI) is actively concentrated in a variety of malignant tumors such as sarcomas, breast, brain, lung and thyroid cancers.⁸² MIBI imaging closely reflects myeloma disease activity in bone marrow with very high sensitivity and specificity.^{83,84} Additionally, bone marrow MIBI uptake is linearly related to bone marrow biopsy results and MIBI was reported to be localized inside the plasma cells infiltrating the bone marrow.^{85–87}

In MGUS patients, MIBI is always negative^{83,88,89} and it cannot be used to predict MGUS transformation; thus it is not useful in MGUS work-up.⁸⁸ MIBI imaging can detect soft and skeletal lesions in MM patients and is more sensitive than conventional radiography.⁹⁰ Its overall sensitivity is approximately 92% and its specificity is 96%.⁸⁹ However, MIBI imaging has inferior value compared to FDG-PET/CT,⁹¹ and found to underestimate the extent of myelomatous bone marrow infiltration in the spine, especially in patients with low disease stage, compared to MRI.⁹² The pattern of MIBI uptake is significantly different in MM patients. Focal uptake reflects active myeloma sites, whereas diffuse uptake without the presence of focal uptake does not indicate active myeloma.⁹³ MIBI score was significantly related to ISS, bone marrow biopsy infiltration rate

and serum β 2-microglobulin.^{88,94} Furthermore, MIBI washout may predict for response to conventional or high-dose chemotherapy.^{95,96} MIBI scan added no relevant prognostic information to the ISS in patients with stages I and III MM, but the MIBI scan was of prognostic value in stage II MM patients.⁸⁸ MIBI scan cannot detect the necrotic lesions of osteonecrosis of the jaw in myeloma patients.⁹⁷

Positron emission tomography

PET is a tomographic nuclear imaging procedure that uses positrons as radiolabels and positron–electron annihilation reaction γ -rays to locate the radiolabels. A low dose of a radiopharmaceutical labeled with a positron emitter, such as 18-fluorine-fluoro-deoxyglucose (FDG), is injected into the patient, who is scanned by a tomographic system. The main limitation of PET scanning is limited spatial resolution; thus subcentimeter lytic lesions seen on plain radiographs may not be detectable on PET scanning.⁹⁸ The advent of fusion scanning combining both PET and CT addresses the issue of limited spatial resolution. In PET/CT fusion scanning, the patient receives an injection of FDG about 1 h before image acquisition. After the patient is positioned on the scanner bed, an initial topogram is acquired to define the examination range for the PET/CT image acquisition (usually from the ears to the hips). A spiral CT is then performed after which the scanner bed is moved back to the starting position and the PET scan commenced. Reconstruction of the image, incorporating PET and CT data are completed soon after PET image acquisition. The actual scanning time is shorter for PET/CT (approximately 30 min) than a PET scan alone (approximately 1 h) because CT data are used to perform attenuation correction.⁹⁹

Several studies have shown PET/CT is reliable for most bone lesions that are at least 1 cm in diameter using a standard SUV cutoff of 2.5 to indicate the presence of disease.¹⁰⁰ For lesions smaller than 5 mm in diameter, it has been suggested that any amount of FDG uptake should be considered positive regardless of SUV. Lesions between 5 and 10 mm are considered indeterminate if the SUV is less than 2.5. The patient's weight and body mass are additional factors that affect the SUV.¹⁰¹ The sensitivity of FDG PET in detecting myelomatous involvement is approximately 85% and its specificity is 92%.⁹⁸ The first assessment FDG PET in myeloma, a study of 66 patients followed serially, showed that FDG PET allows identification of high-risk myeloma and can be used to monitor nonsecretory myeloma as well as patients in CR without measurable M-component.¹⁰² This led to the inclusion of myeloma into larger studies of PET/CT in the United States.^{103,104} The National Oncologic PET Registry (NOPR), a large prospective program, enrolled 22 975 cancer patients in the first year and revealed that 36.5% of the time treating physicians changed the intended management of the basis of PET/CT results. The registry has thus far included over 1300 myeloma patients. PET/CT has been included as an option in the diagnosis and monitoring of myeloma patients within NCCN guidelines.¹⁰⁵ Further targeted studies in myeloma are required to further clarify aspects of the specific utility in myeloma patients. In addition to demonstrating persistent or recurrent osseous disease, PET/CT studies are more sensitive than other imaging modalities for localizing extramedullary sites of disease, where they reveal additional lesions in almost 30% of the patients who had been diagnosed with solitary plasmacytoma by MRI.^{10,106,107} In two recent studies in patients with SBP, PET/CT allowed detection of other unsuspected sites of bone involvement, upstaging the extent of

the disease and significantly affect the therapeutic decisions.^{108,109}

In a prospective comparison among 18F-FDG PET/CT, MRI and conventional radiography (whole-body X-rays) in 46 newly diagnosed myeloma patients, PET/CT was superior to plain radiographs in 46% of patients, including 19% with negative X-rays. However, in 30% of patients, PET/CT scans of the spine and pelvis failed to show abnormal findings in areas in which MRI revealed an abnormal pattern of bone marrow involvement, more frequently of diffuse type. In contrast, in 35% of patients, PET/CT enabled the detection of myelomatous lesions in areas which were out of the field of view of MRI. By combining MRI of the spine/pelvis and PET/CT the ability to detect sites of active MM, both medullary and extramedullary, was as high as 92%. Following ASCT, 15 out of 23 patients had negative PET/CT scans (including 13 with a very good partial response or at least a near CR), but only 8 had normal MRI.¹¹⁰

There are several small studies supporting that either 18F-FDG PET/CT was comparable to MRI in the detection of focal lesions in the spine and pelvis, but it was superior for an accurate whole-body evaluation,¹¹¹ or MRI is superior to FDG-PET in detecting bone marrow involvement in the spine of patients with advanced MM.¹¹² In summary, although all reported studies have confirmed the superiority of PET/CT over conventional radiography, they have also revealed that if PET/CT was the sole imaging study done, it would miss many additional small lytic skeletal lesions and could miss diffuse spine involvement compared to MRI.^{113,114} Another disadvantage of PET/CT is the false-positive results it has especially in areas of inflammation or infection, deposits of brown fat (especially in the mediastinum and neck), postsurgical changes, vertebroplasty changes and occasionally other benign or malignant processes, such as renal, pancreatic, uterine and prostate cancer.^{115–117}

FDG PET/CT was found more sensitive than MRI for making the diagnosis of mandibular osteonecrosis,^{97,118} although it is not an accurate method for the detection of femoral head osteonecrosis.¹¹⁹ To override these problems, novel radiolabeled agents have also been used in PET/CT. The use of the radiolabeled amino-acid carbon 11 (¹¹C) methionine with PET/CT showed ¹¹C-methionine-positive lesions in normal cancellous bone in the majority of 19 MM patients, and in all patients with extramedullary diseases.¹²⁰

In general, MIBI and PET/CT are useful additional diagnostic tools for detecting otherwise occult sites of myeloma. A recent large study of NOPR on the relative impact of PET on patients with 18 different types of known cancers for three distinct indications (initial staging, restaging and detection of suspected recurrence) revealed that when intended management was classified as treatment or nontreatment, physicians changed their intended management for almost 49% of myeloma cases.¹²¹ This result depicts the change of management of MM patients with the broad use of PET in myeloma. However, further studies are needed before the recommendation of using PET as a standard tool in both diagnosis and follow-up of MM patients. Finally, the use of MIBI PET should particularly be considered in the evaluation of a patient with an early-stage MM to exclude the presence of more extensive disease.⁹

Dual-energy X-ray absorptiometry

Osteoporosis in the general population is currently diagnosed using dual-energy X-ray absorptiometry (DEXA). In MM patients, reduced lumbar spine bone mineral density correlates with

increased risk for early vertebral fractures.¹² This makes DEXA a valuable test to consider, as it may also influence the decision to begin bisphosphonate treatment, which can produce a 5–10% improvement over a 6-month period.¹⁰ Another advantage of DEXA is that the technique, which involves assessment of bone mineral density (BMD) in the lumbar spine, hip and distal radius, is a quick, noninvasive investigation that uses a small dose (<1 ISV) of radiation.¹²² Disadvantages of the method includes its influence by spondylosis, spinal osteophytes¹²³ and the presence of vertebral collapse, and its difficulty to recognize myeloma osteoporosis from malignant osteoporosis. Furthermore, sequential DEXA-scans show heterogeneous local BMD changes, and cannot predict disease progression.¹²

Conclusions

Various imaging technologies have been used for the diagnosis and management of myeloma patients. As part of the staging procedure of newly diagnosed myeloma, the skeletal survey is mandatory and should include a posteroanterior view of the chest, anteroposterior and lateral views of the cervical spine (including an open mouth view), thoracic spine, lumbar spine, humeri and femora, anteroposterior and lateral views of the skull and anteroposterior view of the pelvis. In addition, symptomatic areas should also be specifically visualized. Whole-body, low-dose MDCT has substituted conventional radiography in some centers for both diagnosis and follow-up of MM patients and the clinicians have to take this method into consideration if it is available. Whole-body MRI can give complementary information to skeletal survey and is recommended in patients with normal conventional radiography. MRI of the whole spine should be performed in addition to the skeletal survey as part of staging in all patients with an apparently solitary plasmacytoma of bone irrespective of site of index lesion. Urgent MRI is the diagnostic procedure of choice to assess suspected cord compression in myeloma patients even in the absence of vertebral collapse. Urgent CT may be used to establish the presence of suspected cord compression in cases where MR imaging is unavailable, impossible due to patient intolerance or contraindicated, for example, intraorbital metallic foreign bodies or cardiac pacemakers. CT of the spine or other areas of the skeleton may be considered to clarify the presence or absence of bone destruction in cases of clinical concern. Furthermore, CT is indicated to clarify the nature and extent of soft tissue disease and, where appropriate, to guide tissue biopsy. MRI should be used to clarify the significance of ambiguous CT findings, as these two imaging techniques can give complementary information, whereas both can be used before vertebroplasty or kyphoplasty. Bone scintigraphy has no place in the routine staging of myeloma, although sequential DEXA scans are not recommended. Based on the currently available evidence, neither PET nor MIBI imaging can be recommended for routine use in the management of myeloma patients, although both techniques may be useful in selected cases that warrant clarification of previous imaging findings, but such an approach should ideally be made within the context of a clinical trial.

In the event of disease progression, the skeletal survey should be repeated as part of the restaging process. Any newly symptomatic areas of the skeleton should be specifically targeted. MRI should be performed in all patients with negative skeletal survey. MRI or CT can be used for monitoring the response of soft tissue masses to therapy. The usefulness of PET/CT and MIBI on the follow-up of myeloma has not been

confirmed and further trials are needed. Treating physicians must keep foremost in mind that myeloma bone disease is often the cause of the most disabling problems that patients face and, therefore, careful baseline and serial radiographic assessments are essential to maintaining and improving their patients' quality of life.

Conflict of interest

The authors declare no conflict of interest.

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