

Nuclear medicine in multiple myeloma — more than diagnosis

Giuseppe Lucio Cascini¹, Vincenzo Cuccurullo²,
Oscar Tamburrini¹, Luigi Mansi², Antonio Rotondo³

¹Department of Radiological Sciences, University of Catanzaro,
Catanzaro, Italy

²Nuclear Medicine Division, Second University of Naples, Naples, Italy

³Department of Radiological Sciences, Second University of Naples,
Naples, Italy

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Abstract

Multiple myeloma (MM) is a neoplastic monoclonal proliferation of plasma cells, mainly involving bone marrow. To properly stage and manage patients with MM the clinician needs, at first, a complete skeletal survey, being more rarely present also extra skeletal locations. Today none of the available diagnostic imaging methods is able alone to answer to all the questions regarding staging, treatment, and follow up. Continuing to be alive the role of traditional radiology, implemented information can be added by CT and MRI. Concerning nuclear medicine, bone scintigraphy is affected by its low sensitivity. Tc-99m MIBI has been proposed in staging and in follow up, with most relevant clinical information deriving from the correlation of its whole body uptake's distribution with extent and activity of the disease. The prognostic value of MIBI has also been demonstrated. PET-FDG has been proposed in MM for its ability to detect whole-body metabolic active disease, giving relevant information in staging and prognosis. First studies have demonstrated that PET-FDG is more sensitive than other imaging modalities for localizing extra medullary sites of disease.

Key words: myeloma, diagnostic imaging, nuclear medicine, Tc-99m MIBI, PET-FDG

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Correspondence to: Vincenzo Cuccurullo
Medicina Nucleare
Seconda Università di Napoli
P.zza Miraglia, 2–80138 Napoli
e-mail: vincenzo.cuccurullo@unina2.it

Introduction

Multiple myeloma (MM) is a neoplastic monoclonal proliferation of plasma cells within the bone marrow, which accounts for 1% of all malignant disease and 10% of haematological malignancies. It typically affects elderly patients with median age of presentation around 70 years; fewer than 2% of patients are under 40 years of age [1]. Monoclonal gammopathy of undetermined significance (MGUS; a premalignant disorder in which a clone of plasma cells produces a monoclonal paraprotein that does not cause end-organ damage) is present in 2% of persons older than 50 years, and the risk of progressing to multiple myeloma is 1% each year [2].

The clinical presentation of MM is variable, and up to 20% of cases are asymptomatic and may be found incidentally [3]. Fatigue, anaemia, recurrent infection due to bone marrow invasion, bone pain, pathological fractures, and renal failure are relatively common. An incidental discovery on comprehensive laboratory panels is also frequent. Less often, acute hypercalcaemia, symptomatic hyper viscosity, neuropathy, spinal cord compression, amyloidosis, and coagulopathy are seen at presentation. In the majority of patients the disease is characterized by plasma cell infiltration in the bone marrow, osteolytic bone lesions, and the presence of a monoclonal protein in the serum and/or in urine. In 5% of cases, a solitary skeletal lesion without bone marrow involvement (solitary plasmacytoma) is present. Myeloma may also affect extra medullary and extra osseous sites, most commonly the nasopharynx, larynx, and upper respiratory tract. Less common sites include the gastrointestinal tract, pleura, testis, skin, peritoneum, liver, endocrine glands, and lymph nodes. The disease is diagnosed with serum or urine protein electrophoresis or by immunofixation and bone marrow aspirate analysis.

Although myeloma may affect different tissues and organs, the bone compartment, both in terms of incidence and clinical impact, is the leader in clinical scenarios. Irrespective of initial skeletal involvement at diagnosis, up to 90% of patients develop osteolytic lesions during the course of the disease. The main mechanism for bone destruction is the increased osteoclastic bone reabsorption unbalanced by a reduced osteoblastic activity. Lesions can involve all bones, but typically occur in the axial skeleton, as well as in the proximal areas of arms and legs [4].

In fact to properly stage and manage patients with MM the clinician needs a complete skeletal survey. Using standard X-ray,

detection of a lytic lesion may be difficult due to the coexistence of other bone degenerative alterations like osteopaenia or osteoporosis, affecting more than 10% of patients; these conditions may already be present at diagnosis, but can also be frequently induced by treatment, reducing the diagnostic accuracy of standard radiological procedures. Likewise the detection of a skeletal lesion should not be directly assigned to an active myelomatous erosion, because lesions rarely “radiologically” heal, even when the patient is in complete remission.

For all these reasons, the appropriate use of imaging techniques other than standard X-ray alone is pivotal to identify and characterize skeletal alterations in MM. The optimal imaging method should be able to:

- cover the whole skeleton;
- recognize bone marrow infiltration and not only bone erosion;
- detect and predict skeletal complications;
- diagnose extramedullary foci of disease;
- estimate treatment efficacy during and after therapy;
- stratify the prognosis, differentiating high from low risk MM patients [5].

To date, none of the different morphological and functional imaging methods is able to address alone all of these issues, and we lack a consensual and standardized imaging protocol for newly diagnosed myeloma patients or for following patients in the course of treatment and disease progression [6].

In this review, after a brief description of the contribution deriving from radiological procedures and traditional radionuclide techniques, we will mainly analyze the possible role of Positron Emission Tomography (PET) with F-18 fluorodeoxyglucose (FDG) in patients with MM.

Morphological imaging

Plain X-ray

Complete skeletal X-ray evaluation has been for many years the cornerstone of the staging system, as published by Durie and Salmon in 1975 [7]. At present, the role of traditional radiology continues to be alive, mainly in differentiating subjects with normal bone or single plasmacytoma (stage 1) from those with “advanced lytic bone lesions” (stage 3). Conversely, many studies have shown that a whole body radiographic survey, used alone as staging procedure, significantly underestimates skeletal and bone marrow involvement [8]. The main limitations are dependent on the late detection of bone erosion, determining as a consequence an under staging. In fact, using standard X-ray, the presence of osteolytic lesions can only be detected when bone decalcification rises to at least 70% [9].

Moreover, radiography is affected by major problems when evaluating MM patients in follow up. In particular, using standard X-ray, no differential diagnosis can be achieved between active and non-active osteolytic lesions when monitoring treatment response [10].

Computed tomography (CT)

Computed tomography (CT) allows the detection of small osteolytic lesions in MM, even when undetectable by plain radiography [11]. CT scanning alone is more sensitive than plain radiography, particularly in finding lesions in small, long bones; moreover,

CT can differentiate benign from malignant fractures determined by vertebral compression in patients who are not candidates for magnetic resonance imaging (MRI). Further advantages of CT lie in its capability to evaluate soft tissue involvement and to guide needle biopsy for histological diagnosis [12].

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) is a first-line procedure when spinal compression or soft-tissue plasmacytoma are suspected [13]. Allowing visualization of the medullary cavity, MRI can help in evaluating the presence and the extent of cord or nerve root compression. Therefore, the integration of MRI findings into the Durie and Salmon staging system (PLUS classification) allows more precise and reliable staging of patients with multiple myeloma [14]. Bone lesions have been shown by MRI in about 50% of asymptomatic myeloma patients with normal plain radiographs [15].

Dual energy X-ray absorptiometry (DEXA)

Dual energy X-ray absorptiometry (DEXA) has no role in diagnosing multiple myeloma [16].

Radionuclide imaging

The MM classification system includes biochemical parameters of disease activity and the evaluation of bone lesions. At presentation, diagnostic imaging plays an important role in establishing the extent of disease to permit an accurate staging [17].

In this scenario, radio compounds such as gallium-67 citrate and ^{99m}Tc-diphosphonate have been proposed [18] without finding a significant clinical role.

Bone scintigraphy

Bone scintigraphy has a high sensitivity in the detection of bone metastases from solid tumours, but its value in MM and solitary plasmacytoma is very low. In fact, due to the high bone reabsorption in the presence of reduced and/or absent osteoblastic activity, determining osteolytic lesions, bone scintigraphy presents a lower sensitivity than conventional radiographs in myeloma. Moreover, skeletal trauma, degenerative diseases, and many other benign disorders of bones and joints may produce false-positive results. As a consequence, bone scintigraphy may detect lytic lesions in 35–60% of MM patients, but its specificity and sensitivity at the time of initial diagnosis, in follow-up studies and in the evaluation of bone pain, is lower compared to conventional radiography [19]. The inferiority of bone scintigraphy is primarily due to the osteoblastic dysfunction present in myeloma, being skeletal uptake of ^{99m}Tc-diphosphonates dependent on osteoblastic activity. As a consequence, bone scintigraphy is frequently normal in myeloma, the presence of areas of decreased uptake also being possible, representing bone destruction and replacement by myeloma cells, without a significant osteoblastic reaction.

In whole skeletal evaluations in myeloma patients, the skull, extremities, iliac, and pubic bones are better assessed by plain radiography, whereas bone scintigraphy can increase sensitivity in detecting new vertebral lesions or lesions in the ribs and sternum [20].

Therefore, despite its low sensitivity, on the basis of possible favourable mismatches with respect to X-ray, bone scintigraphy has been proposed in evaluating areas of the skeleton "mute" on plain radiography, such as the ribs and sternum.

^{99m}Tc-sestamibi (MIBI)

^{99m}Tc-labeled hexakis-2-methoxyisobutylisonitrile (^{99m}Tc-sestamibi, MIBI) is a lipophilic cationic gamma-emitting radiopharmaceutical originally introduced and widely used as a myocardial perfusion imaging tracer. Because of its biochemical characteristics, which favour accumulation in tissues with high cellularity in the presence of a mitochondrial activation, MIBI may be concentrated in a variety of malignant tumours such as sarcomas, breast, brain, lung, and thyroid cancers [21–23]. The capacity of MIBI to concentrate in multiple myeloma cells has been under investigation since 1996 [24]; the results, showing high sensitivity and specificity, led to clinical interest in its role in diagnosis and in follow-up of MM patients [25].

The most important information achievable by MIBI imaging in myeloma derives from the correlation of its whole body uptake distribution with the extent of the disease; these data have been positively correlated with other parameters of disease activity, such as lactate dehydrogenase, C-reactive protein, and β_2 microglobulin [26].

In 1998 Pace et al. studied whole body MIBI distribution in patients with MM; the incidence of various patterns of focal and/or diffuse MIBI uptake was evaluated to assess their relationship with clinical status and stage of disease. The scans were classified as follows:

1. Pattern N (normal), when only physiological uptake was present.
2. Pattern D (diffuse), when diffuse bone marrow uptake was observed.
3. Pattern F (focal), when areas of focal uptake were evident.
4. Pattern D+F, when both D and F distributions were observed.

Both extension and intensity of diffuse bone marrow uptake correlated with the amount of the monoclonal component and the percentage of bone marrow plasma cells. The distribution of the MIBI uptake patterns differed among patients in different stages of disease. Using as criteria for advanced stage the presence of either focal uptake (pattern F or D+F) or pattern D with a high score, a high diagnostic accuracy was obtained. In particular, MIBI showed a positive predictive value of 100% and a negative predictive value of 83%, in the diagnosis of active multiple myeloma, being 84% the positive predictive value and 100% the negative predictive value in identifying advanced stages (i.e. II or III) of disease [27].

In 2002 Alexandrakis et al. assessed the correlation between MIBI uptake and prognostic factors in newly diagnosed MM patients. In particular, serum marker values reflecting disease activity and bone metabolism were compared with the distribution and intensity of MIBI's uptake. In the study conclusion, patients who presented with extensive disease activity, as evaluated by high levels of CRP, b2M, IL-6, and sIL-6r, also showed a higher uptake of the radiotracer [28].

Erten et al. compared MIBI with MRI, skeletal X-ray survey, and biochemical markers of disease activity in MM. They found no significant differences between MIBI scan and MRI in predicting

the extension of bone marrow infiltration, while MIBI was superior in defining disease activity with respect to skeletal X-ray survey [29].

An Italian multicentre study evaluated the additional benefit of MIBI with respect to standard X-ray in MM patients either at diagnosis or during follow-up. In 229 MIBI scans performed at diagnosis, 146 (64%) were positive while X-ray was only positive in 97 cases (45%). In 81 patients, discordant results between X-ray and MIBI were observed. Sensitivity of MIBI and X-ray were 77% and 45%, respectively. Among 168 scans performed during follow-up, MIBI scans presented a higher specificity in patients showing a complete response (86%) and correlated with myeloma activity and with response to therapy [30].

In two other papers Pace et al. (2001, 2005) investigated the prognostic impact of MIBI in MM patients. The first study [31] evaluated 30 MM patients who had undergone two MIBI studies at least 2 months apart. The patients received chemotherapy in the interval between the two scans. A significant association was observed between the baseline scintigraphic pattern and clinical status at follow-up. A negative baseline MIBI scintigram showed high predictive accuracy (100%) for remission, while the presence of pattern F or F+D was often associated with a less favourable outcome. In the second study, disease restaging was performed at a mean time of 32 ± 20 months. Patients showing disease progression at restaging had higher MIBI washout, calculated comparing two scans acquired at 10 and 60 minutes after injection, than patients in remission. Disease-free survival was significantly better in patients with lower MIBI washout. No differences in therapeutic regimen and stage of disease at admission were found between the two groups [32].

In 2001 Fonti et al., studying the in vitro uptake of MIBI by myeloma cells, demonstrated a close correlation between the amount of tracer uptake and the bone marrow plasma cell infiltration ratio in patients. The conclusion was that MIBI scan reveals the presence of infiltrating myeloma cells rather than its consequence, the bone's destruction [33]. It means that MIBI could occupy an original and/or integrative position in the diagnostic tree of patients with MM. Interesting perspectives, not yet clinically validated, are connected with SPECT-CT, allowing the integration between data on bone lesion, as defined by CT, and myeloma infiltration, as shown by MIBI.

Somatostatin receptor scintigraphy

Somatostatin receptor scintigraphy (SRS) using ¹¹¹In-pentetreotide (OCT) is widely used, mainly for the detection of neuroendocrine tumours, having also been proposed in patients with aggressive malignant lymphoma, especially to define the extent of the disease. In vitro studies with plasma cell lines have shown that somatostatin receptors are expressed on malignant plasma cells. In particular, it has been shown that subtypes sst2, sst3, and, predominantly, sst5 were present and that in vitro growth of myeloma cells can be inhibited by somatostatin or its analogue octreotide.

In a recent paper, Agool et al. performed SRS in 29 MM patients. A positive SRS was demonstrated in 44% of the newly diagnosed patients and in 83% of the relapsed patients. The SRS findings were in agreement with radiographic abnormalities in 40% of the subjects. Among the relapsed patients 60% also demonstrated increased OCT uptake in areas normal at X-ray. The

positive SRS corresponded to lesions with histologically proven active disease, and responded upon treatment [34].

Positron emission tomography

The “gold standard” for myeloma imaging has for a long time been complete skeletal X-ray evaluation, although plain radiography in MM lacks efficacy in the early detection of bone erosion. Indeed, a recent revision, the Durie/Salmon Plus staging system, takes into account imaging with magnetic resonance imaging (MRI) and/or positron-emission tomography (PET) with 2-[18F]-fluoro-2-deoxy-D-glucose (FDG) to discriminate single solitary lesion from diffuse disease, which is staged on the basis of the number of detectable lesions [14].

This new approach is not yet stated in clinical practice, being different from the standard clinical staging system utilized at present; although, it represents the first strong evidence of the primary diagnostic value of FDG-PET and MRI in patients with MM. The availability of hybrid machines further stimulates the possible clinical contribution of PET-CT, because of the complementary information achievable by FDG and CT, allowing a higher accuracy.

For these reasons we would like hereby to analyse main issues concerning the use of PET-FDG, as a premise to the possibility of finding a position in the clinical tree, answering to the main questions in patients with MM.

PET-FDG in staging

In agreement with the favourable results obtained in the majority of tumours, PET-FDG has also been proposed in patients with MM for its proficiency in detecting metabolic active disease with complete coverage of the patient's body, in a reasonable time, using a single technique acquisition.

The first reported case of a positive FDG-PET in MM was published by El-Shirbiny et al., who noted a mismatch between FDG and MIBI; in this case, PET showed a focal intense uptake of FDG whereas a diffuse pattern was seen on MIBI images, also in areas where PET was negative. This case demonstrates that MM patients can take up FDG with a higher intensity in more active lesions, with a possible role in differentiating rapidly growing lesions from slower ones [35].

One of the first systematic studies on the role of FDG-PET in MM was reported by Schirrmeyer in a series of 43 patients with solitary plasmocytoma and MM. True positive results were obtained in 92.7% of the radiographically documented osteolytic lesions; moreover, PET-FDG documented a greater extent of disease with respect to X-ray in more than 60% of patients with bone lesions [36].

In the initial experience, starting from previous data obtained with MIBI, attention was paid to the possibility of individuating different distribution patterns; the goal was to have the capability to better differentiate, using FDG, patients showing a different prognosis. Foremost interest was devoted to the analysis of subjects showing focal uptake or a mixed pattern, including focal and diffuse disease.

All patients showing a focal or a mixed focal/diffuse FDG pattern had active disease, as demonstrated by increased haematic paraprotein levels and/or by high myeloma cell counts at bone marrow biopsy. False positive results may occur after treatment,

because of the effect of chemotherapy on bone marrow cells. In fact, a homogeneous diffuse FDG bone marrow uptake is often observed in patients during or after chemotherapy; a similar behaviour determining false positive results can also be observed in the presence of infectious disease, when present in patients with myeloma. The article of Schirrmeyer focused attention on the positive predictive value (PPV) of 100% in patients with at least one focal “hot” lesion, decreasing PPV to 75% in patients with diffuse bone marrow uptake. Starting from these data, the authors concluded that focal uptake is a reliable sign of active disease, whereas a diffuse FDG uptake cannot be conclusive for disease persistence.

The advent of fusion images obtained with hybrid machines, combining both PET and CT, addresses the issue of limited spatial resolution. In PET-CT scanning, the patient receives an injection of FDG about an hour before image acquisition. After the patient is positioned on the scanner bed, an initial topogram is acquired to define the examination range for the PET-CT image acquisition. However, the acquisition range should be as large as possible to avoid repositioning. Finally, patients should be positioned with the arms down to allow a complete exploration of bone marrow and to increase patient comfort.

The PET-CT system represents a major improvement in terms of diagnostic accuracy in MM patients; a higher clinical advantage is obtained in the presence of lesions showing moderate or poor FDG uptake; in general the definition of focal disease is considered reliable for SUV higher than 2.5; using PET-CT it can be attributed also to osteolytic lesions with mild uptake, slightly higher with respect to surrounding tissues. For lesions smaller than 5mm in diameter, it has also been suggested that any lesion showing FDG uptake should be considered positive regardless of SUV. However, SUV higher than 2.5 strongly support the presence of an MM active lesion.

In a recent paper, Fonti et al. compared whole-body FDG PET-CT with whole-body MIBI scan and MRI of the spine and pelvis. In this study, analysing thirty-three newly diagnosed patients with MM, PET-FDG was positive in 32 (97%), MIBI in 30 (91%), and MRI in 27 patients (81%). In this experience, in analysis of the spinal and pelvic region, PET and MRI were comparable, allowing both to visualize a higher number of lesions with respect to MIBI. On the other hand, MIBI and MRI detected a higher rate of patients with diffuse pattern with respect to PET-FDG. In particular, MIBI performed better than FDG in the detection of a diffuse pattern of bone marrow uptake both in the whole data (33% of patients positive at MIBI versus 9% at PET) and in the spinal and pelvic analysis (54% of positive MIBI versus 18% using FDG). It should also be pointed out that false negative results can be observed with MIBI because of the possible over expression of P-glycoprotein (Pgp), which can be associated with multi drug-resistant myeloma [37].

The National Oncologic PET Registry (NOPR) enrolled 22975 subjects with cancer in the first year including over 1300 myeloma patients; in this extensive population an overall change in intended management reached values of up to 35%. National Comprehensive Cooperative Network guidelines updating this experience on more than 1700 patients finally reported a change of management in 48% of patients with myeloma. On this evidence, insurance policies in the United States started to cover FDG-PET for staging and for treatment strategy evaluation in patients with MM.

In addition, PET-FDG is more sensitive than other imaging modalities for localizing extra medullary sites of disease, having the capability to detect additional lesions in almost 30% of patients, previously diagnosed as solitary plasmocytoma by MRI. The overall sensitivity of FDG-PET in detecting a myelomatous involvement is approximately 85% in the presence of a specificity of 92%.

Therefore, although PET-FDG appears comparable, with respect to MRI, in the detection of focal lesions in the spine and pelvis, it permits more accurate whole-body coverage not allowed by standard MRI, with better definition of staging and severity of disease. At present, new whole body (WB) MRI techniques have started to be routinely used in a reasonable time, being well tolerated by patients. WB-MRI has been demonstrated to be highly effective in the management of patients with MM, especially in the newly diagnosed setting. Moreover, WB-MRI, as already standard MRI, is superior with respect to FDG-PET in detecting diffuse bone marrow involvement in the spines of patients with advanced MM [38].

In summary, although all reported studies confirm the superiority of PET-CT over conventional radiography, they have also revealed that PET-CT may not be used as an imaging study alone.

PET-FDG in treatment monitoring

The treatment monitoring of patients with myeloma represents a significant problem for all diagnostic procedures; there are persistent uncertainties concerning the optimal imaging method to be used to address this issue.

Being based on the evaluation of bone lesion, it is well known that standard radiography remains positive after treatment even in the case of a complete remission. Similar findings may be observed on CT images. Conversely, MRI evaluating bone marrow presents a significant advantage with respect to X-ray techniques because its signal progressively follows changes in bone the marrow cellularity induced by treatment. This skill to dynamically assess the biological process becomes an advantage in clinical practice, in particular in patients treated with colony stimulating factors or after radiotherapy. As also demonstrated in a wide range of solid tumours, PET may be of value for these purposes given that the therapeutic response can be carefully monitored by changes in FDG uptake.

Although FDG-PET is extensively used after treatment, only a few reports have systematically analyzed this topic in patients with MM. Zamagni et al. [39] have demonstrated in 65% of studied patients that PET-FDG scans normalize following autologous transplantation, this finding being an early marker of tumour response. In contrast, normalization of the MRI pattern was seen only in 35% of patients. In 2 out of 8 patients with a persistent abnormal MRI pattern, an improvement was recognized after 3 months. A possible explanation of the earlier therapeutic response in FDG scan can be given remembering, as previously reported, that the effect of treatment on the bone marrow microenvironment affects more seriously and longer the pathophysiological issues shown in MRI, than in FDG-PET.

More recently, Shortt et al. [40] have compared FDG-PET and WB-MRI for the assessment of disease activity, comparing imaging results with bone marrow aspiration and biopsy. This well conducted study reported a PET sensitivity of 59%, with a high rate of false

positive results probably induced by bone marrow reconversion after therapy. The authors reported negative predictive values of 50% and 59% for PET and MRI, respectively, which became 64% by combining both techniques. This finding suggests that a negative MRI and/or PET cannot exclude disease persistence.

Anyway, two remarks at least should be made concerning the issue of treatment evaluation:

1. None of the imaging techniques to date can be used to reliably estimate the different degrees of response, given that the new concepts of stringent complete response, complete response, and very good partial response are replacing the traditional complete response.
2. Which golden standard should be used? Bone marrow aspiration and/or biopsy, immune fixation, serum/24hours urine electrophoresis, and serum free light chains assay are now complementarily used in all major centres with MM expertise, but these centres represent only a small fraction of the institutions in which MM patients are managed.

PET-FDG and prognosis

Diagnostic tools with the capability of early detection of areas at risk of future bone injuries, before lytic irreversible changes occur, could represent a major acquisition in patients with MM. Of note, MRI has already demonstrated its capability to detect bone marrow infiltration, as focal, variegated, or diffuse patterns, in the absence of bone destruction. Moreover, its proficiency in early and accurate detection of MM focal and diffuse lesions has important implications for prognosis because the number of focal lesions or a diffuse pattern are positively related to unfavourable prognosis. A prognostic value based on the extension of disease has also been demonstrated by using a skeletal radiographic survey. FDG-PET potentially overcomes the prognostic stratification based on the number of lesions, introducing the new concept of degree of metabolic activity expressed as SUV.

One of the first studies in high-risk patients was conducted by Durie et al. in 2002 [41]. They demonstrated a negative FDG-PET pattern; therefore, to be intended as a favourable prognostic factor in all subjects with stable monoclonal gammopathy of undetermined significance (MGUS). Conversely, in patients presenting with a positive FDG relapse in extramedullary sites the median survival was 7 months.

Interesting new relationships are emerging from the combined use of diagnostic imaging and gene profile. By examining gene expression in plasma cells from untreated patients undergoing comprehensive skeletal imaging, a link between focal lesion number detected by MRI and the level of molecules associated with poor prognosis like DKK1 has been demonstrated. Bartel et al. [42] have shown in 238 newly diagnosed MM patients that X-ray MRI and FDG-PET are correlated with relevant prognostic parameters at baseline. In particular, the SUV of focal lesions is positively linked to high levels of β -2-microglobulin, C-reactive protein, and LDH. The number of focal lesions detected by PET was statistically correlated with high risk gene profiles and inversely related to bone events, as vertebral fractures. Moreover, the presence of more than 3 focal lesions was demonstrated to be an independent parameter associated with lower overall survival. This prospective study revealed a better outcome in patients showing a complete

disappearance of FDG-avid focal lesions both in high and low risk patients. The FDG suppression before transplantation was recognized as an independent favourable prognostic variable and should be considered as a goal to be reached for durable and efficient disease control and for long survival.

Conclusions

Many imaging technologies have been used for the diagnosis and the management of myeloma patients. As part of the staging procedures of newly diagnosed patients with myeloma, the X-ray skeletal survey is still mandatory, at least as a first step. Many studies have already clearly demonstrated that more sophisticated imaging techniques, such as CT and MRI, may evidence a higher number of lesions, therefore individuating a higher number of patients with MM as compared with plain radiography. Whole-body MRI can give complementary information with respect to the skeletal survey, and it is recommended in patients with normal conventional radiography, with medium-high probability of disease. Bone scintigraphy has no place in the routine staging of myeloma. Based on current evidence, neither PET nor MIBI imaging can be recommended as a single technique in the management of myeloma patients. The original information achievable with respect to the alternative imaging techniques creates for PET-FDG (and MIBI) a possible clinical indication in staging, in the evaluation of tumour response, in prognostic analysis. In fact, both PET-FDG and MIBI can provide complementary information in MM patients with respect to more consolidated and widely used radiological procedures.

In particular FDG-PET, mainly when acquired with a hybrid scanner, can already be useful in some individual cases, in combination or as alternative with respect to MRI. Further studies are needed to better understand the best diagnostic tree in MM, including new powerful instruments such as PET and MRI.

The complementary information achievable from CT - analysing bone lesion, and PET-FDG - defining the presence of an active malignant disease, could certainly stimulate a wider diffusion of this technique. The incremental value of PET-CT with FDG in defining the best diagnostic and therapeutic strategies in patients with MM has already been demonstrated, for example with very convincing data from the National Oncologic PET Registry (NOPR).

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