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REVIEW ARTICLE

Imaging myeloma and related monoclonal plasma cell disorders using MRI, low-dose whole-body CT and FDG PET/CT

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Abstract The identification of bone lesions and extramedullary disease is crucial in the diagnosis of myeloma. Whole-body X-ray (WBXR) is considered the gold standard for the detection of myeloma bone lesions. Nevertheless, the International Myeloma Working Group recently updated the disease definition and emphasised the value of magnetic resonance imaging (MRI), computed tomography (CT) alone or combined with ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET). The presence of more than one focal lesion with MRI or the presence of one or more lytic bone lesion with CT (including low dose CT alone or combined with FDG PET) is considered as myeloma defining events (if 5 mm or more in size). Due to its higher sensitivity to detect bone lesions (in comparison with WBXR), MRI of spine and pelvis is mandatory for patients with solitary plasmacytoma as additional bone lesions can be detected in approximately one-third of cases. MRI is also recommended in patients with smouldering myeloma and may be considered for the staging of multiple myeloma (MM). Moreover, accurate imaging of MM and related plasma cell disorders using MRI and/or FDG PET/CT may provide information on tumour burden, aggressiveness and tumour heterogeneity. Nonetheless, inclusion of MRI and FDG PET/CT for MM patient stratification and therapeutic decisions remains to define.

Keywords Myeloma · Imaging · PET · MRI · Staging · Prognosis

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Introduction

Multiple myeloma (MM) is the most common plasma cell (PC) dyscrasia characterised by the autonomous proliferation of monoclonal PC in the bone marrow (BM) and by the overproduction of either intact immunoglobulin molecules (M-component or M-protein) or immunoglobulin kappa or lambda free light chains (FLC). Myeloma is rare among individuals younger than 40 years, but its incidence rises in subsequent decades and exhibits a slight male predominance. Myeloma belongs to a spectrum of diseases ranging from monoclonal gammopathy of undetermined significance (MGUS) to plasma cell leukaemia. The frontiers between these different entities were recently redefined by the International Myeloma Working Group (IMWG) and are summarised in Table 1 [1].

The earlier definition of MM implicated the presence of overt clinical manifestations of serious end-organ damage such as osteolytic bone lesions and renal failure. This was acceptable as long as the available treatment options could not improve the survival and quality of life of patients presenting a smouldering myeloma (sMM, also named asymptomatic myeloma in the literature). However, this approach is difficult to justify with the improved treatment schedules and the potential devastating complications of

Table 1 Revised diagnostic criteria of the main monoclonal PC disorders

Monoclonal PC disorder	M-protein in serum (and/or urine)	Clonal BMPC infiltration	End organ damage[a]
MGUS	<30 g/L in serum	And <10 %	And absent
Smouldering MM (sMM)	≥30 g/L in serum (or ≥500 mg per 24 h in urine)	And/or 10–60 %	And absent
Solitary plasmacytoma (SP)	No	And absent	And absent[b]
MM	Present (or absent[c] in non-secretory MM)	And ≥60 %	And ≥1[d]

[a] Related to monoclonal PC disorder: CRAB: hypercalcaemia, renal insufficiency, anaemia and/or ≥1 bone lytic lesion on skeletal radiography, CT or FDG PET/CT

[b] Except a single biopsy-proven bone lesion or extramedullary clonal PC tumour

[c] As determined by immunofixation

[d] In the absence of end-organ damage, ≥1 of the following biomarkers of malignancy: clonal BMPC percentage ≥60 %; involved: uninvolved serum FLC ratio ≥100 or >1 focal lesions on MRI studies

myeloma (e.g., renal failure with dialysis, vertebral fracture or neurological complications) [2]. There is a growing consensus amongst myeloma experts that sMM patients who present a very high likelihood of progression to symptomatic disease should be treated earlier in their disease course [1]. Therefore, the IMWG aimed at identifying biomarkers that were associated with an approximately 80 % probability of progression to MM within 2 years, with a 12-month median time to the development of end-organ damage [1].

Traditionally, bone disease has been identified on the basis of conventional skeletal radiography [3, 4]. The current disease definition also includes the presence of osteolytic bone destruction (≥5 mm in size) seen with computed tomography (CT, including low-dose CT) and/or ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET/CT) [1]. Correct assessment of BM infiltration, identification of bone lesions and extramedullary disease (EMD) are crucial in the diagnosis of MM. This non-systematic review discusses the additional value of magnetic resonance imaging (MRI) and FDG PET/CT in the identification of bone and BM lesions and in the general management of PC disorders.

Clinical presentation of MM

A small percentage of patients are asymptomatic and the diagnosis is raised when routine laboratory testing for a coexisting disorder reveals an abnormally high serum protein level or unexplained proteinuria. When MM becomes symptomatic, anaemia is a common manifestation. In most patients, suppression of some or all marrow cell lineages may be far greater than would be expected solely on the basis of the apparent degree of BM replacement by malignant cells. Back pain is particularly common because of bone involvement [5].

Localised proliferation of malignant PC in the marrow and bone may produce painful osteolytic lesions visible on plain films. Bone involvement may produce several important clinical problems (e.g., pathologic fractures) increasing pain and skeletal instability. Hypercalcaemia may develop in patients with extensive bone disease. Neurological problems are an important cause of morbidity since vertebral osteolytic lesions may produce spinal cord compression or radiculopathy. Solitary plasmacytoma (SP) may develop in both bone marrow and extramedullary (EM) locations. True SP is rare, and nearly all patients with a solitary bone lesion later develop disseminated myeloma. In contrast, soft tissue plasmacytomas often remain localised (the most common site being the gastrointestinal tract) and may be cured with local treatment [6].

Occasionally, symptoms of MM are related exclusively to the excessive protein production and can result in a hyperviscosity syndrome (including neurological symptoms, visual changes and coagulation abnormalities). Although MM is characterised by excessive production of monoclonal immunoglobulins, levels of normal immunoglobulins usually are depressed, which can contribute to a general susceptibility to bacterial infections. Renal failure is a common problem in patients with MM. Excessive production of light chains can cause the so-called myeloma kidney, characterised by irreversible renal tubular damage. Hypercalcaemic nephropathy and hyperuricemia secondary to degradation of a large tumour cell mass may also cause renal failure. In some cases, the amyloid deposition in the kidney can cause renal failure.

Staging systems

MM is a heterogeneous disease, associated with variable patient outcomes that depend on the disease biology, global disease burden, presence of disease-related complications

and health status of the patient [7]. All these different parameters may influence the choice for a particular treatment. A standardised prediction system may help to distinguish aggressive disease forms from slowly progressive diseases and the proposed treatments can be tailored according to this risk stratification. An ideal staging system would utilize routinely available parameters and should be able to separate patients into groups with similar outcome [7].

Initially, Salmon and Durie proposed a staging system that was based on the tumour burden and presence of disease complications that categorised patients into three stages [8]. Median survival for patients with stage I disease is longer than that for those with stage III disease. As it is an important prognostic factor and generally is associated with poor survival, the presence of renal failure is used to divide the main disease stages into two sub-stages depending on the presence or absence of renal failure.

Other staging systems have been developed over time and the International Staging System (ISS) is currently the most commonly used because of its simplicity and efficacy. From a large dataset that included patient and myeloma-related laboratory variables, beta-2 microglobulin (β2M) and albumin levels emerged as the most consistent prognostic factors that could be correlated with survival duration. Based on these two factors, the ISS provides highly statistically significant stratification [9]. The β2M is the light chain component of the major histocompatibility class I complex; it is expressed by all nucleated cells and normally eliminated by the kidneys. Blood level of β2M increases when renal function declines. Serum β2M level correlates with tumour burden and turnover rate and reflects renal impairment. Serum β2M level is considered to be an important independent prognostic factor in MM and predicts the survival of MM patients regardless of the Salmon and Durie stage [10, 11]. Albumin levels are routinely available blood test that is a good prognostic marker. Several studies have suggested that low serum albumin levels correlate with increased serum concentrations of interleukin-6, a PC growth factor [12]; low serum albumin levels may also be related to patient nutritional and performance status [13].

Imaging techniques in MM

Radiological skeletal survey

Skeletal radiography is the primary imaging study to detect destructive bone changes in MM. It continues to have an important role in the Durie–Salmon clinical staging criteria for newly diagnosed MM. 75 % of patients with MM present with positive radiographic findings [14]. The presence of two clearly defined lytic lesions indicates high tumour burden and stage III disease [8]. Approximately 50 % of bone destruction must occur before there is radiographic demonstration, which may present as a solitary lesion (plasmacytoma), diffuse skeletal involvement (myelomatosis), diffuse skeletal osteopenia and sclerosing myeloma [15]. Diffuse myelomatosis usually manifests as osteolytic lesions with discrete margins and uniform size, subcortical, elliptic and confluent lesions causing large segments of destruction. Diffuse skeletal osteopenia without well-defined lytic lesions predominantly involves the spine. Multiple compression fractures may be seen with X-Rays with this condition. Bone sclerotic lesions may be rarely seen in MM and are associated with the polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS syndrome) [16, 17]. A complete skeletal survey (WBXR) should include a postero-anterior and lateral view of the skull, spine, humeri and femora, as well as an antero-posterior view of the pelvis and chest [18].

While remaining a standard method for assessing bone disease in MM, WBXR has several advantages and limitations. Advantages include its low cost and ability to detect the areas mainly involved in the disease, as well as the risk of fracture in long bones. On the other hand, it provides low sensitivity [19]. This ultimately means that it underestimates bone involvement in the 30–70 % range. In addition, some areas, such as the sternum or sometimes the spine, are not well visualised due to superimposed images of the bowel (Fig. 1), or cannot be detected because they are outside the field of view (FOV). Moreover, focal lesions (FLs) are almost invisible inside the trabecular bone. In a prospective comparison of WBXR versus FDG PET/CT in a series of 46 newly diagnosed MM patients receiving up-front autologous stem cell transplantation (ASCT), WBXR underestimated the extent of bone involvement in approximately 40 % of patients [20]. At the same time, the specificity of WBXR is not high, especially in the spine, where it fails to distinguish myeloma-related osteoporosis from benign osteoporosis [21]. Another major limitation of conventional radiography is that it cannot be used for the assessment of response to treatment or during the follow-up (FU) phase, because healing of lytic lesions is a rare event, even in patients who achieve sustained CR [22]. In light of these observations, though WBXR is still widely used in daily clinical practice for the assessment of bone disease and is considered as a standard tool in most clinical trials and guidelines, it is likely that newer, and more sensitive, imaging techniques will replace conventional X-rays in the near future.

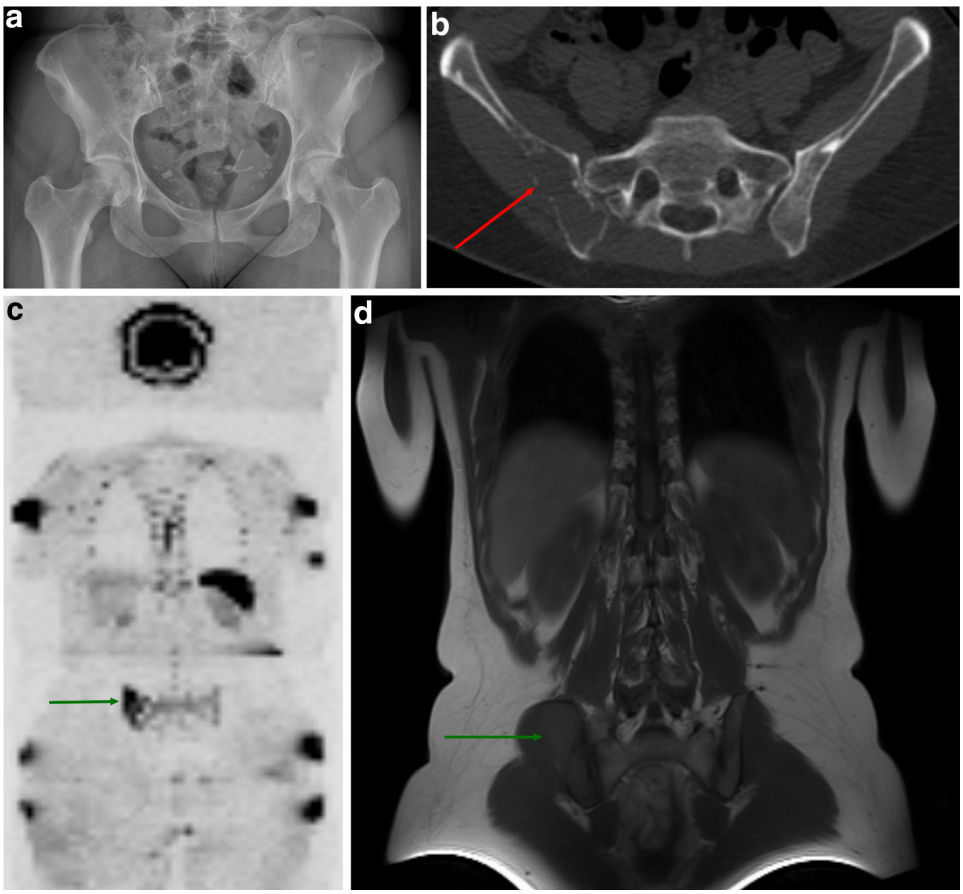

Fig. 1 Images of a 46-year-old patient with MM (IgG kappa). No bone lesion was detected with the WBXR (**a** pelvis X-ray image). In contrast, an extensive bone lytic lesion of the right iliac bone was demonstrated with the low-dose CT performed with FDG PET (**b** *red arrow*; 3 mm slice thickness; tube voltage: 120 kV and tube current–time product: 50 mAs). The MRI confirmed the bone marrow infiltration in the right iliac bone (**c** *green arrow*: whole-body diffusion-weighted MRI and **d** *green arrow*: T1-weighted spin-echo sequence) (colour figure online)

Low-dose CT

CT is a sensitive tool for detection of bone-destructive effects in MM. CT findings consist in lytic lesions, expansive lesions with soft tissue masses, diffuse osteopenia, fractures and, rarely, osteosclerosis [20]. Multi-detector row CT (MDCT) is superior to conventional X-Rays for defining lytic lesions. In comparison to WBXR, CT more accurately assesses the extent of bone destruction [23] and was also found to correlate significantly with whole-body MRI (WB-MRI) in the staging work-up. However, while persistent osteolytic lesions after treatment were still shown by CT, resolution of marrow signal abnormalities was observed at MRI [24]. Although the current experience with CT in MM is relatively limited, interest in the use of this technique as an alternative to standard radiography is increasing. Notably, CT may identify lesions that are negative on WBXR and should be primarily considered in patients with bone pain and lack of evidence of osteolysis on the skeletal survey and/or in patients for whom MRI is contraindicated. The MDCT allows a better evaluation of areas at risk for fracture. However, CT imaging, as well as plain radiography, is not suitable for the evaluation of therapy response since most of lytic lesions remain morphologically stable despite a complete response to therapy and, therefore, it may have a predominant role only during disease staging.

The CT acquisition protocol can be optimised to reduce patient's radiation exposure: before the CT image acquisition (e.g., the tube current can be adapted to the patient's body weight or body mass index), during CT image acquisition (e.g., the tube current can be modulated to the body region using dedicated software) and finally, after image acquisition (e.g., CT images can be reconstructed using iterative algorithms allowing dose reduction without degrading image quality) [25]. The radiation exposure of a diagnostic CT of the thoracic and lumbar spine can reach 36.6 mSv [26] in comparison to 1.5 mSv for a low-dose CT with the use of a tube current modulation software [24]. The radiation exposure of a WBXR is around 1.7 mSv [24]. A low-dose CT is generally associated with the acquisition of FDG PET images and in this setting it could replace conventional WBXR for the morphological evaluation of the skeleton (Fig. 1).

MRI

MRI is an imaging procedure particularly accurate in the evaluation of bone and soft tissues diseases. Bone marrow MRI appearance depends on the relative presence of fat, cells, trabecular bone, water and protein contain. The normal BM is divided into red marrow (predominantly composed of hematopoietic cells with rich vascular supply) and yellow marrow (in which fat cells are predominant and poorly vascularised) and proportion of each compartment varies with age [27]. Trabecular bone decreases with age and is replaced by yellow marrow (BM conversion) so that in adulthood red marrow is confined to the axial skeleton, skull, ribs, sternum, pelvis and proximal femurs and humeri. Signal intensity of normal BM and myeloma lesions are detailed in the Table 2. MRI is widely employed in patients affected by MM and was included in the Durie and Salmon Plus staging system. The combination of the diagnostic accuracy afforded by current MRI units and the extensive coverage by phased-array spine coils allows the acquisition of survey studies of long segments of the axial skeleton within a reasonable time period. MR images can then be used to determine the exact location, size and local compressive effects of lesions and possible associated fractures. Furthermore, it provides excellent imaging due to its improved sensitivity over conventional radiography [28]; it accurately shows the presence of any spinal cord and/or nerve root compression and enables the recognition of soft tissue masses [29]; it can predict the risk of vertebral fracture, even though it does not help in predicting the level of fracture (the risk of vertebral collapse is sixfold to tenfold higher in patients with more than 10 FLs on MRI in comparison with those with a normal BM pattern or <10 FLs) [30]; it is the best tool for distinguishing between benign and malignant osteoporosis-induced vertebral fractures; it can accurately evaluate the percentage of vertebral height loss before percutaneous vertebroplasty or kyphoplasty [31, 32]; it allows to detect complications such as soft tissue amyloid deposits, and is the standard technique to be used in the diagnosis of avascular necrosis of the femoral head [33].

Drawbacks of MRI include a limited specificity, especially early after therapy. Persistent red marrow islands or haematopoietic red marrow that appears after chemotherapy may be falsely diagnosed as MM lesions. Regenerative red marrow (in case of recent chemotherapy or due to anaemia) may be confused with diffuse MM infiltration. In response to treatment (chemotherapy or radiotherapy), necrosis appears in MM lesion responsible for a decreased signal intensity on T1-weighted sequence and higher signal on T2-weighted images (due to increased water content). Two to three weeks later, the replacement of the lesion by fatty bone marrow induces higher signal intensity on T1-weighted images [34]. The administration of growth factors may delay the timing of fatty replacement or induce reconversion of yellow marrow to hematopoietic red marrow [34]. The presence of metallic orthopaedic hardware can be responsible for artefacts where the implant is located, although they can be minimised using specific MR sequences [35, 36]. Furthermore, the possibility to obtain a WB scan (including the axial skeleton, skull, ribs, sternum, pelvis and proximal femurs and humeri where MM lesions are frequently present) is not widely available yet and, therefore, MR is usually used for the evaluation of the spine and pelvis only. The type of MR sequence applied greatly affects the MR diagnostic power and may vary in the clinical practice from centre to centre. Multiple sequences have been proposed for identifying focal or diffuse

Table 2 MR signal intensity of normal bone marrow and MM lesions [27, 34, 93]

MR sequence	Yellow marrow SI	Red marrow SI	MM lesion SI
T1-weighted SE	>Muscle/disc[a] and =subcutaneous fat	≤Muscle/disc[a] <subcutaneous fat	≪Muscle/disc[a] and ≪subcutaneous fat
T2-weighted FSE with fat-saturation or STIR	<Muscle/disc[a]	=Or slightly >muscle/disc[a]	≫Red/yellow marrow or may be lower[b]
DWI[c]	No diffusion restriction	No diffusion restriction	Diffusion restriction
DCE-MRI	–	–	Amplitude A and exchange rate constant (kep) significantly increased[d]

SI signal intensity, *SE* spin-echo, *FSE* fast SE, *STIR* short tau inversion recovery, *DWI* diffusion-weighted imaging, *DCE-MRI* dynamic contrast-enhanced MRI

[a] When the disc is normal and not dehydrated

[b] Signal may be lower in case of osteoblastic lesions or lesions with high protein contents or with high amyloid deposits

[c] With high *b* value images (800–1200 s/mm^2)

[d] Reflecting vascular volume (A) and permeability (Kep)

disease of the BM. These sequences include spin-echo, turbo (flash) spin-echo, gradient-echo, STIR and contrast material–enhanced spin-echo (with and without fat suppression) [34, 37–40]. Contrast-enhanced studies with fat suppression can supplement these other studies with demonstrate ion of enhancement in focal or diffuse disease. At initial evaluation and FU in MM patients, MR images of the entire axial skeleton are useful. The WB diffusion-weighted MRI (WB-DW-MRI) is a relatively new imaging sequence which seems to be sensitive in the detection of both spinal and extra-spinal bone MM localisations (Fig. 1). However, this technique is not widely available yet and no sufficient results were produced in terms of therapy response assessment [41–43]. In MM, localisation of tumour spread using MR imaging closely mimics the findings in patients with spinal marrow metastasis. In general, abnormalities are identified as hypointensities on T1-weighted images, hyperintensities on STIR images and enhancement on gadolinium-enhanced images. These imaging features are not pathognomonic for MM and may also be seen in other diseases that affect the marrow. However, it is worth noting that these signal modifications can also be observed after chemotherapy and the use of growth factors or in young individuals with hyperplasia of normal haematopoiesis. Thus, the clinical context should be taken into account when evaluating MRI images, and MRI should not be performed close to chemotherapy.

By using MRI in MM it is possible to distinguish five different patterns of marrow involvement, especially at staging: (1) normal, typical of MGUS and detectable at diagnosis in 50–75 % of patients with smouldering/Durie–Salmon stage I MM; (2) focal (30 % of the patients); (3) diffuse, (nearly 80 % of patients with advanced disease or high tumour burden); (4) combined diffuse and focal (10–20 % of cases); (5) variegated or 'salt and pepper' (which reflects non-homogeneous composition of BM; 3–5 % of the patients, typically with early-stage disease) [44]. As described above, direct assessment of BMPC infiltration as afforded by MRI is possible before bone lytic lesions appear on WBXR and/or CT [23]. Several studies aiming to compare MRI of the spine and/or pelvis with WBXR clearly showed the superiority of MRI over conventional radiography in detecting osteolytic lesions [20, 28, 45]. The largest of these studies was recently reported by the Arkansas group on 611 patients homogeneously treated up-front with double ASCT [46]. MRI and WBXR were positive in 75 and 56 % of the patients, respectively. Nearly half of the patients with a negative skeletal survey had FLs on MRI (more frequently in the spine, pelvis and sternum), while in 20 % of the patients with negative MRI a WBXR survey showed the presence of osteolytic lesions, which were out of the FOV of MRI. Based on these results, a careful staging of symptomatic MM should include MRI.

FDG PET/CT

In recent years FDG PET/CT was proposed as an alternative imaging technique to evaluate patients with MM. FDG PET/CT presents some potential advantages over other radiological methods. Most important are (1) extended field of view (which generally includes skull, ribs, upper limbs, femurs, pelvis and spine), (2) absence of possible collateral effects or adverse reactions to FDG, (3) possibility to perform it even in patients with renal failure, (4) fast image acquisition time with 3D tomographs (this is important for patients with fractures, bone pain or vertebral collapses), (5) possibility to evaluate soft tissues and organs at the same time to detect EM and para-medullary disease, (6) possibility to semi-quantify the disease activity by means of SUV_{max} possibility to describe the morphological appearance of bones thanks to low-dose CT images associated with PET images and (7) no restrictions in case of metallic bone implants. Several studies have demonstrated the usefulness of FDG PET/CT in the staging of MM, with a sensitivity and specificity ranging from 80 to 100 % (Fig. 2) [47].

FDG PET/CT was proved to have a better overall sensitivity for bone lesions over the standard WBXR in staging [20], because of both a better spatial resolution and a capacity to highlight lesions before a significant lytic damage has been produced. FDG PET/CT is superior to WBXR in approximately half of the patients [20], although its sensitivity may be suboptimal for the detection of skull lesions due to the high, physiologic uptake of the tracer in the adjacent brain. This is why FDG PET/CT is suggested in patients with presumed SP before a local therapy to unequivocally exclude MM [48]. However, FDG PET/CT is generally less sensitive than MRI in staging. MRI has a higher potential in terms of optimal spatial resolution so that even very small lesions or diffuse BM infiltration may be detected. In a prospective comparison of FDG PET/CT with WBXR and MRI of the spine and pelvis in 46 newly diagnosed symptomatic MM patients, PET/CT proved superior to WBXR in 46 % of cases, with a sensitivity of 92 versus 61 %, and was able to detect myeloma lesions in areas out of the FOV of the MRI in 34 % of the patients. By contrast, the sensitivity of PET/CT in the spine was inferior to MRI, underestimating the disease in 30 % of the patients. On combining MRI and PET/CT the ability to detect sites of active MM was as high as 92 % [20]. Similar results were shown in a very recent systematic review on FDG PET/CT, which analysed 798 patients from 18 studies and compared PET/CT with WBXR and MRI; this confirmed MRI as the gold standard technique for detecting BM involvement of the spine, while PET/CT emerged as a precise technique with higher sensitivity than WBXR with regard to detecting the extent of bone lesions at the onset of

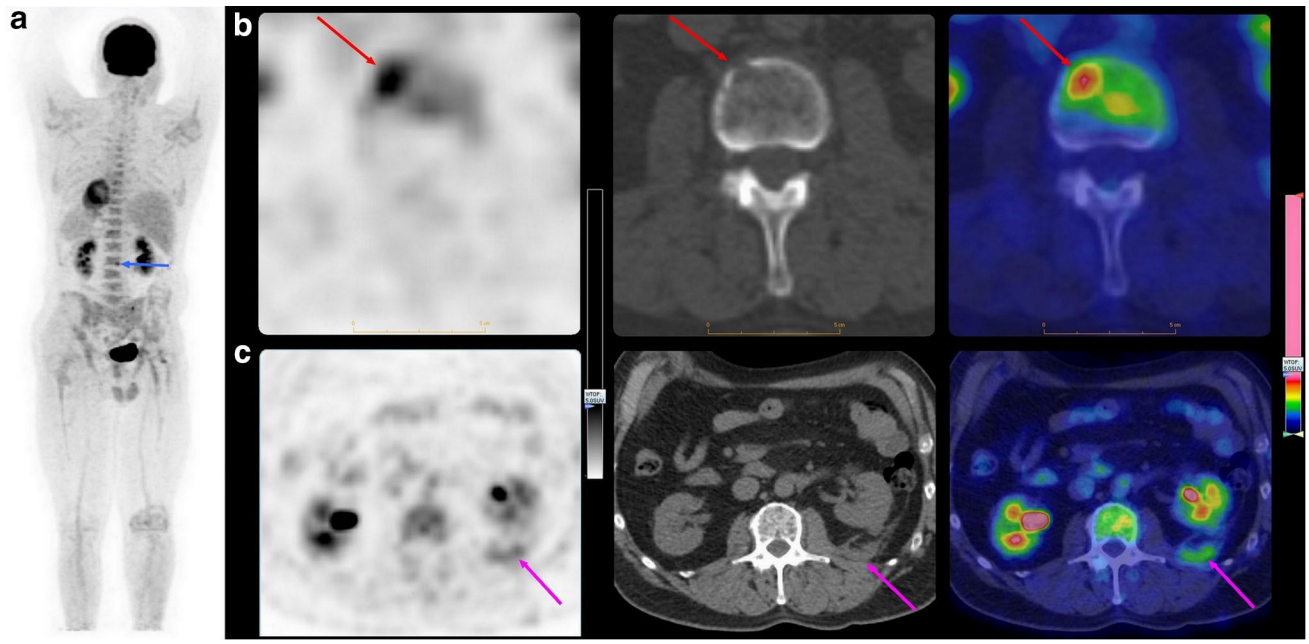

Fig. 2 Shown are FDG PET/CT images of a 67-year-old patient with MM (IgG kappa). The maximum intensity projection (**a**) shows diffuse and moderate FDG uptake in the BM; a focus of high FDG uptake can be distinguished in the right side of L2 (**a** *blue arrow*). The transverse slice centered in L2 (**b**) confirms the presence of an osteolytic lesion (approximate size: 8 mm) with high FDG uptake: SUV_{max} 5.4 (*red arrows*). Additionally, EMD was detected along the posterior sheath of the Gerota's fascia (**c** *purple arrows*). Interestingly, the WBXR of this patient did not show any MM lesion. The BM biopsy revealed BMPC infiltration of 35 % probably responsible for the diffuse FDG uptake in the BM (the complete blood count was normal, excluding a reactive pattern) (colour figure online)

the disease [47]. Finally, a recent large study by the National Oncologic PET Registry on the relative impact of PET on patients with 18 different types of known cancers showed that MM was the disease in which PET had the highest impact on management (49 % of changes of strategy) [49]. In several studies, FDG PET/CT allowed detection of occult sites of bone disease and/or soft tissue masses, not previously assessed by WBXR and MRI of the spine, in 30–50 % of patients with a suspected SP, a finding that changed the ultimate diagnosis and significantly affected therapeutic decisions [48, 50, 51]. In the end, despite WBXR being still considered the reference imaging technique, it was proved that the combination of FDG PET/CT and spine-pelvis MRI provides the highest sensitivity for staging the bone.

A possible interesting evolution of imaging in MM regards the oncoming employment of hybrid PET/MRI scanners, which will certainly allow in the future a very refined evaluation of bone in a single step exam [52]. More recent literature on the application of FDG PET/CT in MM was mainly focused on the prognostic value of PET findings in different phases of the disease. Both the groups of Zamagni and Bartel found a correlation between the overall survival (OS) and progression-free survival (PFS) [53, 54] and PET results at staging in terms of number of PET positive FLs, SUV_{max} and presence of PET positive EMD [55]. Interpretation issues may arise, especially in the case of very recent long bone fractures, vertebral collapses or recent metallic bone implants aimed to a better skeletal stabilisation. These situations cause a significant local inflammation that cannot be easily distinguished from the presence of an active disease focus. The presence of metallic prosthesis is not an absolute contraindication to the execution of a FDG PET/CT, but periprosthetic FDG uptake may be seen and artefacts on both PET and CT images may occur. Finally, due to anaemia, frequently diagnosed in patients affected by MM, diffuse FDG uptake of the reactive BM hyperplasia may mask small hypermetabolic lesions, especially if non lytic. Furthermore, it is well known that the uptake of small lesions is underestimated in PET due the partial volume effect. It is important to mention that the results of the literature showing the superiority of these latest imaging techniques such as CT, MRI and FDG PET/CT in the detection of bone FLs are often limited by the absence of histological gold standard. Indeed, it is not possible to systematically obtain a biopsy and histological confirmation of all detected lesions. Therefore, caution is needed when interpreting imaging studies.

Imaging and biological markers as a prognostic tool

Although MM remains a fatal disease, the introduction of ASCT in the 80s and the use of therapeutics such as immunomodulatory drugs (thalidomide and lenalidomide) and the proteasome inhibitor bortezomib considerably prolonged patient survival [9]. Nonetheless, survival remains dictated by multiple risk factors related to the patient (i.e., age, kidney function, performance status), to tumour characteristics such as the presence of genetic aberration and tumour gene expression profile (GEP) and to tumour burden reflected by the ISS and level of LDH [56–58]. Researchers introduced risk stratification models based on ISS and/or cytogenetic markers to identify patients with high risk (i.e., ISS stage II/III and t(4;14) or 17p13 deletion), standard risk (i.e., ISS I and t(4;14) as its risk can be modulated by bortezomib) or low-risk (i.e., age <55 year and ISS stage I/II without genetic abnormality) [56]. High-risk patients have a median OS of 2–3 years compared with 6–7 years for standard-risk patients [59]. Risk stratification and eligibility to ASCT, therefore, determine therapeutic choices [56, 59].

Accurate imaging of MM using FDG PET/CT and/or MRI may provide additional information on tumour burden, tumour aggressiveness and intra-individual MM lesions heterogeneity. The main imaging high-risk features are presented in Table 3. The number of FLs detected with MRI or FDG PET (/CT) is associated with shorter survival [46, 53]. Patients with EMD or FDG avid MM lesions ($SUV_{max} > 4.2$) have shorter OS [53, 55, 60]. Authors showed that higher metabolic tumour volume (MTV) was associated with a worse OS and PFS of patients with newly diagnosed MM [61]. The BM FDG SUV_{max} correlates with the percentage of BMPC infiltration [62]. The number of FLs and the prevalence of EMD detected with MRI and/or FDG PET (/CT) is higher in patients with high-risk GEP (i.e., GEP-70) or cytogenetic abnormalities reflecting disease aggressiveness [60, 63]. The combination of ISS stage III, high-risk cytogenetics and diffuse BM infiltration seen with MRI is able to identify patients with worse prognosis and a 3-year OS probability of 35 % [64].

Risk stratification according to cytogenetic analyses usually performed in unilateral BM aspirate and/or in a single-lesion biopsy may disregard tumour intra-individual heterogeneity of biological features. In this regard, FDG PET/CT enables visualisation of tumour heterogeneity in vivo (Fig. 3) as opposed to a unique biopsy.

Prediction of monoclonal PC disorders progression to MM

Generally, the sFLC has prognostic value in MGUS, sMM, active MM and SP [65]. Additional predictive factors of progression to active myeloma are under investigation.

MGUS precedes MM in all patients with variable risk of progression (5–58 %) to MM according to laboratory risk factors (serum M-protein $\geq$ 1.5 g/dL, the size of the M-spike > 15 g/L, a non-IgG heavy chain and an abnormal sFLC ratio) [66, 67]. By definition, there is no bone lesion in MGUS; however, Vande Berg et al. [68] demonstrated the presence of BM abnormalities with MRI in 19 % ($n = 7/37$) of patients with MGUS; a treatment had to be initiated in 4/7 MRI-positive patients while none of the MRI-negative patients required treatment after a median FU of 31 months. A group performed FDG PET in 14 patients with MGUS and all had no related lesion [69]. Recently, a group investigated the prognostic significance of WB MRI in 137 patients with MGUS consecutively included [70]. The univariate analysis showed that the risk factors of progression to symptomatic disease were a M-protein >15 g/L (HR 13.51; 95 % CI 3.63–50.31), the presence of FLs with MRI (HR 4.34; 95 % CI 1.23–15.33) and a number of MRI FL >1 (HR 1.09; 95 % CI 1.07–1.12) [70]. However, the early detection of FL and its implication in treatment decision and prognosis remain to be defined. Therefore, WBXR remains the gold standard in the initial workup of patients with MGUS.

The risk of progression of sMM to MM is higher than MGUS; it decreases with time with the highest risk (10 % per year) in the first 5 years from diagnosis. Risk factors predict disease progression to MM: tumour burden (FLC assay, BM plasmocytosis and serum M-protein level), the presence of genetic aberration such as del(17p13), t(4;14), +1q21 or hyperdiploïdy and GEP risk score [71–76]. Interestingly, those patients with sMM and absence of risk factors have similar outcome as the one with MGUS [76]. The presence and number (>1) of FL and the presence of diffuse BM infiltration with MRI are risk factors for progression to symptomatic MM [77]. Researchers explored the predictive value of consecutive WB-MRI in 63 patients with sMM; the risk of developing MM was higher in patients with $\geq$2 FLs at initial WB-MRI (HR 6.6; 95 % IC 2.29–19); progressive disease in sub-sequent WB-MRI was an independent predictor of progression into MM in the presence of M-protein $\geq$20 g/L (HR 14.1; 95 % IC 5.06–39.3) or aberrant PC/BMPC $\geq$95 % (HR 10.4; 95 % IC 2.57–42) [75]. Two other groups showed that the presence of abnormality ($\geq$1 FL or diffuse BM infiltration) with MRI of the spine was associated with a higher risk of

Table 3 MM high-risk imaging features at diagnosis

Modality (field of view)	Imaging feature	Study design, population	Treatment	OS HR (95 % CI)*	PFS (95 % CI)*
MRI (thoracic and lumbar spine and pelvis)	Diffuse BM involvement	Not specified, 228 consecutive patients with MM at diagnosis [64]	Conventional chemotherapy (27 %) or regimens with thalidomide (33 %), bortezomib (27 %) or lenalidomide (13 %)	2.6 (1.0–6.4)[a]	N/A
MRI (thoracic and lumbar spine)	Diffuse/variegated pattern BM involvement	Retrospective, 126 MM patients eligible for ASCT [94]	Induction regimen (VAD or TCD), conditioning regimen (melphalan), ASCT and thalidomide maintenance therapy	NS	1.92 (1.18–3.12)
MRI (axial BM)	>7 FLs	Prospective, 668 newly diagnosed patients with progressive or symptomatic MM [46]	Two cycles of intensive melphalan-based chemotherapy, each supported by melphalan-based chemotherapy, ASCT and thalidomide ($N = 323$) or not ($N = 345$)	1.89 (1.30–2.75)	N/A
FDG PET/CT (from vertex to toes)	>3 FLs	Prospective, 303 symptomatic MM [53]	Induction chemotherapy (VTD-PACE), melphalan-based tandem transplantation, consolidation (VTD-PACE) and maintenance (VTD and thalidomide/dexamethasone)	2.45 (1.30–4.62)	N/A
FDG PET/CT (from vertex to toes)	Presence of EMD	Prospective, 303 symptomatic MM [53]	Induction chemotherapy (VTD-PACE), melphalan-based tandem transplantation, consolidation (VTD-PACE) and maintenance VTD and TD	3.13 (1.34–7.31)[b]	N/A
FDG PET/CT (WB including skull, superior limbs and femurs)	Presence of EMD	Prospective, 192 patients with untreated symptomatic MM [55]	TD incorporated into double ASCT	9.75 (3.44–27.65)	5.28 (1.43–19.5)
FDG PET/CT (WB including skull, superior limbs and femurs)	SUV_{max} >4.2	Prospective, 192 patients with untreated symptomatic MM [55]	TD incorporated into double ASCT	3.23 (1.35–7.72)	2.13 (1.10–4.12)

N/A not available, *NS* not significant, *VAD* vincristine, doxorubicin, dexamethasone, *TCD* thalidomide-based regimen, *VTD-PACE* bortezomib, thalidomide, and dexamethasone and 4-day continuous infusions of cisplatin, doxorubicin, cyclophosphamide, and etoposide, *TD* thalidomide/dexamethasone

* Statistically significant ($p < 0.05$) based on multivariate analyses

[a] Not significant anymore alone when taking into account cytogenetic risk factors

[b] Only when gene array data were not included

progression to MM [74, 76]. The Mayo Clinic investigators suggested considering sMM with high-risk factors (including imaging) of progression as active MM for which treatment initiation could be beneficial [2]. The IMWG recommends MRI in the initial assessment of sMM (or FDG PET/CT or CT depending on availability) [1].

No data are available on FDG PET/CT imaging in patients with sMM. On the other side, the utility of FDG PET/CT in patients with SP has been much investigated. The detection of additional lesions with FDG PET/CT or MRI occurs in approximatively one-third of patients with SP [48, 78–81]. Additionally, the presence of ≥2 FLs in patient with SP detected with FDG PET/CT was independently associated with shorter median time to MM progression (OR 5; 95 % CI 0–9) as well as initial abnormal sFLC [78]. MRI is, therefore, mandatory in the initial workup of SP (or FDG PET/CT or CT depending on availability) [1].

Imaging to predict MM treatment response

The IMWG proposed international uniform response criteria (IURC) for MM to assess treatment efficacy of latest treatment strategies [82]. These criteria incorporated FLC assay and defined new categories of response such as stringent complete response (sCR: normal FLC assay, no monoclonal BMPC) and very good partial response

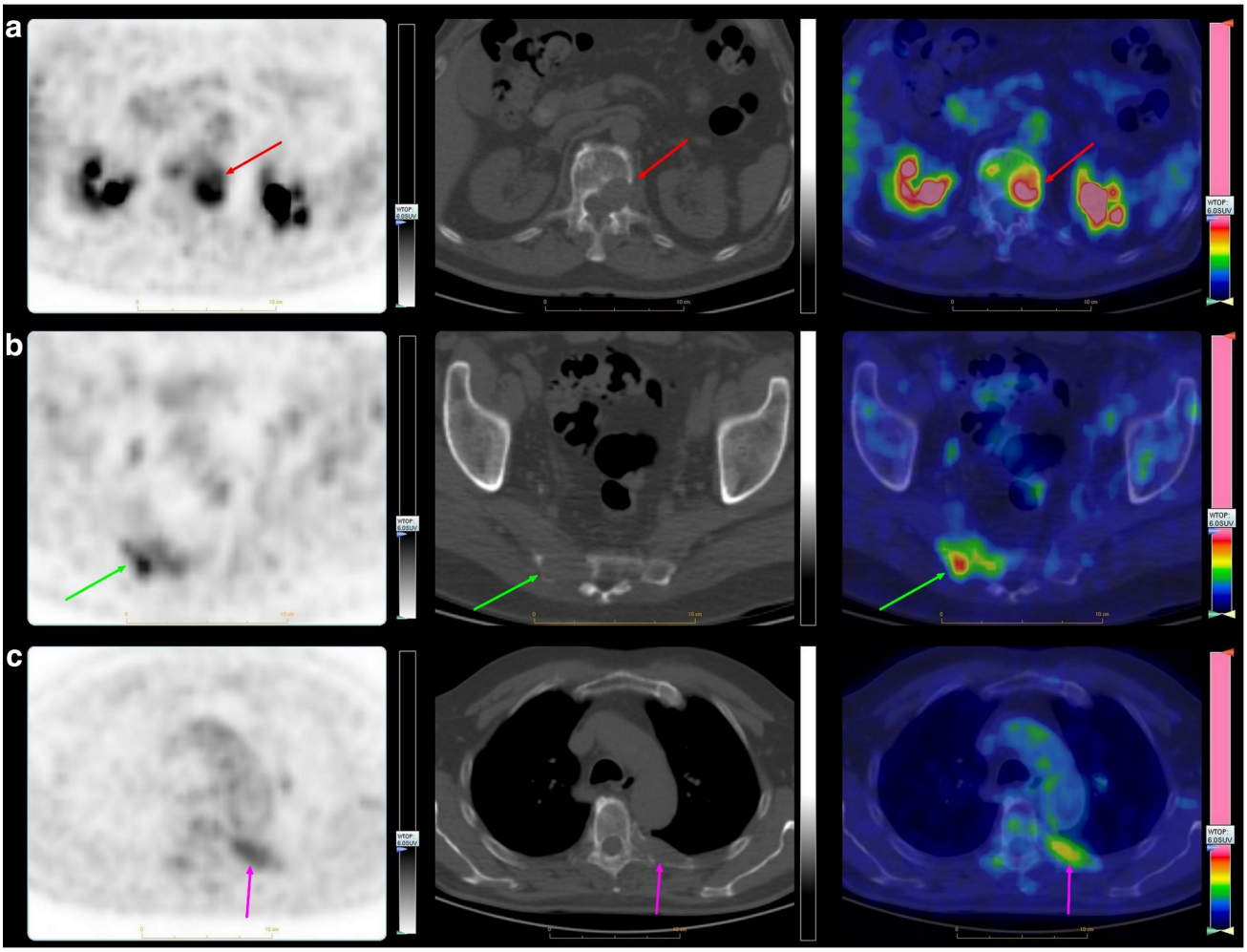

Fig. 3 These FDG PET/CT images of a 76-year-old patient with MM illustrate the heterogeneity of FDG avidity in distinct MM lesions (intra-individual heterogeneity) as well as inside a single lesion (intra-lesion heterogeneity). The osteolytic lesion of the *left* pedicle of L1 (**a** *red arrows*) shows high FDG uptake (SUV_{max} 7.6); the FL of the sacrum (**b** *green arrows*) shows an heterogeneous FDG uptake (SUV_{max} 5.8; SUV_{mean} 3.5 and SUV standard deviation in a 60 % threshold MTV: 0.62) and a FL of the *left* 5th rib (**c** *purple arrows*) with less intense FDG uptake (SUV_{max} 3.9) (colour figure online)

(VGPR: serum and urine M-protein detectable by immunofixation but not on electrophoresis or $\geq$ 90 % reduction in serum M-protein plus urine M-protein level $<$ 100 mg per 24 h). The introduction of FLC in the criteria also allows treatment assessment of oligo-secretory or non-secretory diseases. MRI and/or FDG PET/CT imaging may be considered in a small subset of patients when neither M-protein nor FLC are measurable.

WBXR and CT are not reliable techniques to assess treatment efficacy because their sensitivity to detect lesions is limited and persistence of viable tumour cells cannot be estimated. A study recently showed that the presence of lesion sclerosis on low-dose MDCT images after bortezomib regimen treatment was not a predictor for sustained response to treatment [83]. MRI and/or FDG PET/CT are investigated for the identification of patients with long-term response and those with high-risk of early relapse. At diagnosis, MRI is a highly sensitive technique for the detection of BM lesions; in contrast, the performance of MRI to assess treatment response is limited. The change of signal intensity of lesions or medullar infiltration after therapy results from the appearance of early necrosis and oedema and the subsequent reappearance of fat resulting in the normalisation of the MR signal may take several months [84]. Walker et al. showed that patients with >7 FL at baseline axial MRI had the slowest onset of MRI complete response (MRI-CR: achievement of a hypointense homogenous background signal on STIR images and resolution of FL) and the lowest frequency of MRI-CR compared with those who had no FL or $\leq$7 FL [46]; MRI response did not predict outcome and a significant proportion of patients with MRI-CR had no clinical CR at 48 months of FU [46]. Bannas et al. [85] retrospectively compared MRI response to haematological parameters and found that WB-MRI

Table 4 Imaging guidelines according to the consensus recommendations of the IMWG and/or NCCN guidelines

Monoclonal plasma cell disorder		WBXR	MRI[a]	MDCT[b]	FDG PET/CT[b]
sMM	Staging	Recommended	Recommended	Consider if available	Not recommended (role to define)
	FU	Recommended annually or if symptomatic	Recommended if symptoms and negative WBXR	Consider if available	Not recommended
SP	Staging	Recommended	Mandatory in all patients	Consider if available	Useful in patients with suspected EM plasmacytoma
	FU	Recommended annually or if symptomatic	Recommended if symptoms and negative WBXR	Consider if available	Not recommended (role to define)
MM	Staging	Recommended	Can be considered as routine evaluation; strongly indicated in non-secretory MM, indicated if suspicion of spinal cord compression	Consider if available; indicated if soft-tissue lesion	Helpful for detection of EMD and evaluation of rib and appendicular bone lesions and in patients with elevated LDH
	Treatment response assessment	Not required for assessment of response unless clinically indicated. Indicated for restaging in case of progression	Strongly indicated in non-secretory MM; recommended to monitor soft-tissue mass (or CT); recommended if newly symptomatic area and negative WBXR	Recommended to monitor soft-tissue mass (or MRI); consider if available	Useful in patients with Bence Jones protein escape, and otherwise rapidly recurrent disease
	FU	Recommended once a year	Should be considered if symptomatic and negative WBXR	Consider if available	Not recommended

[a] WB MRI if available or MRI of the spine and pelvis; MRI of another anatomic region if specific symptoms (i.e., for the exclusion of spinal cord compression or a soft-tissue mass)

[b] The use of WB MDCT obviates the need of WBXR

misclassified 7/33 patients (21.2 %). Hillengass et al. [86] also found a weak agreement (kappa coefficient < 0.30) between WB-MRI response and IURC; MRI tended to overestimate the response of diffuse BM infiltration while it underestimated FL response; however, they found that the number of FL after treatment correlated with OS (57–64 % OS in patients with >10 FL compared to 91–100 % in patients with ≤10 FL). Authors demonstrated the feasibility of DW-MRI and dynamic contrast-enhanced MRI for treatment assessment of MM [43, 87–89]. Response assessment using WB-DW-MRI was recently prospectively investigated; MRI misclassified 4/26 patients (15 %) and failed to identify one responder and three non responders according to IURC; they reported a false non-response of a patient who had received G-CSF and pointed the limitation of ADC determination in patients with low tumour burden [43].

In that purpose of treatment assessment, PET/CT imaging seems more promising as it can show viable tumour cell activity. Zamagni et al. [55] demonstrated in a prospective study that persistent FDG uptake ($SUV_{max} > 4.2$) after induction treatment or incomplete FDG suppression at 3 months after ASCT was predictor of worse 4-year PFS and OS.

Current recommendations for the use of PET and MRI

Table 4 summarises the imaging techniques recommended in the different sub-groups of PC disorders for staging and FU according to the consensus recommendations of the IMWG [1, 18, 90]. The role of FDG PET/CT in the staging of patients with sMM, SP and MM remains to define [90]; FDG PET/CT may be considered in patients with metallic foreign bodies that contraindicates MRI. Though, NCCN guidelines recommend MRI and/or CT and/or FDG PET/CT as clinically indicated in patients with SP and sMM [65]. Due the higher sensitivity of CT to detect bone lesions compared with WBXR, CT (without contrast) can replace WBXR [83, 91]. It seems reasonable to suggest the use of MRI or FDG PET/CT if WBXR fails to show bone lesions in a patient with symptoms [65].

Future perspective

Advances in the knowledge of MM at a molecular level reveal that MM as many tumours is characterised by both intra- and inter-tumour heterogeneity [92]. Imaging, especially PET/CT using FDG or novel radiopharmaceuticals targeting other biological processes, may identify tumour heterogeneity. The consideration of tumour heterogeneity in future trials and risk stratification of patients according to risk-models combining genetic, molecular, biological biomarkers together with imaging will probably have an impact on treatment individualised strategies and outcome. These models may help sparing the treatment-related toxicity in patients with favourable outcome while identifying patients with poor prognosis to intensify treatment and extend their survival. Nevertheless, the subsequent implementation of these risk-models into the clinics will require easy and rapid access to all these data.

Conclusion

MRI of spine and pelvis is mandatory for patients with SP as additional bone lesions can be detected in one-third of cases. Due to its higher sensitivity (compared with WBXR) to detect bone lesions, MRI is also recommended in patients with sMM and may be considered for the staging of MM. Additionally, the imaging of MM and related PC disorders using MRI and/or FDG PET/CT may reflect tumour burden and aggressiveness and might provide additional information on tumour heterogeneity. Nonetheless, inclusion of MRI and FDG PET/CT for MM patient stratification and therapeutic decisions remains to define.

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