International Myeloma Working Group Guidelines on Imaging Techniques in the Diagnosis and Monitoring of Multiple Myeloma[1]

Up to 90% of myeloma patients develop osteolytic lesions, a major cause of morbidity and mortality, during the course of their disease. [2] Appropriate use of imaging techniques is essential to identify and characterize skeletal complications resulting from MM, to determine the extent of intramedullary and extramedullary foci, and to evaluate disease progression.

Several imaging techniques are used to clarify bone and soft tissue disease in the diagnosis and management of myeloma: conventional radiography, computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine imaging. The following International Myeloma Working Group (IMWG) guidelines provide recommendations for the use of each of the technologies. The appropriate use of these various technologies for each individual patient should be discussed directly with the treating physician.

1. **CONVENTIONAL RADIOGRAPHY**

- Conventional radiography is still considered the "gold standard" for the determination of the extent of MM bone disease at diagnosis.
- In a complete skeletal survey, it is important to include all areas of possible myeloma involvement: cervical, thoracic, and lumbar spine; skull, chest, pelvis, humeri, and femora.
- Conventional radiography reveals lytic disease only when over 30% of the trabecular bone has been lost. This and other limitations of conventional radiology are listed in Table 1.

Table 1: Conventional Radiology: Limitations

- Some areas not well visualized
- Limited sensitivity: 10-20% of lesions/abnormalities missed
- Reduced specificity vs. benign causes of osteopenia (e.g. steroids/post-menopausal)
- Observer dependent
- Time/Tolerance for standard survey not ideal

- Usually fail to show response to treatment

2. COMPUTED TOMOGRAPHY

- CT scanning allows excellent 3D reconstruction of images.
- In some institutions, CT scanning has replaced conventional radiography as the initial imaging tool used in patients with disease related problems of the spine or pelvis.
- Advantages of CT are detailed in Table 2.

Table 2: Advantages of Computed Tomography (CT)

- Detects small osteolytic lesions
- Faster than standard radiographic survey
- Provides 3D reconstruction of images
- Shows associated soft tissue disease
- Greater sensitivity and specificity versus standard radiography
- Allows estimation of fracture risk
- Excellent for radiotherapy planning and for surgical intervention

- A negative point is that the radiation dose with CT is 1.3-3 times higher than that delivered during standard radiography.

3. MAGNETIC RESONANCE IMAGING

- MRI allows visualization of the medullary cavity and a direct assessment of the degree of MM cell infiltration before bone destruction becomes visible on plain radiographs, without radiation exposure.
- MRI can be used for the accurate illustration of the vertebral fracture or the percentage of loss of vertebral height before vertebroplasty or kyphoplasty.
- Whole-body MRI is superior to whole-body MDCT, a very sensitive CT methodology. [3]
- MRI is useful in determining prognosis based on the number, size, and pattern of MR bone marrow lesions.
- For a list of other advantages of MRI in myeloma, see Table 3.

Table 3: Role of Magnetic Resonance Imaging (MRI)

- More sensitive than standard radiography
- Excellent imaging of axial skeleton
- Discriminates myeloma vs. normal marrow
- Excellent diagnostic discrimination for spinal cord/nerve compression issues, as well as soft tissue disease
- Can detect avascular necrosis of the femoral head
- Can detect amyloid/light chain deposits in the heart and other sites
- Can be used to assess disease status in MGUS, asymptomatic myeloma and for solitary plasmacytomata of bone
- Can be used to monitor response (although improvements can be delayed)

- Caveats:
    - A question was raised at the ASH meeting in December, 2009, regarding the use of gadolinium enhancement in MRI in light of its promotion of myeloma cell growth *in vitro*. [4]
    - The main methodological consideration with MRI imaging is the lack of specificity of the findings.
    - MRI must be performed at least one month after G-CSF administration; diffuse or focal marrow changes after treatment with G-CSF cannot be easily distinguished from active disease.
    - Contraindications to MRI include patient intolerance, cardiac pacemakers, and intra-orbital foreign bodies

4. **NUCLEAR MEDICINE IMAGING**

Technetium bone scintigraphy

- The specificity and sensitivity of technetium bone scintigraphy at the time of initial diagnosis, in follow-up studies, and in the evaluation of bone pain is lower compared to conventional radiography.
- Technetium bone scintigraphy is related mainly to osteoblastic process. Since myeloma is characterized by osteoblast dysfunction, bone scintigrapy is not recommended for the assessment of myelomatous bone disease.

99mTc-sestamibi

- 99mTc-sestamibi (MIBI) imaging closely reflects myeloma disease activity in bone marrow with very high sensitivity and specificity.[5,6]
- MIBI is not useful in MGUS work-up, since it is always negative and cannot be used to predict MGUS transformation.
- MIBI scanning has inferior value compared to FDG-PET/CT, and is inferior to MRI in assessing the extent of myelomatous bone marrow infiltration in the spine.
- MIBI score is significantly related to ISS, bone marrow biopsy infiltration rate, and serum B2M.
- MIBI washout may predict for response to conventional or high-dose chemotherapy.
- MIBI scan was of prognostic value in ISS stage II MM patients, but added no relevant information to ISS in patients with stages I and III.
- MIBI cannot detect ONJ (osteonecrosis of the jaw) in myeloma patients.

Positron emission tomography (PET)

- Subcentimeter lytic lesions seen on plain radiograph may not be detectable on PET scanning.
- Fusion scanning combining both PET and CT addresses the issue of limited spatial resolution and takes less time than (approximately 30 minutes) than a PET scan alone (approximately one hour).
- PET/CT allows identification of high-risk myeloma and can be used to monitor non-secretory myeloma as well as patients in CR without measurable M-component.
- PET/CT studies are more sensitive than other imaging modalities for localizing extramedullary disease; they reveal additional lesions in almost 30% of patients who had been diagnosed with solitary plasmacytoma by MRI.
- In 30% of newly diagnosed patients, PET/CT scans of the spine and pelvis failed to show abnormal findings in areas in which MRI revealed an abnormal pattern of bone involvement.
- Combining PET/CT with MRI of the spine and pelvis increases the ability to detect sites of active MM, both medullary and extramedullary.

- PET/CT has false positive results, particularly in areas of inflammation or infection.
- PET/CT is more sensitive than MRI for making the diagnosis of mandibular osteonecrosis.
- Further studies are needed before the use of PET as a standard tool in both diagnosis and follow-up of MM is recommended.
- The use of MIBI PET should particularly be considered in the evaluation of a patient with an early-stage MM to exclude the presence of more extensive disease.

Dual-energy X-ray absorptiometry (DEXA)

- DEXA may influence the decision to begin bisphosphonate treatment.
- DEXA is a quick, noninvasive investigation that uses a small dose of radiation.
- Its use is limited by spinal disease and the difficulty of distinguishing myeloma osteoporosis from malignant osteoporosis.
- Sequential DEXA-scans are not recommended because they show heterogeneous local BMD changes, and cannot predict disease progression.

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[1]Dimopoulos MA *et al.*International myeloma working group consensus statement and guidelines regarding the current role of imaging techniques in the diagnosis and monitoring of multiple myeloma, *Leukemia* (2009), 1-12. http://myeloma.org/pdfs/IMWG_consensus_imaging.pdf

[2]Terpos E, Dimopoulos MA. Myeloma bone disease: pathophysiology and management. *Ann Oncol* 2005: 16: 1223-1231.

[3]Bauer-Melnyk A *et al*. Whole-body MRI versus whole-body MDCT for staging of multiple myeloma. *AJR Am J Roentgenol* 2008; **190**: 1097-1104.

[4]Fulciniti M *et al*. Gadolinium Containing Contrast Agent Promotes Multiple Myeloma Cell Growth: Implication for Clinical Use of MRI in Myeloma. ASH abstract 1809, 51st annual ASH meeting, poster session on Biology and Pathophysiology of Myeloma

[5]Balleari E *et al*. Technetium-99-sestaMIBI scintigraphy in multiple myeloma and related gammopathies: a useful tool for the identification and follow-up of myeloma bone disease. *Haematologica* 2001; **86**: 78-84.

[6]Tiravola EB *et al*. The use of 99m-Tc-MIBI scanning in multiple myeloma. *Br J Cancer* 1996; **74**: 1815-1820.