IMAGING TECHNIQUES USED IN MULTIPLE MYELOMA

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Abstract:
Multiple Myeloma (MM) is a plasma cell disorder, characterized by bone marrow infiltration with clonal plasma cells; production of monoclonal immunoglobulin (paraprotein); end organ damage; lytic lesions in the bones; renal impairment; hypercalcaemia; and anaemia. Skeleton evaluation in MM is necessary not only for staging purposes but also to detect serious complications such as fractures. Skeletal survey (SKS) is an established first line investigation for this purpose. However, in recent years new imaging techniques such as whole body magnetic resonance imaging (WBMRI) and 2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography-computed tomography (PET/CT) have been used widely. In this article, we review different imaging techniques used in MM and their impact on patient management.

Keywords: Imaging techniques, skeletal survey, MRI, PET/CT, multiple myeloma, osteolytic lesions.

Introduction:
Multiple Myeloma (MM) is a plasma cell malignancy. The aetiology of MM is unknown and it accounts for 10% of haematological malignancies and nearly 1% of all cancers¹. Median age at presentation is 70 years and only 2-3% of patients are younger than 40 years. MM has slight male predominance and is more common among African Americans than white Americans or Europeans². MM is characterised by bone marrow (BM) infiltration with clonal plasma cells, originating from B-cells, and production of immunoglobulins (paraprotein) that can be detected in serum or urine by electrophoresis and/or immunofixation. The paraproteins secreted in MM are IgG (52%), IgA (21%), only light chains (16%) and about 2% of cases are non-secretary. A majority of patients (about 80%) have osteolytic bone lesions (OBL) at diagnosis. Other presenting features are anaemia (72%), hypercalcaemia (13%), renal impairment (19%),

Fig. 1 Diagnostic criteria for MM and related disorders⁵. PC= Plasma cells, PP= Paraprotein.

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recurrent infections. 20% of cases are asymptomatic. Bone marrow biopsy, biochemistry and comprehensive evaluation of skeleton are vital in the diagnosis of MM and to differentiate it from other plasma cell disorders (Fig.1). The minimum criteria for making a diagnosis of MM include bone marrow plasma cells more than 10%, detection of monoclonal proteins in serum or urine, and presence of end organ damage. This group of symptoms is abbreviated as CRAB: hypercalcaemia, renal impairment, anaemia, and bony lesions.

**Myeloma Bone Disease (MBD):**

90% of MM patients suffer from MBD during the course of the disease. Increased osteoclastic activity and suppressed osteoblastic function is a key factor in the pathophysiology of MBD. Classically, these are punched out lytic lesions (Fig.3) without surrounding sclerosis around due to the absence of anabolic activity. Osteolytic lesions are located in close vicinity of plasma cells promoting the notion of interaction between myeloma cells and bone marrow stromal cells leading to release of certain chemokines resulting in up regulation of osteoclastic and down regulation of osteoblastic activity. These lesions arise from medulla and move outward causing endosteal scalloping of cortex and sometimes invading the periosteum leading to formation of extra osseous mass. Other types of lesions are solitary plasmacytomas and in about 10-15% of cases, there is a generalized osteopenia or osteoporosis. The axial skeleton comprising the vertebrae, ribs, skull and pelvis, along with the proximal parts of long bones are most commonly involved (Fig.2). Sclerotic lesions in MM can also be seen in POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) which accounts for less than 1% of MM patients. Osteolytic lesions rarely heal and they are persistent even when disease is in remission. However, with use of novel treatments there is some evidence that certain agents like bortezomib, increase osteoblastic activity in MM patients.

Imaging has a vital role in the assessment of disease at the time of diagnosis and subsequently for the monitoring of response to therapy. Imaging tools also highlight presence or absence of any extramedullary disease and detect complications resulting from bone disease, e.g. fractures. Conventional radiography (skeletal survey) and new imaging modalities are used for the above purposes. All imaging techniques used have some advantages and disadvantages and might be appropriate for certain subgroups of MM.

**Fig. 2** Skeletal site involvement in MBD. Percentages mentioned are not meant to add up to 100% as most patients have multi-site involvement.

**Plain Radiography (Skeletal Survey):**

Skeletal survey (SKS) still remains the primary investigation for initial workup of MM, particularly where other modern facilities of imaging are unavailable. SKS includes about 20 plain films, taken as frontal (AP) and lateral (LA) views of chest, skull, whole spine, pelvis, humeri and femora. It covers a large area of skeleton and highlights common complications of MM including lytic lesions, osteoporosis and fractures (Fig.3). It is readily available, cheap and has a low radiation exposure. Cortical bone lesions are better defined on plain radiograph compared to MRI. However, skeletal survey has a high false negative rate (30-70%), resulting in an underestimation of the stage and the diagnosis. The lytic lesions appear on radiographs when 30-75% of cancellous bone is lost, meaning lesions may not be picked up at an early disease stage.

SKS provides limited information about ribs, sternum and scapulae. Furthermore, it is time consuming with regular posture changes which could be painful for
some patients who may already have fractures. In addition, it is difficult on SKS to differentiate between osteopenia due to MM and that due to other common causes like post-menopause or senile osteoporosis\textsuperscript{11}. As lytic lesions rarely heal, SKS does not help in assessment of response to therapy.

**Table 1. Advantages and Limitations of SKS.**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Readily available</td>
<td>Low sensitivity (47.4%)</td>
</tr>
<tr>
<td>Inexpensive</td>
<td>10-20% lesions are missed</td>
</tr>
<tr>
<td>Detection of lytic lesions, fractures,</td>
<td>Early stage lesions are missed (&gt;30% cortical bone loss should be present</td>
</tr>
<tr>
<td>osteoporosis</td>
<td>before lytic lesions appear)</td>
</tr>
<tr>
<td>Low radiation exposure</td>
<td>Poor tolerability (20 exposures, changing posture, elderly patients)</td>
</tr>
<tr>
<td></td>
<td>Not useful in evaluation of treatment response as lesions rarely heal</td>
</tr>
<tr>
<td></td>
<td>Limited evaluation of certain areas, like scapulae, sternum and ribs</td>
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</table>

**Computed tomography (CT):**

Computed tomography (CT) is another modality used in MM for the evaluation of bony lytic lesions (Fig. 4). Whole body CT was introduced to evaluate the whole skeleton. In some institutions CT is used as initial imaging for assessment of the spine and pelvis. It is an ideal investigation for the detection of early bone destruction. Extramedullary lesions, soft tissue mass, diffuse osteopenia, fractures and rare osteosclerotic lesions can also be detected on CT with a higher sensitivity compared to SKS. Furthermore, it has been reported that CT reveals more lesions in areas that are poorly visualized on plain radiography. CT is superior in assessment of fracture risk in unstable areas compared to both plain radiography and MRI\textsuperscript{12,13}. CT is faster and patient does not need to change postures as in plain radiography and there is no need of contrast media, for skeletal imaging which could be dangerous in MM patients who may already have compromised renal function due to the primary disease. Moreover, multidetector row computed tomography (MDCT), a novel CT technique, is quite sensitive in detection of smaller lytic lesions (<5mm) particularly in the spine area. In addition, with this technique, there is a clear distinction between bony structures and soft tissues leading to less false positive results\textsuperscript{13,14}. Another advantage of CT is its accuracy in demonstration of
extra osseous lesions and is a tool of choice for performing guided biopsy from spine or pelvis (Tab.2). CT is also used for planning of radiotherapy. CT can also be used in the detection of spinal cord compression; however, MRI is the preferred imaging modality in such patients.

When compared to plain radiography, CT carries a high radiation exposure (1.3-3 times higher)\textsuperscript{11} and like conventional x-rays, is non-specific in the assessment of osteopenia. There is a relatively high false negative rate, particularly in cases of diffuse marrow infiltration and in early stages of disease when there is no bone destruction\textsuperscript{15}.

**Fig 4.** Whole body CT of a patient with MM showing multiple lytic lesions.

**Whole-body low-dose computed tomography (WBLDCT):**

Because of high radiation exposure associated with whole body CT, WBLDCT was introduced to overcome this drawback. The effective radiation dose in WBLDCT is much lower compared to standard CT (3.3 milliseverts [mSv] vs 36.6 mSv) and less than double that of SKS (3.3 [mSv] vs 1.7 mSv)\textsuperscript{12,13}. Gleeson et al, reported a high diagnostic accuracy of WBLDCT in the detection of lytic lesions compared to SKS. More than half of the cases were upstaged and WBLDCT revealed additional information, e.g. lymphadenopathy, hepatosplenomegaly, and lung lesions which were not seen on SKS. Moreover, WBLDCT was superior to WBMRI in detection of residual lytic lesions\textsuperscript{13}.

In brief, standard or low dose CT is an alternative to plain radiography in assessment of spine lesions in patients with symptoms of pain, as it provides more comprehensive evaluation in a short period of time. Furthermore, in patients who are symptomatic in spite of negative SKS, CT may reveal additional lesions\textsuperscript{11}.

**Table 2.** Role of CT in MM.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of smaller lesions</td>
<td>High radiation exposure (1.3-3 times)</td>
</tr>
<tr>
<td>Comprehensive evaluation in short time</td>
<td>Non specific in cases of osteopenia</td>
</tr>
<tr>
<td>High sensitivity (70.4%)</td>
<td>High false negative rate (in diffuse or in early phase of disease)</td>
</tr>
<tr>
<td>Detection of extramedullary disease</td>
<td>Cost</td>
</tr>
<tr>
<td>Exact location of lesions (helpful in biopsy)</td>
<td>Availability</td>
</tr>
<tr>
<td>Assessment of fracture risk</td>
<td>Planning for radiotherapy</td>
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**Magnetic Resonance Imaging (MRI):**

There are two types of marrow; the red marrow or active haematopoietic and the yellow fatty inactive marrow. The red marrow converts to yellow fatty marrow as age advances and in adults haematopoietic marrow is mostly localised to the axial skeleton. There are five patterns of bone marrow infiltration seen on MRI. These are: (1) normal marrow (low tumour burden), (2) focal lesions, (3) variegated (salt and pepper appearance), (4) diffuse disease, and (5) focal and diffuse infiltration. Thus, MRI appearance in MM patients will be dependent on the status of the underlying bone marrow (red or yellow) and pattern of involvement\textsuperscript{16,17}. The appearance of bone marrow infiltration correlates with disease stage; normal and variegated pattern is consistent with stage I, whereas focal and diffuse infiltration was associated with stage II or III\textsuperscript{18}. Normal bone marrow appearances are present in about 50-75% of untreated stage-I
(according to Durie-Salmon staging system) and in 20% of untreated stage-III disease.

**MRI Sequences:**

The most common MRI sequences used in MM are T1-weighted, the T2-weighted with fat suppression, the short time inversion recovery (STIR) and the gadolinium T1 weighted with fat suppression. The classic myeloma lesions appear as low signal intensity on T1-weighted images and hyperintense on T2 weighted and STIR images. They show enhancement with gadolinium.

**Fig** T1 low, T2 isointense and post gadolinium T1 enhancing focal vertebral lesion represents myelomatous deposits in the lumbar (White arrow) and sacral vertebral body. The associated lobulated enhancing soft tissue (Red arrow) in relation to the sacral vertebral body is extending in the sacral neural foramina and compromising sacral nerve roots.

**Uses in Multiple Myeloma:**

MRI is ideal in detection of bone marrow infiltration with myeloma cells even before bone destruction is evident on plain radiographs. This is an investigation of choice in cases of suspected spinal cord compression. It provides comprehensive assessment of the extent and exact site of compression. MRI can be helpful in differentiation of malignant from benign lesions and in the evaluation of fracture risk. MM patients with more than 10 lesions on MRI have 6-10 times higher risk of fracture compared to those who had either no or less than 10 lesions. MRI has a vital role in the detection of certain complications, e.g. avascular necrosis of head of femur and amyloid deposits in heart or in other soft tissues.

**Role of MRI in Solitary Plasmacytoma/Smouldering MM/MGUS:**

MRI is also recommended in all cases of solitary bone plasmacytoma (SBP) and may reveal additional lesions which were not detected on plain radiography. In one study, MRI of spine detected additional foci in 4 out of 12 patients. In cases of smouldering multiple myeloma (SM), MRI detected marrow abnormalities in 30-50% of patients. Furthermore, in one study it was demonstrated that median time to start treatment was 16 months in...
patients with abnormal MRI compared to 43 months with normal MRI (p<0.01)\textsuperscript{17,24}. Based on recent published data, presence of two or more lesions (>5mm) on MRI is an indication to start therapy in these patients\textsuperscript{25}. There are some studies using MRI in monoclonal gammopathy of underdetermined significance (MGUS) patients. In one study, evaluating 24 patients the thoracolumbar spine MRI was normal in all MGUS cases versus only 6 of 44 MM patients who had normal findings\textsuperscript{26}. In another study, Berg et al. reported bone marrow abnormalities in 19% (n=37) of cases. These patients had progression to MM in a shorter time compared to the cases with normal MRI\textsuperscript{27}. It has also been noted that MGUS patients with abnormal MRI have a higher paraprotein and plasma cell percentage in bone marrow compared to cases with normal MRI\textsuperscript{28}. In brief, MRI is very helpful in cases of solitary bone plasmacytoma (SBP), smouldering myeloma (SM); however, in MGUS it may be useful in subgroups of patients who have a high risk of disease progression.

![Fig T1 low, T2 isointense and post gadolinium T1 enhancing focal C2 vertebral bodies shows marrow deposits (White arrow).](image)

**Whole Body MRI**

MRI provides valuable information about most of the axial skeleton; however, some bony areas may not be assessed properly including the skull, ribs and clavicle because of respiratory movements. To resolve this issue and to have a comprehensive view, whole body MRI (WBMRI) was introduced. WB MRI detects significant bone marrow involvement in up to 20% of cases which are negative on SKS. In cases where both modalities were positive MR shows more extensive bone marrow infiltration\textsuperscript{29}. In another, large study (n=611), WBMRI was compared with SKS. WBMRI revealed lesions in 74% of imaged sites compared to 43% with SKS. Moreover, in patients with normal SKS about half showed focal lesions on MRI. The MRI was superior to SKS particularly in spine, pelvis and sternum. However, it
was inferior to SKS in detection of focal lesions in ribs and in long bones\textsuperscript{30}.

When compared to WBLDCT, WBMRI was found to be superior in both focal and diffuse disease appearances and revealed more lesions than WBLDCT\textsuperscript{13}. In one study, Melnyk et al. evaluated forty one MM patients with WBMRI and WBMDCT. WBMRI was better in the detection of the number of lesions as well as severity of involvement. WBMDCT under staged 11 patients compared with MRI\textsuperscript{15}.

**Evaluation of Response to therapy in MM**

MRI is also helpful in evaluation of response to therapy. A complete response (CR) on MRI includes complete disappearance of the marrow abnormalities and partial remission (PR) would be a change from diffuse to focal or variegated pattern\textsuperscript{31}. The signal intensity reduction on T2-weighted images and resolution of enhancement of lesions, if previously present, will suggest response to therapy. Sometimes focal lesions may persist or become more intense which could be due to inflammation or treatment induced necrosis\textsuperscript{32,33}. However, there are certain limitations as it takes about 9-12 months for lesions to resolve. The patient may have received granulocyte colony stimulating factor (GCSF) during autologous stem cell transplant (ASCT) resulting in some changes in bone marrow which can be difficult to differentiate from disease. In such cases, MRI should be done at least one month after ASCT\textsuperscript{34,35}.

**Prognostic significance**

MM patients with the absence of bone marrow abnormalities on MRI, have better survival than those with abnormal findings on MRI\textsuperscript{36}. Furthermore, presence of more than 7 focal lesions on MRI is associated with shorter survival and resolution of focal lesions on post treatment MRI indicates an improved outcome\textsuperscript{30}.

In summary, WBMRI is an ideal first line imaging tool to assess focal and diffuse disease; however WBLDCT or plain radiography may be used as an adjunct to MRI to detect bony destruction and make an assessment of fracture risk. There are certain limiting factor (Tab. 3) to the use of MRI, e.g. long acquisition time, patient may be claustrophobic or have metal devices in situ and the cost. In addition, gadolinium based contrast media may lead to nephrogenic systemic fibrosis or nephrogenic fibrosing dermopathy\textsuperscript{37}.

**Table 3: Advantages and limitations of MRI**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Excellent for axial skeleton</td>
<td>Metallic implants</td>
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<tr>
<td>Best modality for cord compression/nerve root</td>
<td>Claustrophobia</td>
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<tr>
<td>Excellent for detection of diffuse disease as</td>
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<tr>
<td>well as focal lesions</td>
<td>Availability</td>
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<tr>
<td>Can detect complications like amyloid</td>
<td>Cost</td>
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<tr>
<td>deposition in heart or in other tissues and</td>
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<tr>
<td>avascular necrosis of femur head</td>
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<tr>
<td>No radiation involved</td>
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<tr>
<td>Greater sensitivity (83.3%) than plain</td>
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<tr>
<td>radiography</td>
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<tr>
<td>Can be used response assessment</td>
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<tr>
<td>Useful in SBP</td>
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<tr>
<td>May be helpful in SM/MGUS</td>
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**Positron Emission Tomography-computed tomography (PET/CT)**

PET is a nuclear imaging technique in which positrons are used as radiolabels. The most commonly used is 18-fluorine-fluoro-deoxyglucose (FDG). It is injected into the patient who should be fasting 4-6 hours pre procedure. Blood glucose is measured before FDG is injected and patient undergoes scanning about 60-90 minutes after the injection\textsuperscript{4}. Active lesions show FDG uptake that is greater than background level. FDG accumulation is measured quantitatively as standardized uptake value (SUV). However, if the lesions are smaller than 5 mm in diameter, then FDG uptake should be considered positive regardless of SUV and lesions are indeterminate if SUV is below 2.5 and lesion size is between 5 and 10 mm\textsuperscript{11,38}. The PET component provides information about the function of the tissues (such as blood flow, oxygen use and metabolism of glucose) and CT provides structural/anatomical images. The combination of these two modalities can
characterise the abnormal lesions both morphologically (e.g. soft tissues or bony) as well as functionally (e.g. active or inactive). Moreover, with the use of PET/CT, the lesions with subtle activity or very small size can also be detected which could be missed on PET images alone. Moreover the scanning time is shorter with PET/CT (30 min) than with PET alone (about 1 hour)\(^4,39,40\). The extent of bone marrow infiltration and presence of extramedullary disease are important factors in MM patients and have prognostic significance\(^41\). PET/CT and MRI are very sensitive imaging modalities to detect these abnormalities.

**Fig F18 FDG PET CT scan images of a 43 year old patient with multiple myeloma**
(A): Baseline scan shows expansile lytic lesion in right sacral ala [max SUV 7.2]
(B): Post cycle 4 LCD rednuntrates sacral lesion with interval reduction in uptake [max SUV 2.4 = Liver]

**Role of PET/CT at diagnosis:**

PET/CT provides information both about anatomy of lesions as well as highlights if involved area is still active or inactive (depending on FDG uptake). Furthermore, PET/CT detects osseous and extramedullary disease. In addition, there is a possibility to differentiate between diseased tissues and necrotic tissues resulting from radiation therapy\(^40\).

Fonti et al. reported results of 33 MM patients who underwent PET/CT, whole body Tc-MIBI and MRI of spine and pelvis. PET/CT revealed 196 focal lesions (75 were in pelvis and spine), Tc-MIBI detected 63 focal defects (1 in spine and 9 in pelvis) and MRI showed 51 focal lesions (40 in spine and 11 in pelvis). PET/CT detected significantly more lesions compared to Tc-MIBI and MRI. Another finding was that PET/CT and MRI findings were comparable in detection of focal lesions alone or in combination with diffuse pattern. However, MRI and Tc-MIBI did better in detection of diffuse pattern\(^39\). In another comparative study, Shortt et al. compared WBMRI with PET/CT and found a positive predictive value (PPV) of 100% when both were used in combination; however, WBMRI was superior in detection of active disease with higher sensitivity (68% vs. 59%) and specificity (83% vs. 75%)\(^42\). Likewise, Zamagni et al. evaluated 46 MM patients with whole body x-rays, MRI of spine-pelvis and
whole body PET/CT. In this study PET/CT was found to be superior to plain x-rays in 46% of patients (19% of patients were false negative on x-rays). In 35% of cases PET/CT was better than MRI in detection of myelomatous deposits in the areas which were out of field of view of MRI. Conversely in 30% of cases, PET/CT did not reveal any lesions in spine and pelvic areas where MRI revealed bone marrow involvement particularly in a diffuse pattern. Bredella et al. evaluated 13 MM patient with FDG PET. In this study 4 out of 13 patients were upstaged by FDG PET resulting in a change in future management. The sensitivity and specificity of FDG PET to detect the medullary involvement of MM was 85% and 92%, respectively.

Recently Bartel et al. demonstrated in a large group of patients that the number and FDG positivity of focal lesions (FLs) on PET/CT were correlated with high beta 2 microglobulin (B2M), C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels. Furthermore, presence of more than 3 FDG-avid FLs was associated with inferior overall and event free survival. In another prospective study (n=43) PET/CT was positive in 38 out of 41 (sensitivity 92.7%) known lytic lesions due to MM; furthermore, 71 additional lesions were depicted by PET/CT which were not seen on plain radiography in 14 patients which resulted in a change in management plan in about 14% of patients. The positive predictive value (PPV) for active disease was 100% for focal or focal/diffuse pattern and 75% for diffuse bone marrow uptake.

PET/CT is also a useful modality in detection of extramedullary disease and in one study additional lesions were noted in up to 30% of patients who were diagnosed as SBP by MRI. PET/CT is an ideal modality to monitor nonsecretory MM patients and to detect osteonecrosis of jaw related to bisphosphonate therapy.

Role of PET/CT in the assessment of response to therapy:

PET/CT is not only capable of detecting bone lesions and extramedullary disease but also has the ability to distinguish active disease from post therapy necrotic tissue. It is well known that bone defects due to MM rarely heal; thus conventional radiography and CT may not be of much help in assessing the disease response post therapy. The abnormalities noticed on MRI do change or disappear in responding patients; however it takes about 9-12 months for these changes to be appreciated on MRI. In contrast, the changes on PET appear within a few hours to 3-4 weeks of effective treatment, making it the investigation of choice for restaging. The persistence of FDG avid lesions on PET/CT post transplant is a poor prognostic factor and correlates with early relapse (within a 6 months period). In one study, 10 patients had post treatment PET/CT scans and nine of them were negative and one was positive for active disease. None of PET/CT negative patients showed any abnormality on MRI and CT. These patients were followed up clinically for at least 6 months and eight of them remained in remission. Zamagni et al. evaluated 23 patients three months post autologous transplantation with PET/CT and MRI. Fifteen patients (65%) showed normalization of PET/CT scans and in 12 of these patients there was ≥90% reduction in the level of M-protein. On the other hand, of these 15 patients MRI pattern was normal in eight while in 7 patients MRI was either unchanged or revealed low number of lesions. The presence of residual FDG activity after induction therapy predicts poor outcome. Bartel et al. reported that complete FDG suppression before transplantation correlates with superior overall survival (OS) and event free survival (EFS). At 30 months, there was a significant difference in OS (92% vs. 71%) and EFS (89% vs. 63%) between the patients with negative scans and those who did not achieve 100 % suppression, respectively.

In brief, PET/CT is an ideal imaging modality to scan whole body in one procedure and in a reasonable time frame. It provides both functional and morphological characteristics of lesion. It is most sensitive modality in evaluation of treatment response, particularly in non-secretory MM. PET/CT is very useful in detection of extramedullary disease and complications of MM (e.g. infections, ONJ). There are certain pitfalls of PET/CT which should be kept in mind while making assessment. For
example there is high radiation exposure and smaller lesions may be missed due to limited PET resolution. There is risk of false negative results in cases of diffuse disease involving the spine and pelvis. Inflammation, infections and GCSF treatment may increase FDG activity while radiotherapy may decrease FDG uptake on PET/CT (Tab. 4).

Table 7 Advantages and Limitations of PET/CT

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to detect both focal and diffuse disease</td>
<td>High radiation exposure</td>
</tr>
<tr>
<td>Differentiation of active and non-active lesions</td>
<td>Subcentimeter lesions may be missed on PET</td>
</tr>
<tr>
<td>Ideal for response evaluation in non-secretory myeloma</td>
<td>Inflammation, infection, GCSF and radiotherapy can affect FDG uptake</td>
</tr>
<tr>
<td>Detection of osteonecrosis of jaw</td>
<td>Availability</td>
</tr>
<tr>
<td>Prognostic significance (e.g. 3 or more lesions confers poor prognosis, presence of FDG avidity post induction correlates with poor outcome)</td>
<td>Cost</td>
</tr>
<tr>
<td>Detection of extramedullary disease</td>
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99-m Tc-sestamibi (MIBI):

99-m Tc-labeled 2-methoxyisobutylisonitrile (MIBI) is a radiopharmaceutical which emits γ-rays and has predilection to accumulate in tissues with high cell density and mitochondrial activation which could be found in malignant lesions. MIBI actively concentrated in myeloma tissues and bone lesions and is more sensitive to plain radiography. It has been demonstrated that MIBI localizes inside the plasma cells. There are different patterns of MIBI uptake in MM; physiological, focal, diffuse and extramedullary uptake. Focal uptake indicates active myeloma but diffuse uptake without focal positivity does not support active myeloma. Mele et al. evaluated 397 cases of MM with MIBI and conventional x-rays. In a series of 229 MIBI scans done at diagnosis, 146 (64%) were positive and 81 cases were discordant with x-ray results. The sensitivity was higher (77%) with MIBI compared to x-rays (45%). In addition, MIBI results were positively correlated with CRP, bone marrow infiltration and bone pain. In 168 follow up scans, MIBI presented high specificity in patients with CR and correlated with response to therapy. In another study, MIBI was found very effective in determining the active myeloma disease both at diagnosis and relapse. It has been reported that MIBI has the ability to detect active lesions in non-secretory MM and MIBI results directly correlate with clinical outcome after ASCT.

However, MIBI is inferior to PET/CT and MRI in detection of myelomatous involvement. In one study, FDG-PET was better than MIBI in detection of skeletal lesions (93.3% vs. 80%), soft tissue lesions (68.4% vs. 89.5%) and bone marrow infiltration (100% vs. 80%). Fonti et al. reported comparison of PET/CT, MIBI and MRI. In this study PET/CT was superior to MIBI in detection of focal lesions but inferior in cases of diffuse disease. Likewise, MIBI was inferior to MRI in detection of disease particularly in spine and pelvis. In brief, MIBI is a useful whole body imaging modality in MM particularly if PET/CT and MRI is not available.

Bone Scan (bone scintigraphy):

Bone scan is a whole body imaging to detect metabolic activity in the entire skeleton using 99m Tc-diphosphonate as radiopharmaceutical. The mechanism of uptake is directly correlated with blood flow and osteoblastic activity of the lesion. In MM, the bony lesions are due to increased osteoclastic activity and suppressed or absent osteoblastic function; thus, bone scan is not very useful in these patients. Ludwig et al. reported a comparison of bone scan and plain radiography in 41 MM patients. In this study, plain radiography was superior to bone scan. Plain radiography detected 97 myeloma related lesions compared to only 16 with bone scintigraphy, giving a sensitivity of 91% and 46% respectively. In another study, 27 MM patients were monitored for about 5 years with bone scintigraphy and skeletal survey every six months. The skeletal survey revealed myeloma related lesions with high sensitivity and specificity at the diagnosis, follow-up cases and in the assessment of bone pain than...
Bone scintigraphy. To sum up, bone scan is not routinely used in MM, the major reason being the primary dysfunction of osteoblasts in MM and 99mTc-diphosphonate uptake is dependent on osteoblastic activity. However, bone scan can be helpful in detection of fracture sites.

**Dual-energy X-ray absorptiometry (DXA):**

DXA scan is a method of choice for the diagnosis of osteoporosis. There is an increased risk of early vertebral fracture in MM patients who have reduced lumbar spine bone mineral density (BMD). This makes DXA scan an important test to consider in these patients particularly when there is no focal lytic lesion. However, DXA may not be able to differentiate between myeloma related osteoporosis from other causes of osteoporosis. Abildgaard et al. evaluated 34 newly diagnosed MM patients with DEXA and demonstrated that osteopenia of spine correlates with increased risk of vertebral fracture. DXA may be useful to identify high risk patients who may need intensive chemotherapy or bisphophonate treatment. In one study, 66 MM patients were monitored with DEXA scan to assess BMD. Patients were treated either with conventional therapy or intensive therapy with peripheral blood stem cell transplantation. After intensive therapy, the increase of lumbar spine BMD was higher in men than women. There was correlation with changes in BMD and M-protein in urine or serum. The presence of lytic lesions, vertebral collapse and spinal osteophytes may cause difficulties in some patients to do DEXA scan. In selected cases femoral and radial BMD can be relied upon.

**Conclusion:**

Due to the complex nature of human skeleton, a single imaging technique cannot provide a comprehensive picture of the whole body. All imaging modalities have some advantages and disadvantages. Plain radiography is still accepted as primary investigation for screening of MM patients. However, WBMRI, CT and PET/CT scans have replaced plain radiography in some institutions and should be considered depending on availability. The cost of these imaging tools and the availability of trained professionals are major obstacles to using them widely. WBMRI should be performed in the cases of MM with normal SKS at diagnosis, particularly in patients with SBP. An urgent MRI is indicated in suspected spinal cord compression. CT of spine may be an alternative if MRI is not available. CT may also be considered for further evaluation of lesions which are inconclusive on MRI to detect structural damage of the bone and extramedullary masses. PET/CT is most sensitive in diagnosing extramedullary disease and is also considered ideal in patients with non-secretory MM. In addition, PET/CT appears to be better in the assessment of response to therapy than other available techniques and should be considered. Based on available data, the MIBI, bone and DEXA scans do not have a significant role in the management of MM and are not used routinely.

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