International myeloma working group consensus recommendations on imaging in monoclonal plasma cell disorders

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Recent advances in the treatment of multiple myeloma have increased the need for accurate diagnosis of the disease. The detection of bone and bone marrow lesions is crucial in the investigation of multiple myeloma and often dictates the decision to start treatment. Furthermore, detection of minimal residual disease is important for prognosis determination and treatment planning, and it has underscored an unmet need for sensitive imaging methods that accurately assess patient response to multiple myeloma treatment. Low-dose whole-body CT has increased sensitivity compared with conventional skeletal survey in the detection of bone disease, which can reveal information leading to changes in therapy and disease management that could prevent or delay the onset of clinically significant morbidity and mortality as a result of skeletal-related events. Given the multiple options available for the detection of bone and bone marrow lesions, ranging from conventional skeletal survey to whole-body CT, PET/CT, and MRI, the International Myeloma Working Group decided to establish guidelines on optimal use of imaging methods at different disease stages. These recommendations on imaging within and outside of clinical trials will help standardise imaging for monoclonal plasma cell disorders worldwide to allow the comparison of results and the unification of treatment approaches for multiple myeloma.

Introduction

Multiple myeloma is caused by the infiltration and proliferation of malignant monoclonal plasma cells, primarily in the bone marrow. Evidence suggests that multiple myeloma is always preceded by precursor stages of monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma.[1] Early stages of multiple myeloma are defined by the presence of monoclonal plasma cells in the bone marrow, with 10% or more monoclonal plasma cells defining the percentage for a smoldering multiple myeloma, which is less than 10%, diagnosis compared with MGUS along with the presence of monoclonal protein in serum or urine, or both.[2] Sometimes, multiple myeloma can be preceded by a solitary accumulation of clonal plasma cells either in the bone or the soft tissue (solitary plasmacytoma) without signs of systemic disease.[2]

Usually, diagnosis of a monoclonal plasma cell disorder is made on the basis of immunofixation electrophoresis of blood serum and urine samples and bone marrow biopsies.[3] The main presenting symptoms of multiple myeloma have been given the acronym CRAB: hypercalcaemia (C) and bone destruction (B), due to an overactivation of osteoclasts; renal impairment, mostly caused by monoclonal light chains affecting the kidneys (R); and anaemia (A) reflecting, among other things, malignant monoclonal plasma cell infiltration of the bone marrow and the replacement of the physiological haemopoiesis.[2] Given that 80–90% of all patients with multiple myeloma develop bone disease,[4] a thorough assessment of the degree of skeletal involvement and damage to structural integrity is of utmost importance. Furthermore, whole-body imaging techniques have revealed that multiple myeloma does not always affect mineralised bone and bone marrow in a homogeneous way. In fact, approximately 60% of patients with multiple myeloma have plasma cell accumulation and bone destruction occurring in a focal or patchy way. Only lesions detected by MRI and PET are referred to as focal lesions and are different from lytic lesions (detected with CT) where bone destruction has already taken place.[5]

Clinical use of imaging modalities to diagnose multiple myeloma is often influenced by the availability and affordability of different techniques rather than by scientific data alone. Therefore, the present guidelines, based on the available literature, aim to provide a rationale for the use of different imaging modalities at various timepoints along the continuum of plasma cell disorders, as well as to provide recommendations regarding imaging in specific clinical scenarios. These guidelines can also serve as the basis for further research questions.

General clarifications

Importantly treatment should be considered for any patient meeting the active multiple myeloma criteria,[2] even if imaging is negative. The same approach should hold true for multiple myeloma in biochemical or clinical relapse or progression. In this Review, we will use the term whole-body MRI, which should not be confused (which can arise due to insurance policies, particularly in the USA) with a cancer screening technique (eg, for

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patients with cancer of unknown primary). Specific recommendations on how to perform whole-body MRI have been published by Messiou and colleagues.[6]

Availability of imaging modalities

Low-dose whole-body CT[7] is recommended over conventional skeletal survey for the diagnosis of multiple myeloma bone disease. However, the International Myeloma Working Group (IMWG) is aware that novel imaging techniques mentioned in this Review are not available in all locations worldwide. We are also aware that in some countries, financial considerations might even preclude the use of conventional skeletal survey for patients in whom multiple myeloma is diagnosed on the basis of other myeloma-defining events. Therefore, despite shortcomings mentioned in this Review, conventional skeletal survey can be used for the diagnosis of multiple myeloma when whole-body CT or other novel imaging methods are not available.

Although whole-body MRI is the recommended imaging technique in some situations, it is not available in many institutions worldwide. MRI of the spine and pelvis is an acceptable alternative to whole-body MRI to provide sufficient bone marrow imaging. PET/CT can be used instead of whole-body CT, but is dependent on availability. However, if PET/CT is used instead of whole-body CT, the CT part of PET/CT must fulfil the criteria of a diagnostic whole-body CT.[7]

Finally, the IMWG recognised that focused imaging of symptomatic areas for multiple myeloma is needed throughout the disease course, and that the choice of the specific imaging modality is dependent on both the location of the symptoms and the area involved (eg, bone *vs* extramedullary). Recommendations on such focused imaging are beyond the scope of this Review.

Replacement of conventional skeletal survey by whole-body CT

Historically, conventional skeletal survey has been used for the assessment of multiple myeloma bone disease because of its low costs and widespread availability.[8] Therefore, conventional skeletal survey has been widely used and has formed the basis for previous management guidelines and diagnostic models.[9] However, conventional skeletal survey has prominent limitations, particularly regarding sensitivity. For example, in 1967, Edelstyn and colleagues[10] showed that 50–75% of bone loss was required before the loss of bone tissue could be detected by conventional X-ray.

Whole-body CT, either alone or in combination with PET, has been shown to provide statistically significantly superior sensitivity compared with X-ray for the detection of osteolytic lesions in patients with multiple myeloma. In a multicentre analysis, the IMWG compared conventional skeletal survey and whole-body CT scans of 212 patients with monoclonal plasma cell disorders. This analysis found that whole-body CT gave a positive diagnosis for monoclonal plasma cell disorder in 25·5% of patients who had negative conventional skeletal survey results.[11] This difference is thought to mainly be the result of superior detection in the spine and pelvis seen with CT imaging because no statistically significant difference could be determined between the sensitivity of conventional skeletal survey and whole-body CT in long bones.[11] Similar findings have been reported in a different series of 32 patients with osteolytic lesions of the spine and pelvis, osteolytic lesions were detected in 50% of participants by X-ray and in 74% of patients by low-dose whole-body CT.[12] In another study consisting of 29 patients, five (17%) patients showed osteolytic lesions in whole-body CT despite negative conventional skeletal survey.[13] Finally, in a cohort of 52 patients who were all at different monoclonal plasma cell disorder stages, 12 people (23%) were shown to be positive for osteolytic lesions following CT despite negative conventional skeletal survey. These results confirm the increased sensitivity of whole-body CT compared with X-ray.[14]

In adult long bones, nodular or diffuse manifestations of multiple myeloma infiltration can be detected by CT, which appears to have prognostic significance as well as correlation with treatment response.[15,16] With some limitations, whole-body CT even allows the detection of extraskeletal lesions. Additionally, compared with conventional skeletal survey, whole-body CT is more comfortable for the patient because whole-body CT is done in the supine position and has a short acquisition time.

Technical considerations with whole-body CT

To avoid missing osteolytic lesions in the humeri in whole-body CT, the patient's arms should not be stretched out above the head but rather bent over the head or next to the body to keep them within the field of view, and should be placed on cushions to avoid weakening of the CT beam around the thoracic and lumbar regions of the spine. In general, a low-dose multidetector whole-body CT is recommended when diagnosing monoclonal plasma cell disorders; doses as low as 3·2–4·8 mSv have been reported to be sufficient for accurate diagnosis. By comparison, radiation dose following conventional skeletal survey is usually 1·2–2·4 mSv.[13,17–19] In 2018, an expert group consisting of radiologists and haematologists analysed data on this topic to provide further recommendations.[7] In brief, recommendations for optimal imaging parameters, interpretation of different findings, and effective reporting are proposed.

Bone marrow imaging

Higher sensitivity of modern imaging techniques, such as PET/CT and whole-body MRI, provide the opportunity not only to determine bone destruction in multiple myeloma but also to assess tumour burden and disease activity in a large area, if not the whole bone marrow compartment. As mentioned, bone marrow infiltration

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in multiple myeloma is not homogeneous for most patients. Therefore, the ability to identify discrete areas of diffuse versus focal plasma cell infiltration by sensitive imaging techniques provides a novel dimension to disease burden and response assessment. To date, in most cases at initial diagnosis, genetic testing for risk assessment and definition of complete remission and minimal residual disease assessment in multiple myeloma has relied on plasma cell percentage and bone marrow specimen biology, which are taken at random from either the iliac crest or the sternum. However, these sites are not always representative of the real disease burden because the biopsy might both hit or miss a focal lesion and thereby over or underestimate the plasma cell percentage. Of note is a retrospective study by Rasche and colleagues[20] that has shown that in some but not all patients genomic findings of multiple myeloma cells from a random sample and an imaging guided biopsy of a focal lesion can be similar in some patients but different in others. In a prospective study,[21] investigators have also shown that the plasma cell percentage differs significantly between random bone marrow biopsy and imaging guided biopsy of an osteolysis. Given this heterogeneity and its potential to affect clinical care decisions, more comprehensive bone marrow imaging is highly desirable in multiple myeloma.

Comparison of PET/CT and whole-body MRI for bone marrow imaging

PET/CT and whole-body MRI provide different and complementary information on the tissue under investigation. Whole-body MRI is based on examining the water and fat composition of tissues whereas PET/CT draws on information from the metabolic activity of the cells within the investigated area that are taking up a radioactive tracer.

The most widely used PET/CT tracer is Fluorodeoxyglucose (FDG) with the radionuclide 18 fluorine (^{18}F); further PET/CT discussion within this manuscript refers to the use of ^{18}F-FDG-PET/CT. FDG is ingested by cells in accordance with their glucose metabolism and therefore with their energy consumption. Tumour cells have abnormally high glucose metabolism because, even in aerobic conditions, tumour cells tend to favour metabolism for energy production by glycolysis over the more effective phosphorylation (Warburg effect).

In whole-body MRI, contrast agents are usually based on gadolinium, which has shown to be relatively inert compared to iodine based CT contrast agents, but in the case of renal insufficiency it can lead to a severe complication, namely nephrogenic systemic fibrosis.[22] However, indications where a contrast agent is needed for whole-body MRI in patients with multiple myeloma are rare, as conventional non-enhanced whole-body MRI has a high resolution and contrast.

PET/CT is superior to MRI regarding the assessment of focal lesion viability, whereas diffuse infiltration can be better assessed by MRI because of its higher sensitivity.[23] Bone marrow hyperplasia (which can occur during recovery after chemotherapy or following the application of growth factors) can lead to false-positive results in both techniques, but this effect is more prominent with PET/CT than MRI.

Diffusion-weighted imaging is an MRI technique measuring the movement of water molecules in the tissue.[24] Other guidelines have already suggested its use in clinical practice. Therefore, we recommend that centres that are able to implement this technique in their MRI protocols should do so to acquire data to strengthen the basis for its more general use.[6] Data from studies investigating the combination of PET/MRI scanners and novel tracers are not mature, and thus are not considered suitable for inclusion within this guideline paper.[25,26]

Recommendations in different stages of the disease

MGUS

MGUS has a high incidence of 3·2% in individuals of 50 years or older and of 5·3% in people of 70 years or older.[27] According to the updated analysis of the southeastern Minnesota cohort,[28] risk factors for MGUS to active multiple myeloma progression include an M-protein of 1·5 g/dL or more and an abnormal free light chain ratio in patients with non-IgM MGUS. Patients with no risk factors had a progression rate of 7% and those with one risk factor had a progression rate of 20% within 20 years, whereas individuals with two risk factors showed a progression rate of 30% in 20 years.[28] Therefore, the IMWG decided to recommend whole-body imaging only in patients with high-risk MGUS. Because the most important symptom to be excluded in patients with monoclonal gammopathy is bone

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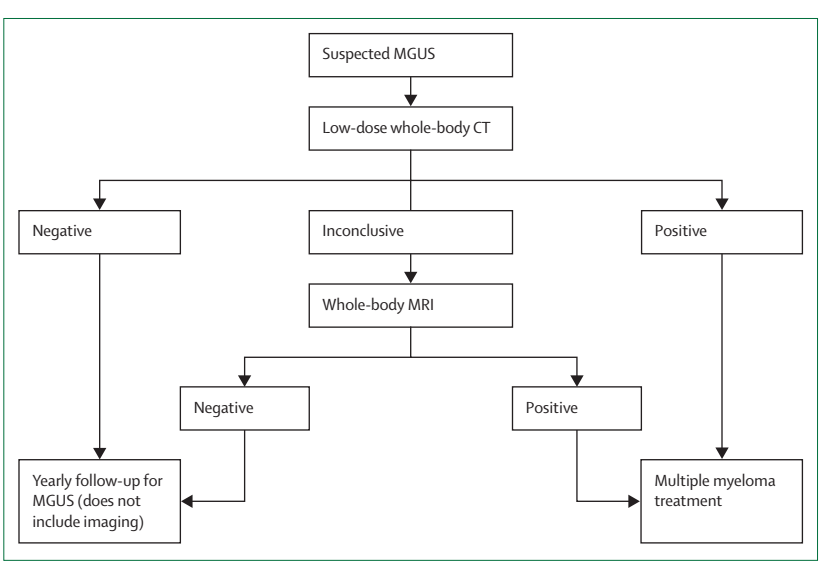

Figure 1: **Imaging algorithm for patients with non-IgM MGUS.**
MGUS=monoclonal gammopathy of undetermined significance.

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destruction and because of the benefits of whole-body CT, this is the primary imaging method we recommend (figure 1). As IgM MGUS usually develops into Waldenstrom's macroglobulinaemia but not multiple myeloma, routine bone imaging is not recommended.

MRI use in the diagnosis of MGUS has resulted in the identification of focal lesions in different reported series from 3·5% to 23·4%.[29–31] However, confirmative histological examination of the focal lesions identified were not done in any of these studies; as a result, a high probability exists for false-positive findings. Whole-body MRI can be useful in selected patients in whom multiple myeloma based on equivocal whole-body CT results is of concern. The prevalence of MGUS increases with age and distinguishing any multiple myeloma-related bone changes from a benign cause becomes very important. For example, as patients get older age-related osteoporosis is usually accompanied by a higher fat content in the bone marrow due to the replacement of the physiological haemopoiesis by fat cells, whereas osteoporosis caused by multiple myeloma is associated with a higher cellularity due to malignant infiltration. These changes can be identified with whole-body MRI, especially in cases of vertebral fractures.[32–34] Furthermore, presence or absence of bone marrow oedema allows an assessment of the age of the fracture (new *vs* old). Oligosecretory disease occurs in 3–5% of patients with multiple myeloma[4] and remains in differential diagnosis during evaluation of a patient with MGUS. Whole-body MRI can help identify this subset of patients as well. To date, there are no published data on PET/CT findings in patients with MGUS. However, if changes suspected to be osteolytic lesions are found with whole-body CT, a PET/CT should be done to rule out myeloma or another malignant disease.

Recommendations

In summary, in suspected high-risk non-IgM MGUS, we recommend whole-body CT to rule out multiple myeloma. If whole-body CT is not available, conventional skeletal survey or whole-body MRI are alternatives (level V; appendix p 1). In patients with equivocal findings on whole-body CT (or conventional skeletal survey) in whom there is a concern for myeloma development, we recommend whole-body MRI (or MRI of the spine and pelvis if whole-body MRI is not available; level IV; appendix p 1). If whole-body CT is positive, a PET/CT should be done (level V; appendix p 1). We do not recommend follow-up bone imaging unless there are signs of progression to symptomatic disease (eg, pain or increase in serological parameters). In patients with MGUS with positive imaging findings for focal and osteolytic lesions, other malignancies should be ruled out as well, if needed a biopsy of such a lesion should be performed.

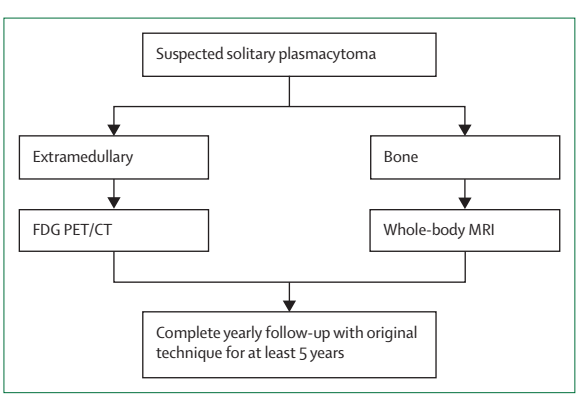

Figure 2: **Imaging algorithm for patients with solitary plasmacytoma**
FDG=fluorodeoxyglucose.

Solitary plasmacytoma

Solitary plasmacytoma can occur as either solitary bone plasmacytoma or extramedullary lesion, with the solitary bone plasmacytoma being about twice as prevalent as extramedullary lesions.[35] Furthermore, solitary bone plasmacytoma has a statistically significantly higher risk of progression to multiple myeloma (35%) compared with extramedullary lesion (7%) within 2 years.[35] The most important information acquired from whole-body imaging in any patients with solitary plasmacytoma is the exclusion of additional osteolytic lesions or further soft tissue masses, which would constitute systemic multiple myeloma. Whole-body MRI and PET/CT provide high sensitivity and specificity to detect further diffuse infiltration and focal bone marrow infiltration. Different guidelines have recommended PET/CT over MRI for imaging of the spine and pelvis, which is a difficult comparison because MRI of the spine and pelvis has a different field of view than PET/CT, which covers the whole body. To our knowledge, no original analyses exist that compare the sensitivity of whole-body MRI and PET/CT. However, since MRI has a higher sensitivity for diffuse infiltration of the bone marrow, whole-body MRI should be the first choice in patients with solitary bone plasmacytoma because, although not considered a myeloma-defining event, diffuse infiltration should lead to further examinations to explore potential reasons for the higher bone marrow cellularity, including multiple myeloma. If a whole-body MRI is not available, PET/CT provides a reasonable alternative (figure 2). In extramedullary lesions, PET/CT is the preferred imaging modality to exclude further lesions.

The risk of solitary plasmacytoma progression to multiple myeloma or relapse is 14–38% within the first 3 years.[36] For early identification of progression, yearly follow-up with the same imaging technique used at first diagnosis should be done for the first 5 years. After 5 years, the same imaging technique should be used only for cases of clinical or laboratory signs or symptoms, even though no clear evidence for the benefit of this procedure yet exists.

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Recommendations

We recommend whole-body MRI (or MRI of the spine and pelvis if whole-body MRI is not available) in patients with newly diagnosed solitary bone plasmacytoma (level V; appendix p 1). We recommend PET/CT in patients with newly diagnosed solitary extramedullary plasmacytoma (level IV; appendix p 1). If whole-body MRI is not available, PET/CT can be used as an alternative in patients with newly diagnosed solitary bone plasmacytoma (level V; appendix p 1); the same technique used at initial diagnosis should be repeated at yearly intervals for at least 5 years (level V; appendix p 1).

Smoldering multiple myeloma

Compared with active multiple myeloma, disease burden is lower in patients with smoldering multiple myeloma, which makes it very important to apply imaging techniques with a high sensitivity to identify bone disease or bone involvement and distinguish smoldering multiple myeloma from active multiple myeloma. Several retrospective analyses, both with MRI and PET/CT, have been done to evaluate the techniques in smoldering multiple myeloma diagnosis. In two independent datasets of patients with smoldering multiple myeloma, the first of which included 149 patients assessed by whole-body MRI, and the second of 67 patients assessed with spinal MRI, an optimal cutoff of two or more focal lesions without underlying osteolytic lesions has been found to be of prognostic significance for progression to symptomatic disease with a 2-year rate of progression of 70–80%. Positive findings of focal lesions were reported in 16% of the whole-body MRI group and 28% of the spinal MRI group.[37,38] PET/CT was also applied in studies of patients with smoldering multiple myeloma. Zamagni and colleagues[39] found that in a cohort of 120 patients with smoldering multiple myeloma, 16% were positive following PET. These patients had a 2-year rate of progression of 58% compared with 33% in PET-negative patients.[39] In this analysis, patients showing osteolytic lesions following CT examination were excluded as recommended by the current definition of multiple myeloma.[2] Another study of 188 patients with smoldering multiple myeloma, defined by the 2003 IMWG diagnostic criteria, showed that 139 patients were still considered to have smoldering multiple myeloma after PET/CT; 18% of patients were PET positive and had a 2-year progression rate of 75%.[40]

Since PET/CT data have been acquired after publication of the most recent guidelines for the definition of multiple myeloma, only MRI focal lesions have been defined as a myeloma-defining event, leading to the IMWG recommendation to treat these patients.[2]

For the same reasons discussed for MGUS, we recommend whole-body CT as the first imaging technique for the identification of osteolytic lesions. If imaging findings are inconclusive, the same imaging technique should be repeated after 3–6 months. In a study by Merz and colleagues,[41] an increase in the number or size of focal lesions in patients with smoldering multiple myeloma identified through follow-up whole-body MRI studies were prognostic for progression to active multiple myeloma requiring treatment compared with patients with smoldering multiple myeloma who had stable focal lesion findings.[41] If only whole-body MRI has been done, other bone imaging techniques (eg, whole-body CT) should be done to identify lytic lesions. The risk of progression from smoldering multiple myeloma to multiple myeloma decreases over time, reflecting the potential presence of a group of patients with MGUS-like low-risk smoldering multiple myeloma.[42] Therefore, if no signs of progression occur regular imaging can be reduced or stopped after 5 years, especially in patients without high-risk features. Because of the complementary findings of whole-body CT osteolytic lesions) and whole-body MRI bone marrow lesions in patients with only one focal lesion, an alternating approach of MRI and CT can be considered. This recommendation is a suggestion based on clinical experience and not on published data. The rationale for this recommendation is that patients with smoldering multiple myeloma with an increased number or size of focal lesions have a higher risk of progression that can be

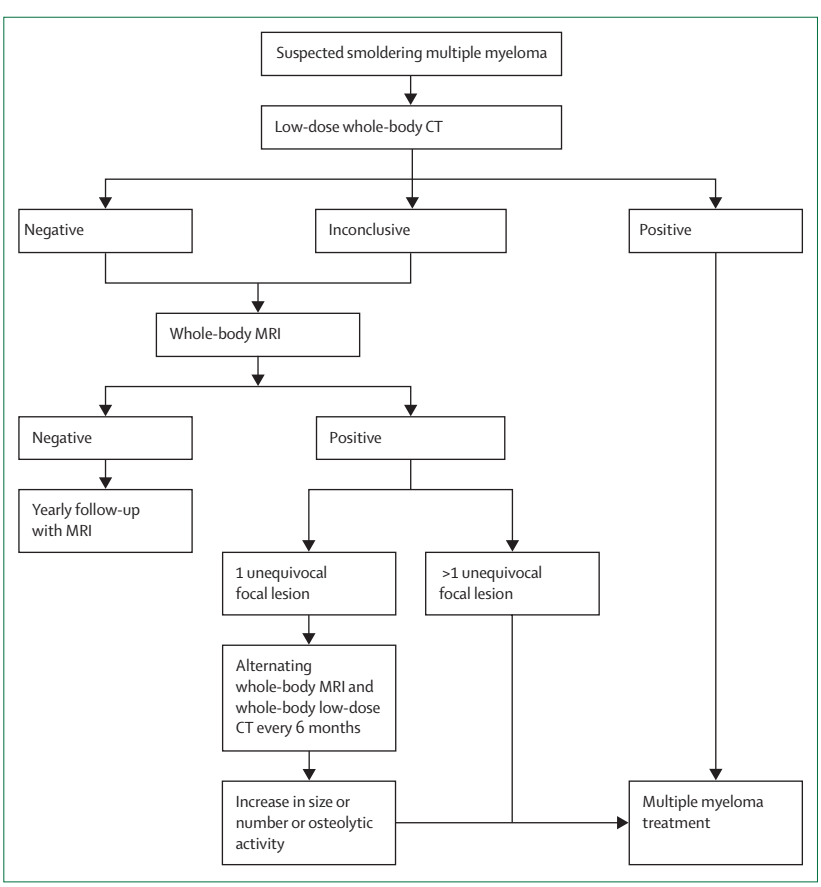

Figure 3: **Imaging algorithm for patients with smoldering multiple myeloma**

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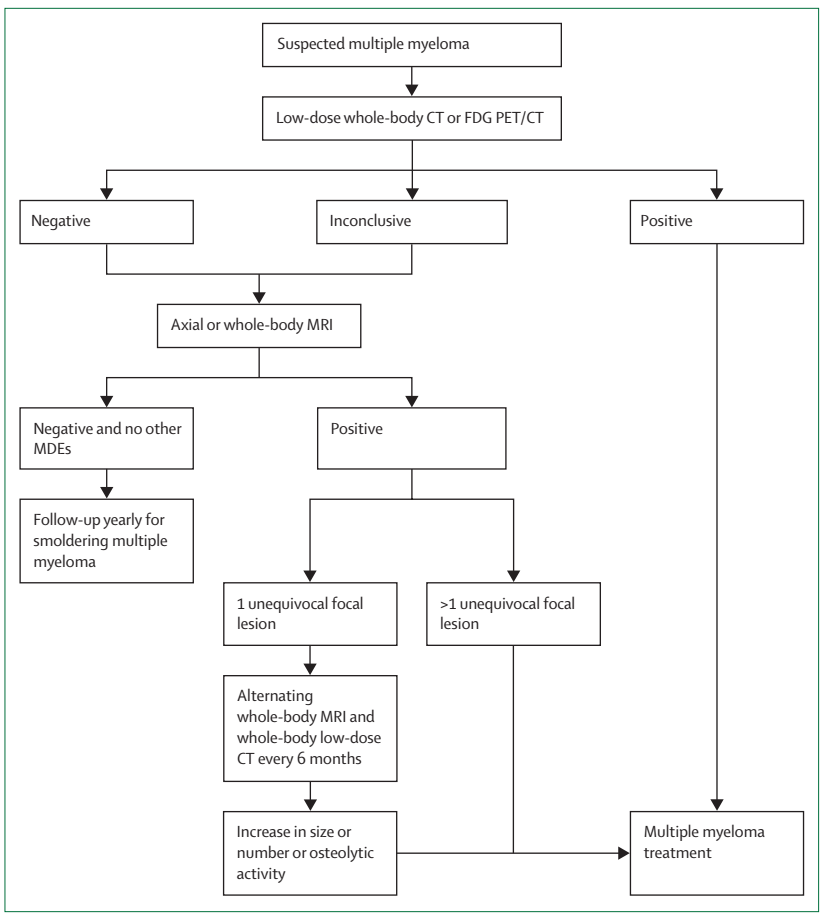

Figure 4: **Imaging algorithm for patients with multiple myeloma at first diagnosis**
Minimal requirements as recommendations for clinical trials. FDG=fluorodeoxyglucose. MDEs=myeloma-defining events.

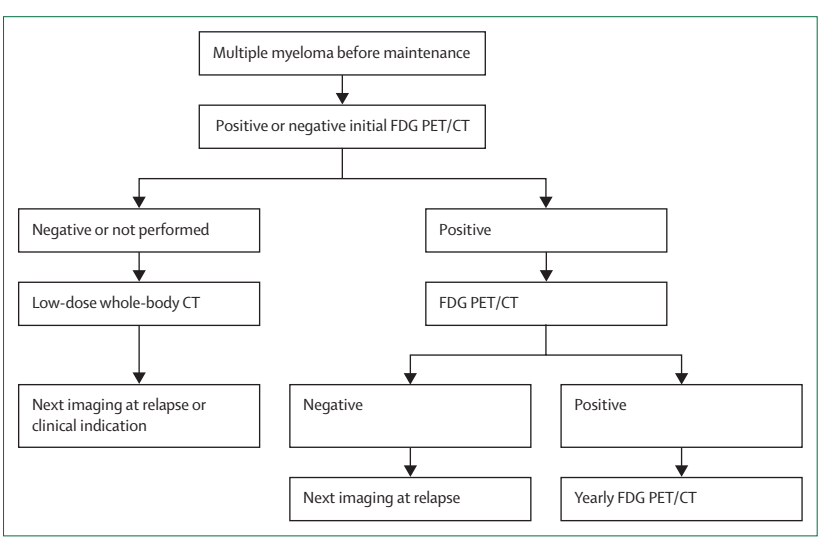

Figure 5: **Imaging during follow-up therapy for response evaluation**
FDG=fluorodeoxyglucose.

seen with MRI, and often manifests as osteolytic lesions for which whole-body CT is the imaging method of choice.[41] Figure 3 shows an algorithm for imaging in patients with smoldering multiple myeloma.

Recommendations

In summary, an accurate smoldering multiple myeloma diagnosis is essential; as a result, conventional skeletal survey is not recommended to determine presence or absence of bone disease (level IV; appendix p 1). Whole-body CT is the first imaging choice to exclude osteolytic lesions (level III; appendix p 1). If whole-body CT is negative, we recommend the use of whole-body MRI (or MRI of the spine and the pelvis if whole-body MRI is not available) as the next diagnostic step because of its high sensitivity and the necessity of excluding focal lesions as myeloma-defining events (level IV; appendix p 1). PET/CT can be used in place of whole-body CT (level V; appendix p 1) and it can be used in place of whole-body MRI if the MRI procedure is not feasible or if other contraindications or patient factors exist that preclude its use (level IV; appendix p 1). The same technique used at initial diagnosis should be repeated at yearly intervals for at least 5 years, depending on risk factors. Furthermore, alternating CT examinations should be done in certain circumstances (high risk of progression) to identify small osteolytic lesions (level V; appendix p 1).

Multiple myeloma

Similar to investigations on early disease stages, imaging at first diagnosis with both PET/CT and MRI, have been shown to provide prognostic information based on the presence and number of focal lesions and diffuse infiltrations of the bone marrow. In analyses of newly diagnosed patients with multiple myeloma in the context of the total therapy protocols, more than seven focal lesions in spinal MRI and more than three lesions and extramedullary disease PET/CT have been shown to be of adverse prognostic significance.[43–46] These data have been confirmed in another cohort of 192 patients by the multiple myeloma group in Bologna and Udine.[47] Although these results are prognostic at diagnosis[46] and serve as a reference point for new emerging lesions at progression, they are not used to escalate or de-escalate therapy. Furthermore, post-therapy imaging interpretation should be done in the context of the same imaging technique (whole-body MRI or PET/CT) that was used at baseline assessment. The novel imaging techniques give a comprehensive assessment of total tumour mass, extramedullary disease, and potentially clinically relevant impairment of the skeletal system or involved organs.

In clinical practice, a careful evaluation of the extent of bone destruction is of utmost importance. Therefore, whole-body CT is the first technique recommended as a minimal requirement that should be used (figure 4). If whole-body CT does not identify any signs of lytic

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lesions or osteoporosis, whole-body MRI should be done as per the aforementioned reasons regarding its use on smoldering multiple myeloma. Because of the prognostic effect at both first diagnosis and after the completion of therapy, PET/CT is recommended within clinical trials and general clinical practice when appropriate. For patients who are negative for all imaging techniques but show other myeloma-defining events the general recommendations[2] of the IMWG should be considered. Certain emergent clinical situations might necessitate imaging, such as an MRI to rule out cord compression, or a CT to assess bone integrity or stability.

Recommendations

For multiple myeloma imaging at first diagnosis, conventional skeletal survey is not recommended to determine the presence or absence of bone disease in myeloma (level III; appendix p 1). Whole-body CT is the first-choice imaging technique to identify and to assess the extent of osteolytic lesions (level III; appendix p 1). PET/CT can be used in place of whole-body CT (level IV; appendix p 1). If whole-body CT is negative, and no other myeloma-defining events are present, we recommend the use of whole-body MRI (or MRI of the spine and the pelvis, if whole-body MRI is not available) as the next diagnostic step because of its high sensitivity and the necessity to exclude focal lesions as myeloma-defining events (level IV; appendix p 1). PET/CT can be used in place of whole-body MRI if the procedure is not feasible or if there are other contraindications or there are patient factors that exist that preclude its use (level 4; appendix p 1). In clinical trials, PET/CT is the preferred imaging method to create a baseline for response assessment (level 4; appendix p 1).

Imaging during follow-up or therapy for response evaluation

In 2016, the IMWG published an updated version of the criteria for assessment of treatment response in multiple myeloma. In this Review, for the first time, the possibility of a focal infiltration pattern has been taken into account, especially in cases of patients achieving complete response or minimal residual disease-negative status, when information derived from whole-body imaging has to be considered.[48] This recommendation is because complete response has low plasma cell counts in the bone marrow and minimal residual disease negativity is defined by no measurable plasma cell counts in the bone marrow. These examinations are usually done in the pelvic bone, where the bone marrow is most easily accessible; however, residual disease at other sites in the body can remain undetected. Several studies have shown that residual focal lesions detected by either PET/CT and spinal MRI, or whole-body MRI are of adverse prognostic significance.[43,49–51] In an Italian study published by Zamagni and colleagues,[49] progression-free survival was 44 months for patients with residual focal lesions versus 84 months for patients without residual focal lesions (p=0·0009). Figure 5 shows a potential algorithm for imaging during follow-up and for response evaluation. The same imaging technique used at initial diagnosis should be used at each stage of follow-up to provide comparability, and, except in instances of progression, no change of treatment can be recommended on the basis of post-treatment imaging results.

Follow-up imaging does not only provide information on disease progression. The more widespread use of CT has revealed that lytic lesions can show signs of bone healing, and residual lesions immediately after intensive therapy can become negative after a long follow-up. Therefore, in cases of PET-avid focal lesions in the setting of serological response, these should be compared with the CT part of the examination, which would show sclerotic versus further lytic activity. Also, conventional whole-body MRI is limited with regard to the evaluation of treatment response and should include diffusion-weighted imaging if PET/CT is not available. In fact, diffusion-weighted imaging has been shown to be superior to PET/CT in several smaller studies.[52–54] If initial PET/CT was negative or not done, at least a whole-body CT is recommended to provide a baseline

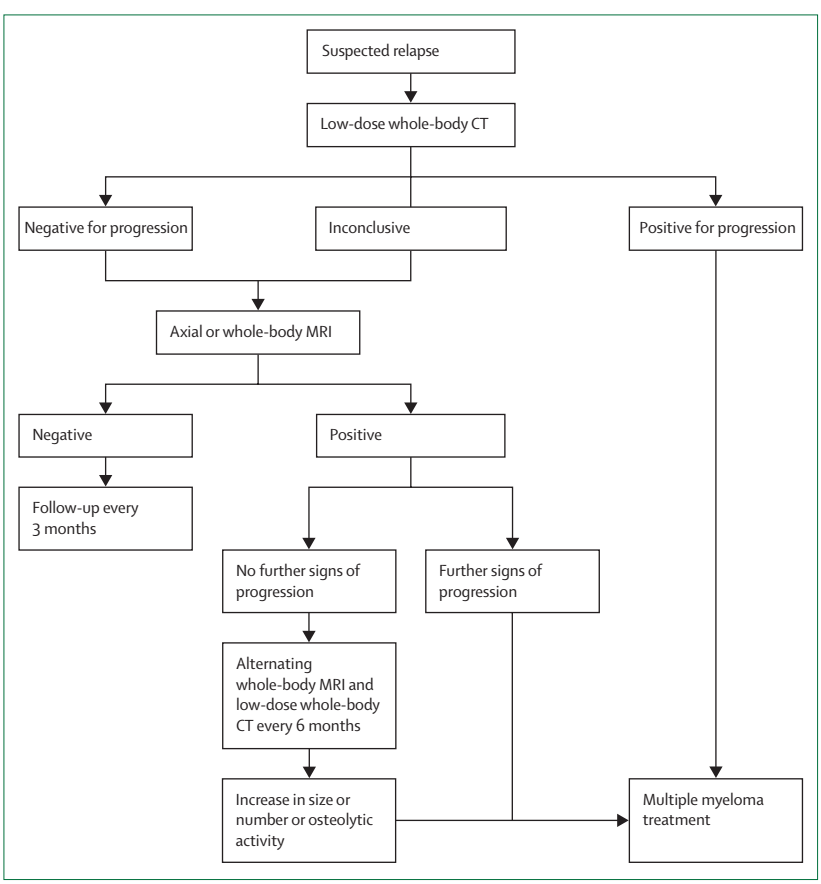

Figure 6: **Imaging algorithm for patients with suspicion of relapsed or progressing multiple myeloma.** In the case of negative findings, follow-up should be done every 3 months with clinical and serological examinations.

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***Panel:* Recommendations on the reporting of imaging results in monoclonal plasma cell disorders**

First diagnosis

A radiological report on whole-body imaging in patients with monoclonal plasma cell disorders should include:

- Infiltration and bone destruction pattern
  - Minimal (normal appearing)
  - Focal lesions
  - Diffuse infiltration and bone destruction
  - Mixed (focal lesions on diffuse background)
- Absolute number of focal lesions
  - For whole-body MRI: 0, 1, 2–7, or >7
  - For PET/CT: 0, 1–3, or >3
- Number of fractures (new *vs* old, location, and likelihood of malignant *vs* benign cause)
- Extramedullary disease
- Soft tissue masses growing out of the bone marrow into the surrounding tissue
- Infiltration of the long bones
- Evidence of surgical procedures at the skeletal system
- Incidental findings

In remission

Differentiate these findings with regards to response to therapy in imaging (guidelines papers for whole-body CT, whole-body MRI, and PET/CT):

- Response
  - Normalisation of bone marrow signal in previously affected areas
  - Decrease in the number and size of focal lesions
  - Resolution of severely infiltrated bone marrow infiltrate into focal lesions
  - Decrease in the of number and size of soft tissue tumours (paramedullary and extramedullary)
- No change
- Progression
  - Worsening of diffuse bone marrow signal or new appearance of infiltration in previously unaffected areas
  - Increase in the number and size of focal lesions
  - Merging of focal lesions into severely infiltrated bone marrow
  - Increase in the size or number of soft tissue tumours (paramedullary and extramedullary)

Specifics for MRI

Cystic or liquid transformation of focal lesions after therapy

for the time of serological relapse. Even if a patient responds to treatment, new bone fractures especially in the spine can occur; these fractures are not necessarily signs of progression but of earlier disease course. To avoid the overestimation of the extent of bone disease at relapse in these cases, a comparison should be made to the whole-body CT after therapy instead of the initial examination.

At relapse, MRI has been proven to be of value for the early detection of recurrent bone marrow infiltration, with a slight superiority over PET/CT. PET/CT has been shown to be better in the early detection of patient response to salvage therapy.[55] However, to our knowledge there are no data that positively supports a change or reinitiation of treatment based on only an MRI or PET without new osteolytic lesions, even though this might be biologically reasonable in certain cases. We recommend whole-body CT when a relapse is suspected (eg, serological relapse or progression) to assess the extent and dynamic of bone destruction as the most clinically relevant parameter (figure 6).

Recommendations

Depending on the availability of baseline examinations and initial results, either whole-body CT to provide a baseline bone status for comparison against potential future relapse, or PET/CT as part of response assessment, should be done. For patients with residual lesions detected by PET/CT, yearly follow-up is recommended because these patients have a high risk of an early progression (level V; appendix p 1).

How to perform and report bone marrow findings from PET/CT and whole-body MRI

Some studies that investigated the use of MRI for monoclonal plasma cell disorders only included imaging of the spine and the pelvis and sometimes the skull (known as axial MRI). A comparative study of axial MRI and whole-body MRI revealed that only ten of 100 patients had focal lesions identified following extra-axial skeletal analysis; these patients would have been misdiagnosed had whole-body MRI not been done.[56] Therefore, if available, we recommend the use of whole-body MRI as the imaging technique of choice.

A description of the specifications for whole-body MRI and PET/CT is beyond the scope of this Review. However, recommendations for the interpretation of PET/CT scans have been published by the IMWG and are being refined by the same group.[57] In brief, focal lesions in PET/CT at first diagnosis of all disorders have been defined by a tracer uptake higher than that of haemopoietic bone marrow or that of the liver. Diffuse uptake should be reported if the uptake lies above the liver. Further efforts to optimise PET/CT imaging are ongoing.

Recommendations for technical specifications of whole-body MRI and whole-body CT by interdisciplinary groups of radiologists, physicists, and haematologists have been published.[6,7] MRI focal lesions are characterised by hypointensity in T1-weighted and corresponding hyperintensity in T2-weighted or inversion recovery images. Diffuse infiltration can be identified if the signal intensity is decreased homogeneously in T1-weighted and increased in T2-weighted images. As a reference, the signal intensity of the intervertebral disk should be used.

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Search strategy and selection criteria

These recommendations were formed and developed as follows. As a first step, a steering committee was identified at an International Myeloma Working Group (IMWG) meeting. No formal comprehensive literature search was done because this Review is a guideline paper rather than a formal literature review. However, the committee searched the PubMed database for articles published in English between Jan 1, 1980, and Jan 31, 2018, that contained the term "multiple myeloma imaging". Only manuscripts with a high level of evidence were chosen; additionally, case reports and case series were not included. For the different stages of multiple myeloma, the literature search was focused on different globally available imaging methods including X-ray, CT, MRI, and PET/CT. PET/CT was limited to fluorodeoxyglucose PET/CT because of the scarce availability of other tracers. In functional MRI, only diffusion-weighted imaging has been included because of the largest number of studies available from different countries. Other functional MRI techniques were not included because of poor global availability. Following the literature search, the steering committee prepared a first set of recommendations. These were discussed at an IMWG meeting in Stockholm, Sweden, on June 12, 2018, before a first draft of the manuscript was prepared. This draft was sent to the members of the IMWG and all feedback was collected. The steering committee then made the relevant adjustments and submitted the final version of the manuscript.

All whole-body imaging should include the vertex of the skull and the knees. If protocols are available, the lower extremities should be shown in full. On the basis of the generally used whole-body MRI slice thickness of 5 mm, the minimum diameter of a focal lesion to be defined as such was arbitrarily set at 5 mm. From a haematologist's perspective, the information in the panel should be provided when reporting findings from PET/CT or whole-body MRI.

Conclusion

This Review aims to provide guidelines on how to use current imaging modalities for the diagnosis and management of multiple myeloma and precursory diseases. New PET tracers and novel technologies such as double-energy CT are likely to be introduced into clinical practice soon. Once incorporated, the use of emerging technologies might lead to a necessity for changes to the current recommendations.

Contributors

JH, SU, and SLe wrote the first draft of the manuscript and included comments from the other authors. SVR and BGMD edited the first draft. All other authors provided feedback either in person or as comments on the second draft of the manuscript.

Declaration of interests

BGMD reports personal fees from Amgen, Celgene, Janssen, and Takeda, outside of the submitted work. MVM reports personal fees from Janssen, Clegene, Takeda, Amgen, GSK, and Pharmamar, outside of the submitted work. SaL reports personal and consulting fees from Millennium Takeda, Celgene, Novartis, Amgen, Sanofi, Janssen, and BMS, outside of the submitted work. KCA reports personal fees from and is an Advisory Board member for Celgene, Millennium, Bristol Myers Squibb, Janssen, Gilead, and Sanofi Aventix, outside of the submitted work. NvdD is an Advisory Board member for and reports Grants and other support from Celgene, Janssen, BMS, Amgen, Novartis; and other support from Bayer, Servier, and Takeda, outside of the submitted work. JGB reports grants from Abbvie, Amgen, Bluebird, BMS, Celgene, Genentech, Glenmark, Janssen, Novartis, Poseida, Sanofi, Takeda, and Teva; and consultancy fees from BMS, Celgene, Karyopharm, CRISPR, Kite Pharma, and Servier paid to his institution, outside of the submitted work. ET reports Grants, Personal fees, non-finaincial support Amgen, Genesis, Janssen, and Takeda; personal fees from Celgene and BMS; and is a an Advisory Board member for Amgen, Genesis, Takeda, Janssen, and Celgene; member of SC for Amgen, Genesis, and Takeda; and is a member of IDMC for Celgene, all outside of the submited work. JSM is an Advisory Board member for Amgen, BMS, Celgene, Janssen, MSD, Novartis, Takeda, Sanofi, and Roche. HG reports other from Amgen, grants personal feels, and non-financial support from BMS, Celgene, Chugai, and Janssen; Grants and non-financial support from Sanofi; Non-financial support from Takeda; Personal fees and other support from Novartis; other support from adaptive biotechnology; and personal fees from Art Tempi, all outside the submitted work. SG reports Grants and Honoria from Celgene, Takeda, Actinuum, Johnson and Johnson, Sanofi, and Amgen; Honoria from Novartis and Jazz; is an Advisory Board member from Celgene; and is on the data safety monitoring board for BMS, all outside the submitted work.SK reports grants from Abbvie, Celgene, Janssen, Merck, Novartis, Roche, Sanofi, Takeda, and Medimmune/Astra Zeneca; and personal fees from Oncopeptides Adaptive, outside of the submitted work. NR Holds advisory roles for Amgen, Clegene, Takeda, Janssen, and BMS. HL reports grants from Amgen and Takeda; personal fees from Amgen, Takeda, Celgene, BMS, Janssen, and Pharmamar. EO reports personal fees and research support form Amgen, Mundipharma; personal fees from BMS, Oncopeptides, Bayer, Pharmamar, Abbvie, Seattle Genetics, and Tecnofarma; Research support from Array Blopharma and IDP Pharma; and personal fees and non-financial support from Celgene, Janssen, Takeda, and Novartis Oncology. HE reports grants and personal fees and is an Advisory Board member for Janssen, Celgene, and Amgen; and reports personal fees and is an Advisory board member for BMS, Takeda, and Novartis, uring the conduct of the study. JJL reports personal fees and Honoria from Janssen, Takeda, Celgene, and Amgen. SLe reports personal fees from and is the Chief Scientific Advisor for Caelum Biosciences; personal fees from and is the Study Chair for Bayer; and personal fees and is an Advisory Board member for Janssen, Takeda, BMS, Abbvie, and Proclara. JH, SU, SVR, CJ, RGS, ERS, JD, EZ, RAK, RS, FS, WMC, NA, BCL, DD, BMW, MD, MC declare no competing interests.

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