The role of multimodality imaging in Multiple Myeloma: Past, Present and Future

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Learning objectives

- To review the established uses of radiography, computed tomography, magnetic resonance imaging and nuclear medicine in the assessment of multiple myeloma;
- To illustrate the key imaging modalities and findings for multiple myeloma;
- To discuss current approaches and emerging techniques for the study of this disease.

Background

Multiple myeloma is a malignancy characterized by a proliferation of malignant plasma cells and a subsequent overabundance of monoclonal paraprotein. It represents the second most frequent blood malignancy and the most frequent cause of primary malignancy in bones.

Being diagnosed accidentally in 30% of the patients, it is usually recognized through routine blood screening when they are being evaluated for unrelated clinical situations. In some patients, multiple myeloma is detected after a pathologic fracture occurs; normally affecting the axial skeleton.

Patients usually present bone pain, pathologic fractures, weakness, anemia, infection, hypercalcemia, spinal cord compression or renal failure.

One of the most consensual staging systems for multiple myeloma is the Durie and Salmon system that has been adapted to incorporate imaging findings to laboratory findings, such as, levels of hemoglobin, serum calcium and M protein. This modified version is known as Durie and Salmon Plus and the imaging information consists on the number of focal lesions with 5 mm or more in size and the extent of diffuse bone marrow disease seen at MR imaging or FDG PET/CT). (Table1)

Multiple myeloma still remains as an incurable disease but treatment options like autologous stem cell transplantation, radiation, drug therapies and surgical care in certain cases, are available focussing on the disease progression and its complications.
**Table 1:** Durie and Salmon Plus system for staging of Multiple Myeloma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Laboratory Findings</th>
<th>Imaging Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>≥ 10% plasma cells</td>
<td>Limited disease or plasmacytoma</td>
</tr>
<tr>
<td>IB</td>
<td>≥ 10% plasma cells, end organ damage</td>
<td>Mild diffuse disease, &lt;5 focal lesions,</td>
</tr>
<tr>
<td>IIIA,IIIB</td>
<td>≥ 10% plasma cells, end organ damage</td>
<td>Moderate diffuse disease, 5–20 focal lesions</td>
</tr>
<tr>
<td>IIIA,IIIB</td>
<td>≥ 10% plasma cells, end organ damage</td>
<td>Severe diffuse disease, &gt;20 focal lesions</td>
</tr>
</tbody>
</table>
Findings and procedure details

In the past years plain radiography has been the imaging reference standard and, although still being the recommended method for initial diagnostic imaging evaluation according to the International Myeloma Working Group consensus statement (2), the growing use of computed tomography (CT), whole-body magnetic resonance, and fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) with CT has improved the sensitivity for earlier detection of multiple myeloma, the accuracy of therapy assessment and better prediction of patient outcome.

Plain Radiography: Skeletal survey

The radiographic skeletal survey represents the most utilized imaging method when it comes to evaluate myeloma-related bone lesions. They usually manifest as lytic lesions with absence of reactive sclerosis borders and can affect any part of the skeletal system, being the most common sites the vertebrae in 65% of patients, ribs in 45%, skull in 40%, shoulders in 40%, pelvis in 30% and long bones in 25% (2).

The imaging characteristics of these lesions can range from endosteal scalloping, to mottled areas of multiple small lesions, to large destructive lesions and can also manifest as diffuse osteopenia with or without well defined areas of lysis. (fig. 1-3)

The skeletal survey includes 13 films:

- Skull (Frontal and lateral views)
- Cervical spine (Frontal and lateral views)
- Dorsal spine (Frontal and lateral views)
- Lumbar spine (Frontal and lateral views)
- Pelvis (Frontal)
- Femur/humerus (Frontal)

Main advantages:

- Being a low-cost and easily available technique.
- Good for evaluating cortical destruction

Main disadvantages:

- Time needed to acquire the 13 films with patients that usually are in a lot of pain.
- Limited sensitivity: 10-20% of lesions/abnormalities missed
• Radiation

Computed tomography (CT)

Represents a more sensitive imaging tool than the plain film, giving much more detailed information about the cortex and the trabeculae, which allows the analysis of bone quality and estimation of the fracture-risk.

On CT, myeloma lesions usually appear as punched-out lesions, with cortical and trabecular destruction and early stages of diffuse osteopenia can be detected. (Fig. 4,5)

Main advantages:

- Shorter acquisition time than plain radiography
- Visualization of cortex and trabeculae: bone quality and fracture-risk
- Detection of smaller lytic lesions
- Evaluation of soft tissue disease
- Guidance for spinal and pelvic biopsy

Main disadvantages:

- High radiation dose delivered to patients
- Not recommended for follow-up

Magnetic resonance imaging (MRI)

In the past decade MRI has assumed a very important role in the management of myeloma patients in dedicated centers. Not only due to its high sensitivity for detection of bone marrow infiltration but also because it provides an accurate assessment of the level and extension of nerve root compression, the size of the tumor mass and the degree to which it has extended into the epidural space.

In terms of treatment, MRI is used for planning radiation therapy and to inquire about the treatment response. It has a high prognostic significance, showed in the latest studies, where the presence of more than seven focal lesions with a diameter of more than 5 mm was correlated with a significant decrease in survival (3) and that the presence of normal bone marrow in patients with stage III disease of the Durie and Salmon staging system has been associated with a significant increase in survival rate (4).

The patterns of bone marrow infiltration at MRI can have a diffuse or focal appearance, showing low signal intensity on T1-weighted images and a high signal intensity on T2-
weighted and STIR images and generally showing enhancement on gadolinium contrast-enhanced images.

Five different infiltration patterns have been described: normal appearance of bone marrow despite minor microscopic plasma cell infiltration, focal involvement (Fig.7), homogeneous diffuse infiltration (Fig. 6), combined diffuse and focal infiltration and finally "salt-and-pepper"-pattern with inhomogeneous bone marrow with interposition of fat islands (Fig.8).

Main advantages:

- No radiation
- Assessment of complications
- Whole body technique
- Follow up and treatment monitoring

Main disadvantages:

- Availability
- Acquisition time (40 min...)
- Cost
- Contrast agent

**Fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT**

FDG PET/CT represents a whole body screening tomographic nuclear imaging technique that depicts and quantifies metabolic activity of bone lesions and the presence of extramedullary disease.

The combined information from PET and CT serves as a significant tool in the staging and prognosis of multiple myeloma due to the fact that active lesions will show FDG uptake greater than the basis level (Fig 9,10).

This technique also has an important role in the monitorization of the patient response to the treatment, especially in the cases of successful treatment of focal multiple myeloma lesions, where the decreased bone marrow activity will be represented by decreased FDG uptake.

The presence of false-negative is a possibility, especially in lesions smaller than 10 mm, when a threshold of 2.5 is used for calculating the standardized uptake value and in patients that are being treated with corticosteroids, reason why they have to suspend the corticosteroid treatment 5 days prior to the exam.
Another fact to bear in mind is that patients with monoclonal gammopathy of undetermined significance (MGUS) are FDG negative.

Main advantages:

- Whole body technique
- Systemic intra and extramedullary disease can be diagnosed.
- Follow up and treatment monitoring
- Assessment of complications

Main disadvantages:

- Availability
- Duration of the exam
- False-negative in small lesions and with corticosteroid treatment
- MGUS patients are FDG negative
- Cost

**Up-to-date recommendations for multiple myeloma imaging:**

- Radiographic skeletal survey continues to be the standard baseline evaluation for myeloma patients
- In patients without abnormal findings on the skeletal survey and MGUS or a solitary plasmocitoma, whole-body MRI is recommended.
- If spinal cord or nerve root compression is suspected, MRI is the exam of choice
- MRI or FDG PET/CT can be used for assessment of therapy response and presence of residual disease

**Images for this section:**
Fig. 1: A and B - Anteroposterior and lateral skull plain X-rays that show innumerous diffuse lytic lesions in a multiple myeloma patient, giving classical "pepper pot skull" appearance.
Fig. 2: Anteroposterior plain X-rays that show a large lytic lesion on the right humeral proximal diaphysis (A) and small lytic lesions on the distal diaphysis of the radius (B) in multiple myeloma patients.
**Fig. 3:** Expansive lytic lesion on the left isquiopubic rami in a multiple myeloma patient, seen on a AP pelvic plain X-ray.
**Fig. 4:** Axial Bone window on head CT scans of a multiple myeloma patient with small osteolytic skull lesions (A) and one milimetric osteolytic lesion on the right mandibular condyle (B)
Fig. 5: Axial CT neck: diffuse myeloma involving the scapulas and clavicle bones bilaterally, with cortical destruction of the right scapula bone (arrow)
Fig. 6: MRI sagittal T1-weighted sequence lumbar spine: diffuse low signal myelomatous marrow lesions throughout the lumbar spine.
**Fig. 7:** Axial MRI T1 Weighted images from a myeloma patient with focal lesions on the sacrum and right iliac crest (A) and on the body of L3 with cortical breakthrough and extension into the left psoas major muscle (B).
**Fig. 8:** Micronodular ("salt-and-pepper") multiple myeloma on sagital T2-weighted MR image. Multiple small foci of high signal intensity throughout the marrow combined with the presence of multiple pathological fractures in vertebral bodies that have already been treated with vertebroplasty.
**Fig. 9:** Appearance of multiple myeloma at FDG PET. Coronal image shows multiple foci of intramedullary metabolic activity.
Fig. 10: Axial FDG PET-CT scan showing a hypermetabolic sacrum lesion.
Conclusion

There are a number of imaging modalities available for multiple myeloma with the radiographic skeletal survey still being recommended for all patients in whom the presence of this disease is suspected and newer, more advanced imaging for those with either a normal radiographic skeletal survey and monoclonal gammopathy or a solitary plasmacytoma.

Personal information

References