Imaging of patients with Multiple Myeloma and associated Plasma Cell Disorders: Consensus Practice Statement by the Medical Scientific Advisory Group (MSAG) to Myeloma Australia.

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Abstract

Imaging modalities for multiple myeloma (MM) have evolved to enable earlier detection of disease. Furthermore, the diagnosis of MM requiring therapy has recently changed to include disease prior to bone destruction, specifically the detection of focal bone lesions. **Focal lesions** are early, abnormal areas in the bone marrow which may signal the development of subsequent **lytic lesions** that typically occur within the next 18-24 months.[1]

Cross-sectional imaging modalities are more sensitive for the detection and monitoring of bone and bone marrow disease and are now included in the International Myeloma Working Group (IMWG) current consensus criteria for initial diagnosis and treatment response assessment. [2,3] The aim of this consensus practice statement is to review the evidence supporting these modalities. A more detailed Position Statement can be found on the Myeloma Australia website.

Imaging Modalities Available

1. Whole Body X-Ray

Whole body X-Ray (WBXR), otherwise known as 'plain radiograph skeletal survey' consists of plain radiographs of the axial skeleton and proximal limbs. However, lesions typically require 30% to 50% of trabecular bone resorption before they become apparent. [4,5] Recent studies have shown that WBXR is negative in over 25% of patients who have bone lesions detected on cross-sectional imaging. Based on current criteria, this has implications for diagnosis and can result in treatment delay in many of these patients.[6,7]

2. Computerised Tomography (CT)

Whole body low dose CT (WBLDCT) is significantly more sensitive than WBXR for detecting myelomatous lesions. Conventional CT previously incurred substantial radiation exposure however, the recent improvements in CT technology have allowed a marked reduction in radiation exposure with no appreciable compromise in diagnostic accuracy (table 1)[7]. WBLDCT is now considered standard of care for the detection of lytic lesions as well as the extent of bone disease at diagnosis which includes long bones to assess for lytic lesions that may be at risk of fracture (figure1). We recommend that it also be utilised in initial screening cases of smouldering myeloma (figure 2) [6] .

3. Magnetic Resonance Imaging (MRI)

Unlike skeletal surveys and CT, MRI provides a detailed assessment of soft tissue, bony trabeculae as well as the degree of bone marrow infiltration. Therefore, MRI can detect *focal* lesions prior to bone destructive *lytic* lesions. **Thus, MRI findings can show a higher disease burden than otherwise suspected (upstage) in asymptomatic patients at diagnosis as well as assisting with response. Detection of more than one focal lesion ≥ 5mm in size by MRI meets diagnostic criteria for active MM requiring treatment.** [1] When WBMRI is not available, MRI spine and pelvis can be performed and has been found to detect up to 90% of focal lesions found on whole-body imaging.

4. Positron Emission Tomography-Computed Tomography (PET-CT)

Positron Emission Tomography-Computed Tomography (PET-CT) is a combined functional and anatomical imaging modality. ^{18}F-FDG PET-CT can detect sites of disease in the bone marrow (focal lesions), the bony skeleton and extra-medullary disease. It can be used to assess treatment response where a reduction in SUV is expected with a good response.[8] Thus, being a particularly useful modality for assisting with the diagnosis and response in patients with non-secretory myeloma. Similarly the IMWG has recently included PET complete metabolic response as a subcategory to their response criteria. [9]

5. Technetium-99m-Sestamibi Scintigraphy (MIBI)

MIBI is a lipophilic molecule whose uptake targets cellular mitochondrial activity which are increased in neoplastic plasma cells. MIBI has a high sensitivity and specificity for the detection of myeloma activity in the bone marrow at diagnosis and at follow-up. It correlates with markers of disease activity including LDH and beta-2 microglobulin. When compared with WBXR, MIBI has increased sensitivity for the detection of bone disease. [10,11] This technique has largely been replaced by more modern imaging modalities but may be an alternative where PET-CT is unavailable.

6. Technetium Bone Scintigraphy

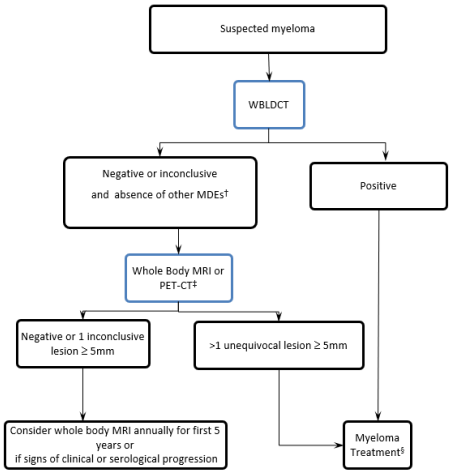
Traditional bone scintigraphy has a clinical role in the detection of solid tumours which metastasize to the skeleton but is usually ineffective to detect bone disease in multiple myeloma and solitary plasmacytomas because these lesions are typically “cold lesions”. Therefore, technetium bone scan has NO ROLE in the imaging of multiple

myeloma. There is a potential role for Technetium Bone Scintigraphy during cardiac work up for Systemic Amyloidosis. [12]

Utilisation of Available Imaging Clinical Practice in Symptomatic Myeloma

The IMWG definition for diagnosis of myeloma includes cross sectional imaging as a method to define bone disease. Consequently, plain X ray skeletal survey is no longer recommended in the initial workup of suspected myeloma. Because of its improved sensitivity and ability to determine the extent of osteolytic bone destruction WBLDCT is recommended as first line imaging in all cases of suspected or confirmed multiple myeloma.

Where lytic lesions are confirmed on WBLDCT, further imaging may not be necessary. If, however, spinal cord compression is a possibility, MRI should be performed [8]. If the suspicion of myeloma is high and the CT is negative or equivocal and there are no other myeloma defining events (MDE), whole body MRI or PET-CT should be considered (figure 1). Whole-body MRI or PET-CT are more sensitive and have the potential to detect osseous and focal lesions and extra-medullary lesions that would not have been visualised on CT.



†If other MDE's (myeloma defining events (Hypercalcaemia, Renal Impairment, Anaemia, light chain ratio > 100, bone marrow plasmacytosis > 60%), myeloma diagnosis is established: role of imaging is to assess bony involvement rather than to establish the diagnosis.

‡ When WBMRI is not available, MRI spine and pelvis can be performed and has been found to detect up to 90% of focal lesions found on whole-body imaging [6]. PET-CT may be an alternative depending on availability and in certain situations e.g., suspected solitary plasmacytoma and extra medullary disease.

§With myeloma diagnosis established with above imaging consider additional cross-sectional imaging.

- MRI if spinal cord compression is suspected.
- MRI or PET-CT if baseline imaging for ongoing disease monitoring is to be considered.

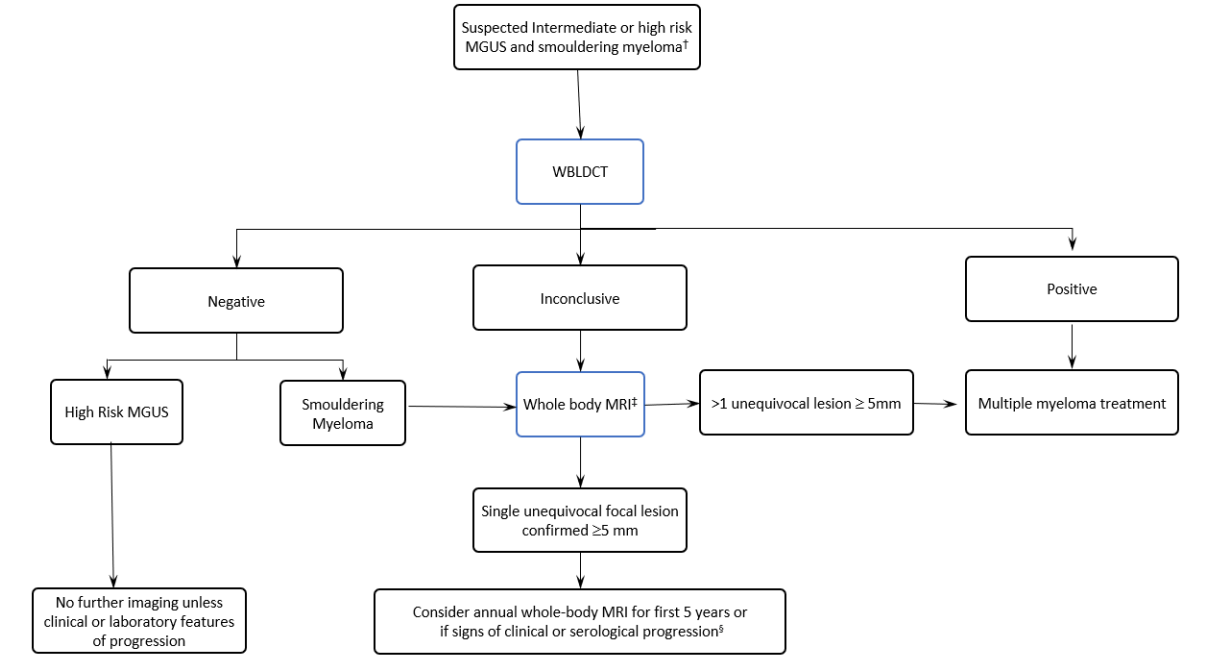
Figure 1: Suggested algorithm for the imaging workup of suspected multiple myeloma.

As lytic bone lesions often persist post-treatment, CT has limited role in monitoring the response to treatment.[13] CT is however recommended when disease relapse is suspected (e.g., serological progression) to assess the extent of bone destruction. PET-CT is more specific for the detection of response and is therefore endorsed as the preferred imaging modality for this purpose. [14] Additionally, imaging assessment with PET-CT has been incorporated into minimal residual disease negative status by IMWG multiple myeloma response criteria.[3]

Initial Diagnosis of Asymptomatic Disease

Smouldering multiple myeloma (SMM) is an earlier stage asymptomatic clonal plasma cell disorder defined by the IMWG as presence of a serum monoclonal protein of ≥ 30g/L or urinary monoclonal protein ≥ 500mg per 24 hours and/or clonal bone marrow plasma cells 10-60% in the absence of myeloma defining events or amyloidosis. [1] Currently patients with smouldering myeloma are not treated until a myeloma defining event develops. Use of MRI and/or PET-CT in these patients can detect occult disease not seen on WBLDCT leading to the diagnosis of myeloma therefore making them eligible for treatment earlier. When the MRI is equivocal, follow up scans are recommended. When the initial screening MRI is negative for symptomatic myeloma annual scanning has been recommended for the first five years where available (figure 2) [1,15,16].

MGUS is a plasma cell disorder defined by a serum monoclonal protein < 30 g/L, clonal bone marrow plasma cells < 10%, and absence of myeloma defining events. Patients with low risk MGUS (monoclonal protein < 15 g/L, IgG isotype, normal free light chain ratio and no concerning clinical features) are less likely to progress and skeletal imaging has low yield and can usually be deferred [17]. In patients with intermediate or high risk MGUS bone marrow examination and WBLDCT is recommended (figure 2)[18]. Detection of bone lesions in these patients may 'up-stage' their disease resulting in earlier treatment. Non-secretory and oligosecretory myeloma as well as solitary plasmacytoma should be considered in the differential diagnosis of MGUS. Clinicians should have a high index of suspicion for these entities and request imaging accordingly.



† No imaging required in low risk MGUS (see definition in text above)

‡When WBMRI is not available, MRI spine and pelvis can be performed and has been found to detect up to 90% of focal lesions found on whole-body imaging [6]

§ Consider more frequent imaging if more high-risk features on MRI (diffuse infiltration ≥ 2 small lesions < 5mm)

Figure 2: Suggested algorithm for the imaging workup of intermediate-high risk MGUS and smouldering myeloma.

Summary

Plain film XR Skeletal Survey is not recommended and is considered inadequate and obsolete. Cross sectional imaging has led to the detection of MM at an earlier stage leading to effective timely therapy and improved outcome for patients with plasma cell dyscrasias. It is the international standard of care for the diagnosis of bone disease. It is recommended for all patients with a suspected diagnosis of multiple myeloma and smouldering multiple myeloma. Similarly, cross sectional imaging is recommended for patients with intermediate and high risk monoclonal gammopathy of undetermined significance and solitary plasmacytoma.

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Table 1: Summary of Imaging Modalities Available

Imaging Modality	Clinical Uses	Advantages	Disadvantages	Radiation Exposure
Whole Body X-Ray	• Assessing for lesions at impending risk of fracture. • Where other imaging modalities are unavailable.	• Currently reimbursed • Wide availability • Large field of view • Good yield in ribs and skull • Relatively low radiation burden	• Low sensitivity, particularly in early stage disease • Difficult to assess some areas due to superimposition of overlying structures • Relatively long imaging time and need for patient repositioning • Unhelpful for assessing response to treatment • Low reproducibility between centres	0.9 mSV
Whole Body Low Dose CT	• To screen for myeloma bone disease • To detect extramedullary disease and long bone disease not imaged in WBMRI • To assess in biopsy and surgical intervention. • Assist in planning of radiotherapy • To act as a baseline post treatment	• Higher sensitivity than WBXR for detecting osteolytic lesions • Readily available • Quick acquisition time • Ability to reconstruct 3D images	• Higher cost (compared to WBXR) • Lacks ability to assess bone marrow involvement and is less sensitive than MRI • Potential for over-interpretation and further investigations • Unhelpful to assess response to treatment • Radiation dose remains higher than WBXR and MRI	5.7 mSV

		• Ability to detect small lesions • Useful for planning interventions (biopsy, surgery, radiotherapy) • Provides information relating to fracture risk and degree of instability • Able to detect other pathological processes	• Increased length of time and expertise to report findings	
MRI	• To screen for myeloma bone disease • To upstage MGUS and smouldering myeloma • To further evaluate for cauda equina in symptomatic patients.	• Highest sensitivity for detecting bone lesions • Allows accurate assessment of nerve impingement, fractures, degree of bone marrow infiltration and soft tissue involvement • No radiation exposure	• Higher cost (compared to WBLDCT and WBXR) • Limited availability • Prolonged acquisition time (~45 mins) • Interference by patient related factors (metal work, claustrophobia) • Increased length of time and expertise to report findings	Nil.

		• Ability to assess response to treatment		
PET-CT	• To screen for myeloma bone disease • Provide information in patients with extramedullary disease and those with non-secretory myeloma • Monitor response to treatment • Assist in prognostication and MRD negativity status	• Functional imaging modality • Whole body imaging and can identify bone and extramedullary lesions • Distinguishes between active and inactive disease • Best modality to monitor response to treatment • Provides information on prognosis • Provides information on complications e.g., avascular necrosis	• Highest cost • Higher radiation dose • Prolonged acquisition time (~60-90 mins) • Requires lesions to be >1cm for detection • Limited availability • Lack of standardised imaging criteria • Poor inter-observer reproducibility	11-20 mSV

Technetium-99m-Sestamibi Scintigraphy (MIBI)	• Assessment of bone disease at diagnosis • Treatment response • Prognostication	• Relatively short acquisition time • Low radiation exposure compared to PET-CT • High sensitivity and specificity for the detection of marrow activity in the bone marrow • Correlates with markers of disease activity • May be an alternative where PET-CT is unavailable	• Radiation exposure • Limited availability outside metropolitan area • Longer acquisition time compared to WBLDCT	11 mSV