

A wide-angle landscape photograph showing a green field in the foreground, rolling hills in the middle ground, and a bright blue sky with scattered white clouds. The sun is low on the horizon, creating a warm glow.

MSAG Guidelines

Imaging of patients with Multiple Myeloma and associated Plasma Cell Disorders

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1 INTRODUCTION

Background

Imaging modalities for multiple myeloma (MM) have evolved over the years to enable earlier detection of disease prior to overt bony destruction and are also now a sensitive measure of residual disease burden. 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 signal the development of **lytic lesions** within the next 18-24 months. The identification of more than one focal lesion of at least 5mm in size is now considered a myeloma defining event and identification of such cases requires more sensitive imaging modalities than plain radiographs [1]. Indeed, plain radiographs as part of a whole-body X-ray (WBXR) (i.e., conventional skeletal survey) which previously were the standard of care for diagnosis of bone disease are now considered obsolete.

Cross-sectional imaging modalities such as whole-body low dose computed tomography (WBLDCT), magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose positron emission tomography with CT (FDG PET-CT) are more sensitive for the detection and monitoring of bone and bone marrow disease. CT scan is able to detect areas of bone destruction (lytic lesions) however it cannot detect the precursor focal lesion which are areas of abnormal bone marrow detected on MRI or PET that signal the development of a lytic lesion in the next 18 – 24 months. The presence of more than one focal lesion ≥ 5 mm in size is a myeloma defining event indicating the need for therapy.

These modalities are now included in the International Myeloma Working Group (IMWG) current consensus criteria for initial diagnosis and treatment response assessment. [2, 3] However, barriers to their use in Australia remain including inadequate funding and availability. The aim of this clinical practice statement is to review the evidence supporting the use of these modalities and thus provide a platform to review appropriate funding models in Australasia.

Key Words: Myeloma, Imaging, CT, PET, MRI, MIBI

Methodology

This clinical practice statement was compiled by the Medical Scientific Advisory Group (MSAG) which is a sub-committee of Myeloma Australia, together with specialised opinion sought from experts in the field of imaging. The group aims to facilitate scientific advances and medical care in multiple myeloma. The aim was to standardise imaging modalities in plasma cell disorders and multiple myeloma and provide an evidence-based clinical practice statement that can assist clinicians in the care of patients with these disorders. Levels of evidence and grades of recommendations were stratified using established criteria as outlined in table 1.

Table 1: Levels of evidence and grades of recommendations [4]

LEVELS OF EVIDENCE	
I	Evidence from diagnostic systematic reviews of randomised control trials.
II	Evidence from well-designed non-randomised with reference standard comparator arm
III	Evidence from other well-designed diagnostic studies including case-control studies
IV	Evidence from diagnostic studies with no reference standard comparators.
GRADES OF RECOMMENDATIONS	
A	Recommendation based on level I or II studies with no low risk of bias and directly application to clinical care
B	Recommendation based on level II and III studies with low risk of bias and generally applicable to clinical care
C	Recommendation based on level III studies with no low risk of bias or level I or II with moderate to high risk of bias and probably applicable to clinical care
D	Recommendations based on level IV studies or level I to III studies with high risk of bias and are inconsistent and not applicable to clinical care

Literature Review

A comprehensive search was performed using PUBMED and MEDLINE for English publications published between 1980 and 2019 with the search terms Myeloma, Imaging, X-Ray, CT, MRI, PET and MIBI. The references of retrieved publications were also reviewed to identify other relevant publications.

Review of the Manuscript

The guideline clinical practice statement is a consensus established by the Medical Scientific Advisory Group (MSAG) to Myeloma Australia which consists of a panel of haematologists and expert radiologists across Australia.

2 IMAGING MODALITIES AVAILABLE

2.1 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 and was traditionally employed as the primary imaging modality to assess for bone disease. Lesions, however, typically require 30% to 50% of trabecular bone resorption before they become apparent. [5, 6] 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. [7, 8]

Advantages:

Advantages include its relatively low cost, wide availability, ability to visualise large areas of the skeleton with a low radiation dose, and ability to screen for lesions at impending risk of fracture.

Limitations:

The main limitations of WBXR are its low sensitivity for detection of early lesions, inability to detect lesions in the bone marrow (focal lesions) and limited specificity for distinguishing myelomatous lesions from those caused by other malignant or pathological processes. In addition, poor reproducibility between different centres, long imaging time on the radiographic table with associated patient discomfort and pain, the inability to assess treatment response, and poor visualisation of bony architecture due to overlying structures in some areas further highlight that this modality is obsolete as a screening tool for the detection of bone involvement for plasma cell dyscrasias. [1, 3, 9]

Summary:

- WBXR has a lower sensitivity and specificity than cross-sectional imaging modalities and underestimates the presence of treatable disease. (Level I, Grade A)
- WBXR is no longer recommended as the primary modality to image myeloma bone disease. (Level I, Grade A)

2.2 Computerised Tomography (CT)

Conventional CT previously incurred a substantial radiation exposure and was previously used primarily for further characterisation of lesions in the spine. [10] However, the recent improvements in CT technology which have allowed a marked reduction in radiation exposure whilst maintaining the intrinsic contrast between high-density mineralised bone and soft-tissue density osteolytic lesions, have meant that there has been no appreciable compromise in diagnostic accuracy. Whole body low dose CT (WBLDCT) protocols are now being used which offer the advantage of covering the whole-body with a lower effective patient radiation dose. [11] Effective radiation dose has been reduced from 25.5-36.6mSV to 5.7mSV with modern tin filtered CT, delivering doses similar to plain x-ray. [12-15] By comparison, estimated effective radiation dose for WBXR varies between 0.9-1.5 mSV depending on patient body habitus and equipment. [11]

WBLDCT is significantly more sensitive than WBXR for detecting myelomatous lesions. A study by the International Myeloma Working Group found that 25.5% of patients with a negative skeletal survey had osteolytic lesions detected on WBLDCT performed at the same time. This had management implications in the majority of patients; over 20% with smouldering MM based on WBXR met the criteria for active MM on CT. [8] Similarly a review conducted by Ippolito *et al.* found that 54% of patients with histological proven myeloma had myeloma defining bone lesions on WBLDCT which were previously unrecognised. [16]

Advantages:

The advantages of WBLDCT is its ability to detect small osteolytic lesions which are not seen on plain films, it has relatively wide availability and low cost (compared to MRI and PET-CT), can detect extramedullary disease, and has the ability to guide biopsy, surgical intervention and radiotherapy. It is also better at determining bone integrity than MRI. [16, 17] Furthermore, the patient can remain supine on the scanning bed and the scanning times are short which means that the scan procedure is much less problematic and painful for the patient when compared to WBXR and MRI. Advances in image reconstruction allow the data to be displayed in multiple planes rather than in 2-dimension (2D).

Limitations:

WBLDCT is unable to detect intramedullary plasma cell infiltration which is a limitation compared with MRI or PET-CT scan. It has increased length of time and complexity for image reporting compared with WBXR. If extra-medullary lesions are detected, careful thought for additional investigation, particularly biopsy should be considered. Alternative pathology including synchronous malignancy may require exclusion. [10]

Summary:

- WBLDCT is more sensitive and specific compared to WBXR for assessing for bone disease but less sensitive than MRI (Level I, Grade A)
- WBLDCT is useful in the planning of surgical intervention and radiotherapy (Level I, Grade A)
- Taking into consideration of local reimbursement issues WBLDCT is mandated as a first-line imaging modality in suspected multiple myeloma (Level I, Grade A)

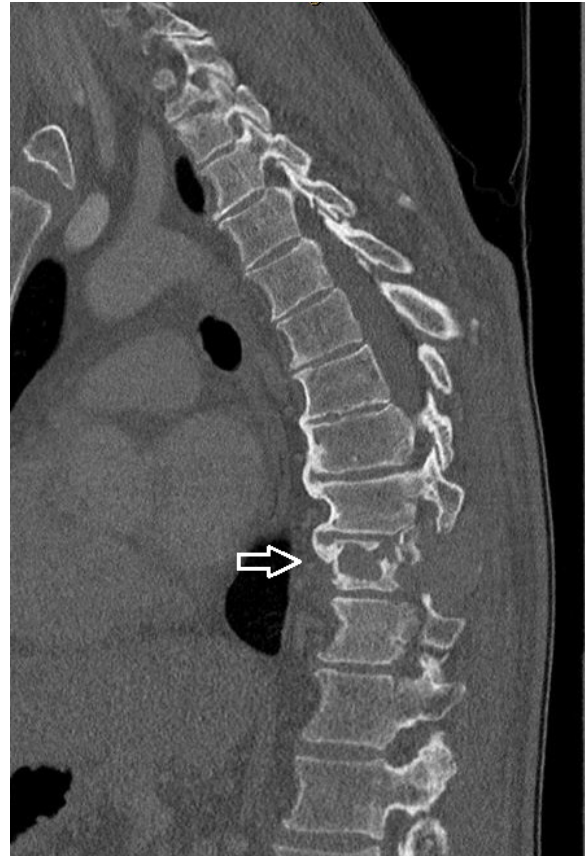
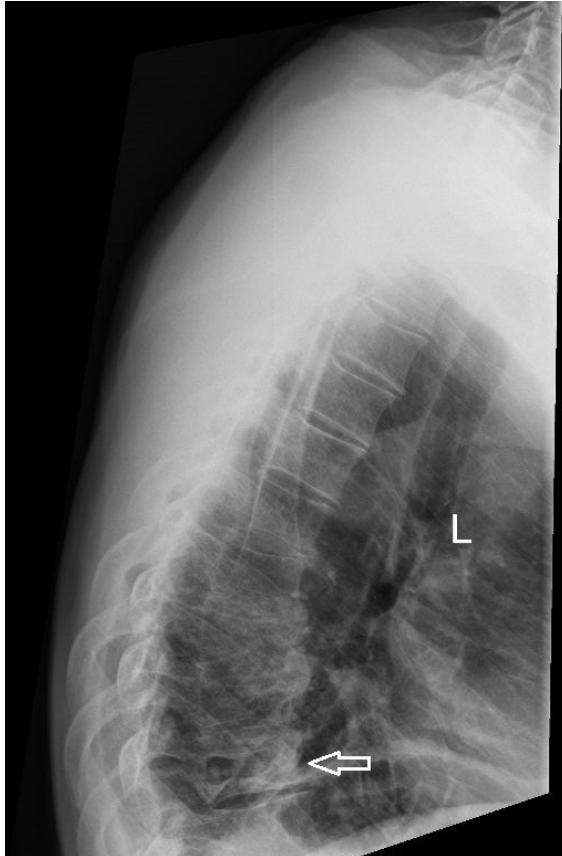


Image 1: Solitary plasmacytoma in the T10 vertebral body which was difficult to appreciate on plain radiography (left) compared to CT (right). The diagnosis was confirmed by CT-guided biopsy (see image 2 below).



Image 2: Axial CT image through the T10 vertebra demonstrating a CT-guided biopsy of the lesion in image 1.

2.3 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. Thus, MRI can upstage asymptomatic patients at diagnosis as well as assisting with response assessment. **Detection of more than one focal lesion \geq 5mm in size by MRI meets diagnostic criteria for active MM.** [1] Focal lesions are early, abnormal areas in the bone marrow that may signal the development of a lytic lesion within the next 18-24 months. An otherwise asymptomatic patient whose MRI scan shows more than 1 focal lesion of at least 5 mm in size has a myeloma-defining event, and treatment for active disease is recommended per the IMWG Criteria.[1]

MRI enables the earlier diagnosis of active myeloma, enabling timely treatment prior to end organ damage and thus improving outcome. MRI also provides prognostic information. The presence of small equivocal lesions is associated with disease progression. A diffuse infiltration pattern on MRI is also associated with increased risk of progression. The detection of > 7 focal lesions on MRI is associated with a shorter time to progression. [6, 18-22]

Various MRI techniques are used in the assessment of MM with many patterns of involvement. Diffusion weighted MRI is the most commonly used technique; it highlights the differences in intra and extracellular water content and is useful before, during and after treatment. [6, 23] New MRI techniques such as Dixon-MRI enable the acquisition of four separate images: in-phase (like conventional T1-weighted images), out-of-phase, water only and fat only. Fat only images in particular have shown to be more sensitive in relation to lesion counts and true positive results. This is likely due to myelomatous infiltration of the bone marrow leading to a reduction in marrow fat content [24].

Whole body MRI (WBMRI) has become an efficient method for total body screening from head to toes and has been recommended in some jurisdictions as the first line investigation in asymptomatic patients; 50% of lesions will be missed if 'MRI spine' alone is performed. 'MRI-spine and pelvis' specifically provides detailed pictures of the spine and/or pelvis and surrounding tissues and specific spinal sequences can be incorporated into WBMRI. [6, 18, 25, 26] When whole-body MRI 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]

Advantages:

The advantages of MRI include high sensitivity and the ability to upstage asymptomatic patients, provide direct assessment of the bony medulla, and ability to detect plasma cell infiltration at an earlier stage of disease which provides extremely important prognostic information with nil radiation exposure. It is the preferred imaging modality for the assessment of spinal cord or nerve root compression given its exquisite anatomical detail. [3, 6, 27]

Limitations:

MRI has limited availability, relatively high cost, prolonged study time, lack of standardisation of technique, and the high level of radiological expertise required for interpretation. There are also limiting patient factors including claustrophobia, patient's size and some *in situ* metal devices such as permanent pacemakers. MRI is also less accurate in detecting disease in certain anatomical regions including the skull, clavicle and ribs where it has relatively high false negative results. Incorporation of newer techniques such as diffusion weighted imaging and whole-body Dixon-based fat fraction evaluation may overcome some of these limitations. [28-32]

Summary

- MRI is recommended in patients with suspected smouldering multiple myeloma when WBLDCT is negative or equivocal as **detection of more than one focal lesion \geq 5mm in size by MRI meets diagnostic criteria for active MM.** (Level II, Grade B)
- MRI is the modality of choice for suspected spinal cord compression (Level I, Grade B)
- MRI is useful for assessment of extra-osseous disease and treatment response (Level II, Grade B)
- When WBMRI is not available, MRI of the 'whole spine and pelvis' can be performed and has been found to detect up to 90% of focal lesions found on whole-body imaging (Level II, Grade B)

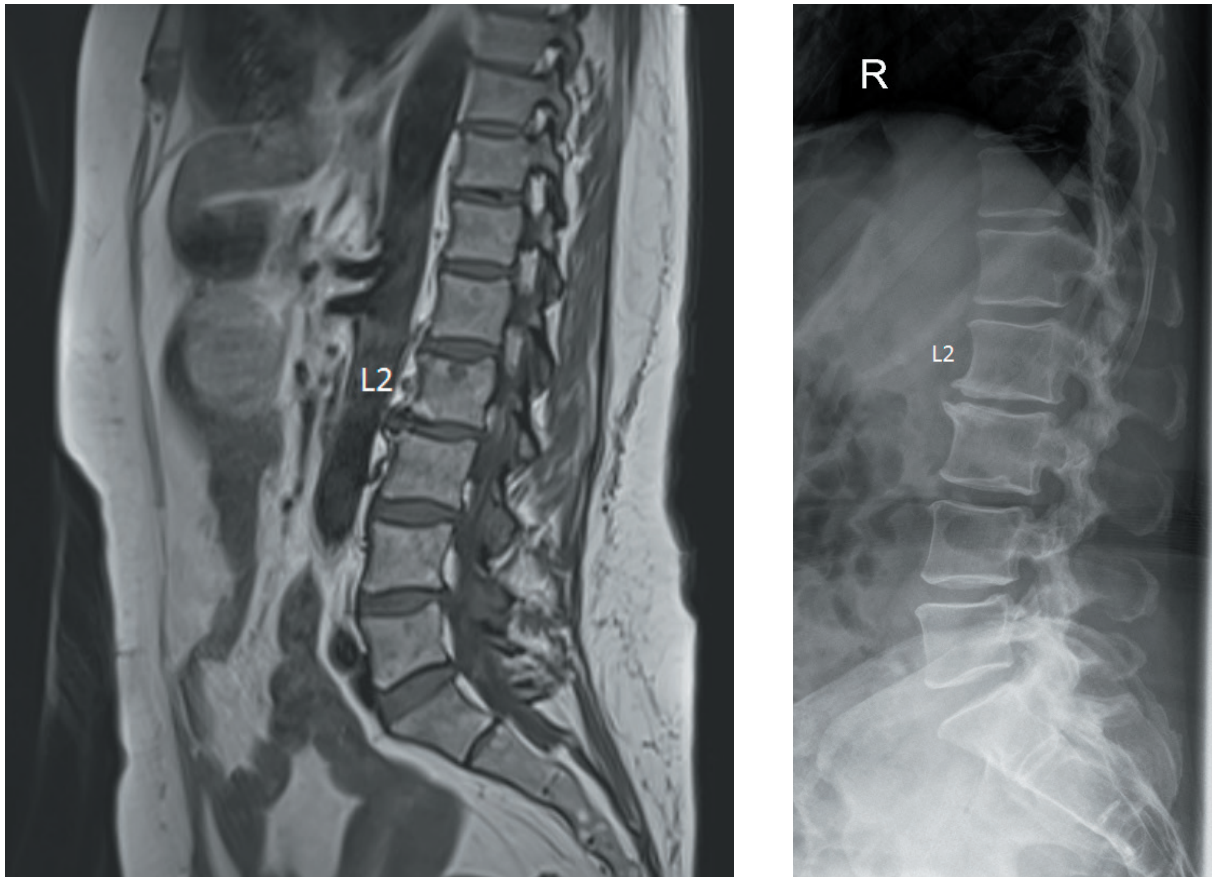


Image 3: Myelomatous bone lesion in the L2 vertebral body demonstrating abnormal marrow signal on T1 weighted MRI of the spine (left) which was not visible on a plain radiograph (right)

2.4 Positron Emission Tomography-Computed Tomography (PET-CT)

Positron Emission Tomography-Computed Tomography (PET-CT) is a combined functional and anatomical imaging modality. In PET-CT, PET detectors are able to localise a PET radiopharmaceutical (or tracer), such as ^{18}F -FDG, which is injected into a vein in the body and the CT is able to localise the site of tracer uptake to provide anatomical localisation. The typical ^{18}F -FDG PET-CT workflow involves the injection of ^{18}F -FDG and then the patient rests quietly for 60 minutes. This quiet rest period is referred to as the 'uptake time'. The patient is then positioned on the scanning bed when the CT acquisition is undertaken, in less than a minute, and the PET acquisition follows with scanning times which vary from 15-45 minutes depending on the extent of the scan and the size of the patient. The degree of FDG, or tracer, uptake can be semi-quantitatively estimated through the standardised uptake value (SUV), which takes into account the dose of administered PET radiopharmaceutical and the patient's weight. An increase in the SUV corresponds to sites of active disease. [8, 9, 33] The SUV, however, is time dependent and increases over time in most malignancies and so to compare sequential (e.g. pre- and post-treatment) studies in the one patient, the uptake time for both scans should be close to identical. ^{18}F -FDG PET-CT is able to detect sites of disease in the bone marrow, the bony skeleton and also extra-medullary disease. It can be used to assess treatment response where a reduction in SUV is expected with a good response. [34] Similarly the IMWG has recently included PET complete metabolic response as a subcategory to their response criteria. [35]

Advantages:

When compared to WBXR and WBLDCT, FDG PET-CT is more accurate for the early detection of bone lesions. It shows similar sensitivity to MRI in the detection of discrete bone lesions and previous reports suggest that PET-CT is less sensitive for the detection of diffuse bone marrow infiltration; these previous reports, however, relied on early generation scanners and the increased sensitivity and improved resolution of the latest generation scanners as shown in Image 4 suggest that this is now, not the case. [8, 17, 36-39].

When performed at diagnosis, PET-CT provides prognostic information as the presence of three or more lesions is associated with a worse prognosis. A positive scan has been found to be an independent predictor of progression free and overall survival. [40, 41] The presence of extra medullary disease is also associated with shorter overall survival. [42]

A major advantage of PET-CT is that it can provide powerful prognostic information *following* therapy. [41] PET-CT after triplet combination therapy and autologous stem cell transplantation therapy correlated with improved progression free and overall survival [39]. Specifically a reduction of focal lesions and bone marrow uptake lower than the liver (Deville score < 4) has been proposed as the standard definition of PET complete metabolic response after therapy. [35]

Limitations:

On PET-CT there can be regions of increased FDG uptake at sites of inflammation, infection surrounding or involving bone and also in tissue surrounding prostheses but these sites of 'false positive' uptake are generally not an issue for experienced readers. [8, 9] FDG uptake relies on the expression of the glucose transporter and some tumours can vary in their expression of this surface receptor. FDG uptake is also reduced with hyperglycaemia and steroid administration. Recently simultaneous FDG-PET-MRI studies reported that a number of myeloma bone lesions were not apparent on PET but visible on MRI with the suggestion that sub-centimetre lesions could not be detected and lesions between 5-10mm were considered equivocal on PET. [6, 40] The PET component of most current PET-MR devices, however, is based on PET technology that is over a decade old.

Additional limitations include radiation exposure, however, similar to CT, instrumentation advances now allow for better image resolution with a lower patient radiation dose. Any assessment of treatment response should include attention to factors that may affect the SUV such as dose and uptake time and consequently standardisation of imaging parameters is crucial. Although the cost for a PET-CT scanner is less than an MRI scanner there is an ongoing cost for the PET radiopharmaceuticals, availability can be limited in regional areas and poor inter-observer reproducibility in interpretation remain limiting factors. [8, 17]

Summary

- Compared to WBXR and WBLDCT, PET-CT is more accurate in the early detection of bone lesions. (Level I, Grade A)
- PET-CT provides prognostic information when performed at diagnosis and following therapy. (Level I, Grade A)
- PET-CT is useful in patients with extramedullary disease and those with non-secretory myeloma (Level I, Grade A)

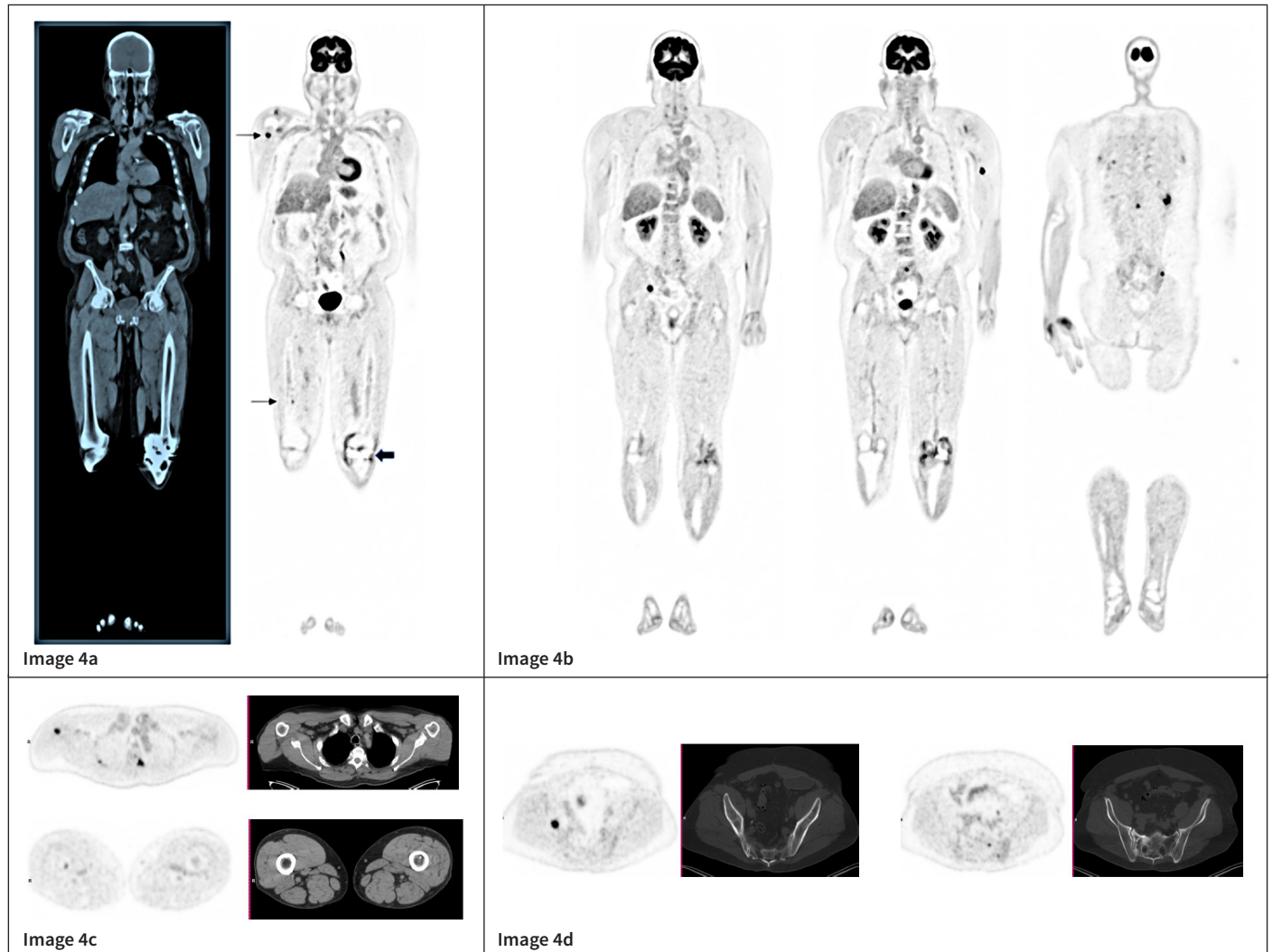


Image 4: 67 yr. old man with MM; FDG PET-CT scan extending from vertex to toes; 304 MBq of FDG; 58-minute uptake and 30 min acquisition. a) single CT and serial PET images show multiple sites of increased FDG uptake; thin arrows show disease in bone marrow (BM); broad arrow shows diffuse moderate uptake surrounding left knee prosthesis that is not confused with a site a disease; b) trans axial images from sites of thin arrows on coronal image; top row shows registered PET and CT images with a 9 mm lesion in proximal right humerus SUV = 9.6; 4 mm lytic lesion, SUV 9.9, in left transverse process of T3; 4 mm lytic lesion in right 3rd rib, SUV 6.0; Bottom row – 2 mm BM lesion SUV 4.6. c) trans axial slice through pelvis: 13 mm lytic lesion in right ilium, SUV 10.4; d) trans axial slice through sacrum showing treated disease on right which is not FDG-avid, SUV 2.5 and small 5 lesion in left sacrum SUV 5.6- and 4-mm lytic lesion in left posterior ilium SUV 4.6.

2.5 Technetium-99m-Sestamibi Scintigraphy (MIBI)

Another nuclear imaging modality uses technetium 99 sestamibi (MIBI). This modality has relatively short acquisition times and acceptable radiation exposure of 11 mSV. 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.

MIBI and PET-CT were previously shown to be superior to MRI predicting the outcome of MM patients although such studies predated modern MRI techniques. [43]

When compared with WBXR, MIBI has increased sensitivity for the detection of bone disease. MIBI and PET-CT perform similarly in the detection of diffuse bone disease however PET-CT is superior for the detection of focal lesions. [44, 45] MIBI however may be an acceptable alternative where either availability or reimbursement barriers limit the availability of PET-CT. [46]

Summary:

- Short acquisition time (Level II evidence, Grade B)
- High sensitivity and specificity for myeloma activity in the bone marrow at diagnosis and follow up (Level II, Grade B)
- Correlates with serological markers of disease such as LDH and Beta-2 microglobulin (Level II, Grade B)
- MIBI may be an alternative where other functional imaging techniques (i.e., PET-CT) are not available or there are reimbursement barriers.

2.6 Technetium Bone Scintigraphy

Traditional bone scintigraphy has a clinical role in the detection of solid tumours which metastasise to the skeleton but is usually ineffective to detect bone disease in multiple myeloma and solitary plasmacytomas because these lesions are typically “cold lesions”. Bone scintigraphy is useful for detecting osteoblastic lesions. MM bone lesions are caused by osteoclastic bone destruction and bone scintigraphy therefore has low sensitivity for detecting bone lesions in MM with fewer lesions at diagnosis compared with WBXR. [47] There is a potential role for Technetium Bone Scintigraphy during cardiac work up for Systemic Amyloidosis. [48]

Technetium Bone Scintigraphy Summary:

- Technetium bone scintigraphy **HAS NO ROLE** in the imaging of multiple myeloma and plasma cell disorders (Level II, Grade B)

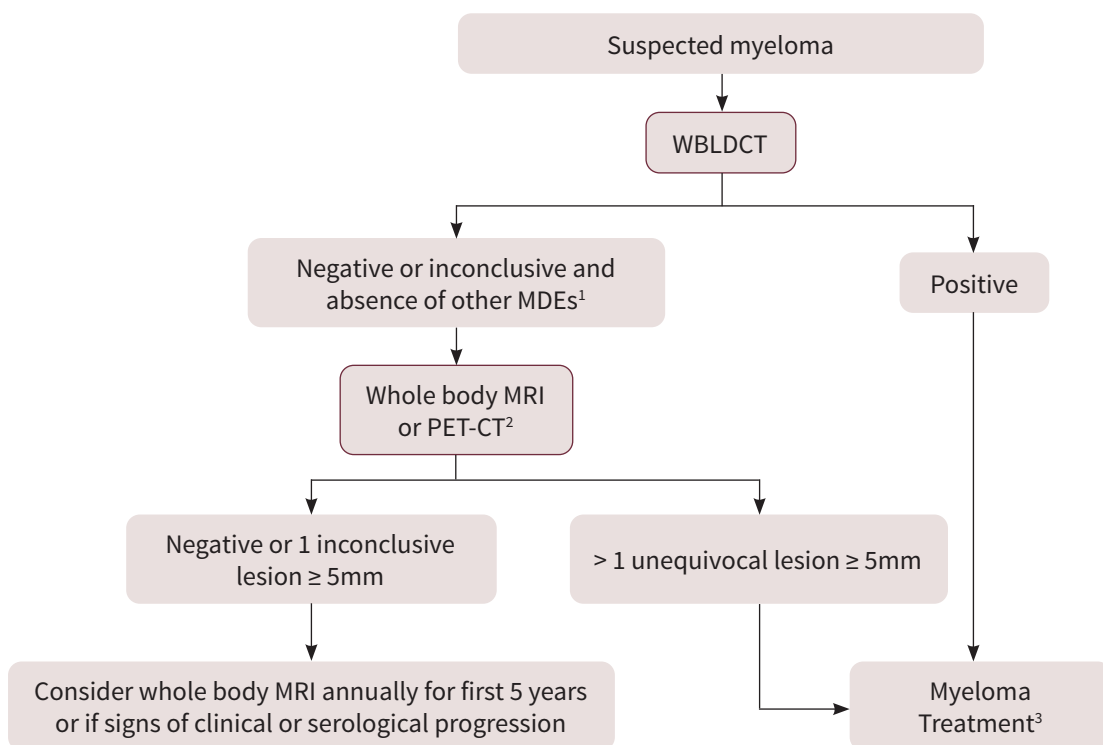
3 UTILISATION OF AVAILABLE IMAGING CLINICAL PRACTICE IN SYMPTOMATIC MYELOMA

3.1 Initial Diagnosis of suspected myeloma

The IMWG definition for diagnosis of myeloma includes cross sectional imaging as a method to define bone disease. Whole-body low dose CT offers improved sensitivity in the assessment of lytic lesions, at all sites but particularly of the sternum and scapulae that are difficult to visualise. Consequently, plain X ray skeletal survey is no longer recommended in the initial workup of suspected myeloma.

It is imperative to ascertain the extent of bone destruction at diagnosis with any unequivocal lytic lesion confirming the diagnosis of myeloma as a myeloma defining event. 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.** WBLDCT is generally readily accessible for most treating centres and is mandated subject to local reimbursement issues. (figure 1).

Where lytic lesions are confirmed on WBLDCT, further imaging may not be necessary. Of note however, if spinal cord compression is a possibility, additional MRI should be performed. [34]. 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 (subject to local reimbursement issues) (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. Both MRI and PET-CT can provide prognostic information although this is not used at present to guide therapy. [18, 19, 22, 39-42]



1 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.

2 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.

3 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.

Summary:

- All patients with suspected myeloma must undergo cross-sectional imaging. (Level I, Grade A)
- Whole body low dose CT is mandated for the detection of lytic lesions. (Level I, Grade A)
- 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. (Level I, Grade A)
- MRI is gold standard for assessment of suspected spinal cord compression (Level I, Grade A)

3.2 Evaluation of Fracture Risk

Due to osteoclast activation and osteoblast inhibition pathological fractures are frequent in patients with multiple myeloma. Assessing for spine fractures in multiple myeloma may be challenging due to coexisting osteoporosis. The presence of fractures in myeloma has been linked to reduced overall survival and increased mortality. [49]

Most patients with a pathologic fracture of the extremity present with pain and deformity. Pathological fractures of the thoracic and lumbar spine should be considered when patients report acute onset pain, inability to ambulate or neurological deficits. The diagnosis of a complete or impending fracture should be made radiographically.

Due to more complex anatomy, urgent evaluation by cross-sectional imaging may be required when involving the spine or pelvis. CT scans are readily available, fast and accurate for assessing the bony cortex and degree of vertebral compression; however, compared to MRI is less sensitive in the assessment of underlying marrow focal lesions. MRI is the most sensitive and specific imaging modality to assess spinal lesions and specifically allows differentiation of insufficiency and pathological fractures. [6] As such, it is often useful to distinguish crush fractures due to MGUS associated osteoporosis from crush fractures due to myeloma bone lesions.

Some patients lack pathological fractures but are deemed at high risk due to large degrees of bone marrow involvement. Consequently, prevention of fractures in this demographic is important goal of therapy. In patients with myeloma, a PET-CT with a SUV max > 3.5 combined with MRI showing diffuse or multifocal signal abnormality is predictive of impending vertebral compression fracture [50].

Fracture Risk Summary:

- Cross-sectional imaging such as CT are useful in assessing bony cortex (Level I, Grade A).
- MRI whole spine is the gold standard for assessing possibility of cord compression and allows differentiation of insufficiency and pathological fractures. (Level I, Grade A)
- PET-CT with a SUV max > 3.5 combined with MRI showing diffuse or multifocal signal abnormality is predictive of impending vertebral compression fracture (Level II, Grade B)

3.3 Imaging Response Assessment and subsequent disease evaluation

As lytic bone lesions often persist post-treatment, CT has limited role in monitoring the response to treatment. [13, 51] CT is however recommended when disease relapse is suspected (e.g., serological progression) to assess the extent of bone destruction.

MRI and PET-CT on the other hand, can differentiate between metabolically active and inactive sites of disease and can therefore assist in assessing degree of bone marrow infiltration. However, studies have shown that the specificity of MRI is unacceptably low and to date has not been linked to prognosis. False positive MRI appearances can be due to infection, osteoarthritis, fracture with bone marrow oedema, vertebral haemangiomas, and artefact around metal implants. [6, 32, 52, 53] MRI is not currently recommended for routine follow-up. [6]

PET-CT demonstrates equivalent sensitivity and is more specific for the detection of response. Therefore, it is endorsed as the preferred imaging modality for this purpose. [17, 53-58] Specifically, ¹⁸F-FDG-PET-CT negativity post autologous stem cell transplant and following triplet therapy has been associated with a longer progression free and overall survival. [39, 43, 52] Imaging assessment with PET-CT has been incorporated into minimal residual disease negative status by IMWG multiple myeloma response criteria. [3]

Summary:

- WBXR has no role in the response assessment of lytic bone disease (Level I, Grade A)
- WBLDCT can demonstrate resolution of extramedullary disease (Level II, Grade B)
- WBLDCT can serve as baseline for progressive disease (Level II, Grade B)
- MRI can provide information on degree of bone marrow plasma cell burden and thus guide assessment of response (Level II, Grade B)
- PET-CT can be used to assess response to treatment and provide prognostic information (Level II, Grade B)
- MRI or PET-CT can be used to assess possible relapse (Level II, Grade B)

3.4 Non-Secretory / Oligosecretory Multiple Myeloma

Non secretory myeloma occurs in 1-2% of patients which is defined when there is no measurable monoclonal protein by electrophoresis in the blood or urine and no measurable free light chain assay abnormality. True non-secretory myeloma is rare, with many patients having abnormalities in the serum free light chain assay. Most of these cases can be followed by the serum free light chain assay, however some of these patients only have low levels of light chains which can fluctuate and be affected by renal function; thus, making response assessment and diagnosis of relapse difficult. [59]

The diagnosis and subsequent follow-up of non-secretory myeloma is challenging. Bone marrow plasmacytosis and PET-CT provide assessment of extent of disease at presentation and response to treatment. [57, 60] MRI shows similar sensitivity to PET-CT scan for initial disease assessment but is not recommended for monitoring. [60]

Where lesions are FDG avid at diagnosis, PET-CT is the best non-invasive modality for assessing response to treatment and should be performed at intervals dictated by the treatment cycles and clinical circumstances. The changes in FDG-avidity post treatment have also been linked to prognosis in overall and progression free survival in this subgroup of myeloma. [59, 61]

Summary:

- Cross sectional imaging with WBLDCT is recommended at presentation to assess extent of bone destruction and lytic lesions (Level I, Grade A)
- PET-CT is useful in the diagnosis, response assessment and monitoring algorithm for non-secretory multiple myeloma (Level I, Grade A)
- MRI is an acceptable alternative to screen for myeloma bone disease (Level II, Grade B)
- MRI is gold standard for assessment of suspected spinal cord compression (Level I, Grade A)
- Imaging intervals to be guided by symptoms or emergence of other MDEs (Level IV, Grade C)

4 INITIAL DIAGNOSIS OF ASYMPTOMATIC DISEASE

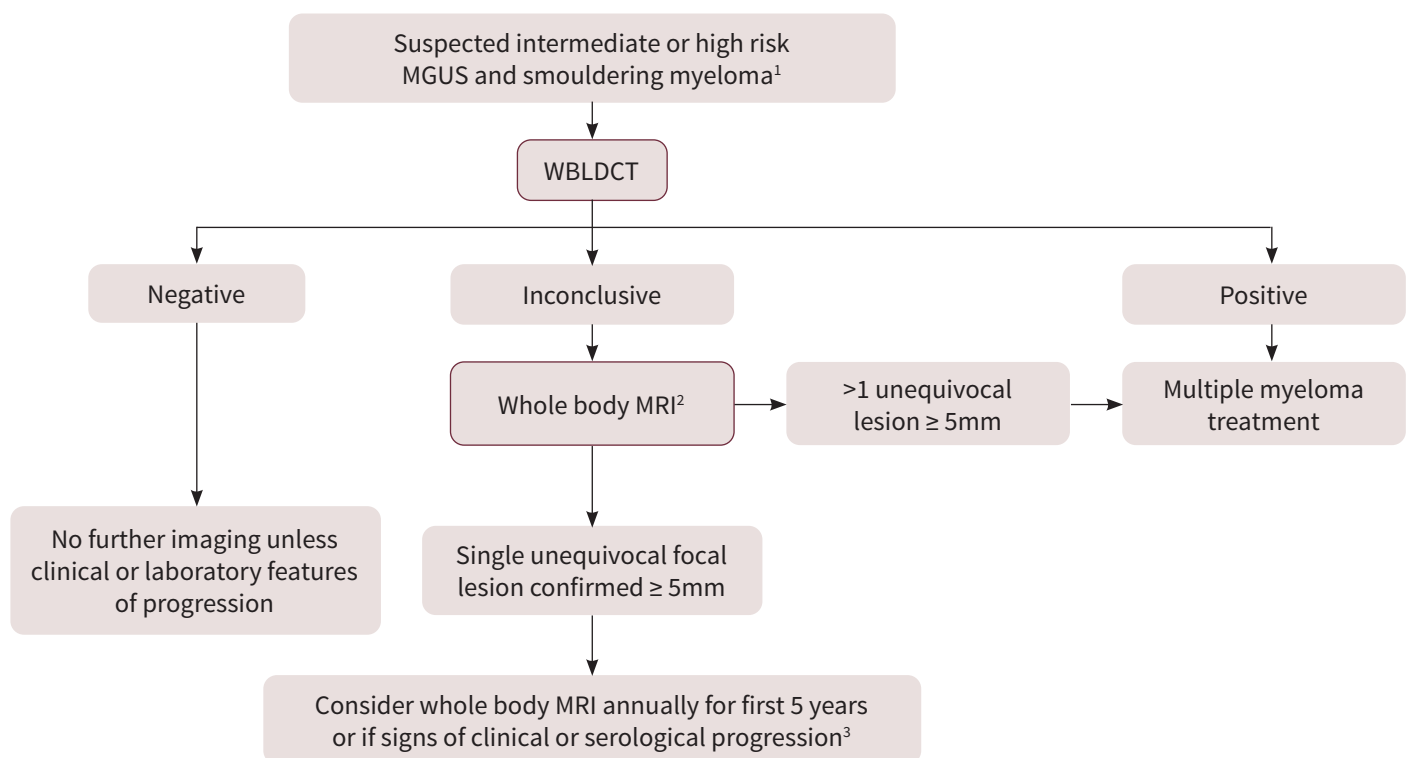
4.1 Smouldering Myeloma and Monoclonal Gammopathy of Undetermined Significance (MGUS)

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 $\geq 30\text{g/L}$ or urinary monoclonal protein $\geq 500\text{mg}$ per 24 hours and/or clonal bone marrow plasma cells 10-60% in the absence of myeloma defining events or amyloidosis [1]. These patients account for 10-15% of those with plasma cell dyscrasias. The progression rate to symptomatic multiple myeloma is 10% per year for the first five years.

Currently outside of clinical trials, patients with smouldering myeloma are not treated until a myeloma defining event develops. From an imaging point of view this occurs when any lytic lesion is detected by CT or there is greater than one focal lesion $\geq 5\text{mm}$ found on MRI or PET-CT [1].

Use of MRI and/or PET-CT in patients with suspected smouldering myeloma 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 earlier follow up scans are recommended (figure 2). Specifically, greater than or equal to 2 lesions less than 5mm or a diffuse pattern on MRI are associated with earlier progression and follow-up scans are recommended at 3-6 months. Approximately 50% of such patients had progressive disease, whilst those with stable MRI findings had no higher risk of progression. [6] When the initial screening MRI is negative for symptomatic myeloma annual scanning has been recommended for the first five years where available [1, 21, 22].

Similarly, PET-CT can provide prognostic information in smouldering myeloma. The risk of progression at 2 years for patients with focal lesions without osteolysis on PET-CT was increased from 33% for negative patients to 58% for those who were positive [62]. Another study showed a 61% 2-year progression in patients with abnormal PET-CT and no osteolysis. [63] However, currently, the IMWG does not incorporate PET-CT into the initial diagnostic algorithm for SMM [1].



1 No imaging required in low risk MGUS (see definition in text above) [65]

2 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]

3 Consider more frequent imaging if more high-risk features on MRI (diffuse infiltration ≥ 2 small lesions $< 5\text{mm}$)

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

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 than those with intermediate or high risk MGUS [64]. Skeletal imaging in low-risk patients have low yield and, as well as bone marrow examination, can usually be deferred [65].

In patients with intermediate or high risk MGUS, bone marrow examination and WBLDCT is recommended (figure 2). 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.

Summary

- Imaging and bone marrow examination can be deferred in patients with low-risk MGUS (Level II, Grade B)
- In patients with intermediate or high-risk MGUS or smouldering myeloma cross sectional imaging and bone marrow examination should be performed (Level I, Grade A)
- WBLDCT is the preferred initial imaging modality (Level I, Grade A)
- Where WBLDCT is inconclusive, WBMRI is recommended (to potentially identify active myeloma requiring therapy. When WBMRI is not available, MRI of the 'whole spine and pelvis' can be performed and has been found to detect up to 90% of focal lesions found on whole-body imaging. (Level I, Grade A).
- Non-secretory and oligosecretory myeloma as well as solitary plasmacytoma should be considered in the differential diagnosis of MGUS (Level IV, Grade C)

4.2 Utilisation of Available Imaging Clinical Practice in Solitary Plasmacytoma

Solitary plasmacytoma (SP) is characterised by a localised accumulation of neoplastic monoclonal plasma cells in the absence of other features of a systemic plasma cell disorder. It is generally sub-classified into a single lytic lesion involving bone or a single lesion at an extra-medullary site. Bone lesions are approximately twice as common as extramedullary lesions are more likely to progress within 2 years and are associated with a worse prognosis. [66]

If the diagnosis of solitary plasmacytoma is suspected, cross sectional imaging is required. PET-CT or Whole-body MRI both have the potential to upstage a solitary plasmacytoma to symptomatic myeloma requiring systemic therapy. The sensitivity and specificity of PET-CT is superior to MRI for upstaging SP and the specificity of PET-CT is superior to MRI for response assessment. [52, 66] MIBI and PET-CT perform similarly in the detection of diffuse bone disease however PET-CT is superior for the detection of focal lesions. [44, 45] MIBI however may be an acceptable alternative where either availability or reimbursement barriers limit the availability of PET-CT. [46]

Regular follow-up using the same modality as at diagnosis should be considered on an annual basis in the absence of clinical or laboratory evidence of symptomatic disease. [66]

Summary:

- PET-CT should be performed in MGUS patients with solitary plasmacytoma to exclude other sites of disease and assess for extra-medullary involvement (Level I, Grade A)
- If PET-CT is not available, whole body MRI is an acceptable alternative (Level I, Grade A)
- Follow-up using the same modality as at diagnosis should be considered on an annual basis (Level IV, Grade C)

5 SUMMARY

Cross sectional imaging has led to the detection of MM at an earlier stage leading to effective timely therapy and subsequently 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. Plain film XR Skeletal Survey is not recommended and is considered inadequate and obsolete.

5.1 Overall Recommendations

- Due to a lack of sensitivity, there is no role for whole body plain radiograph skeletal survey
- Cross-sectional imaging should be offered to all patients with suspected multiple myeloma, non-secretory myeloma or intermediate-high risk asymptomatic disease
 - Whole body low dose CT has a high sensitivity for the detection of bone lesions but is inaccurate for monitoring response to therapy
 - MRI and PET-CT have a high sensitivity for detecting bone lesions and are helpful to monitor treatment response and to detect disease relapse
- MRI is the gold standard for the assessment of patients with suspected spinal cord compression
- Cross sectional imaging should be performed in all cases of suspected solitary plasmacytoma to exclude further lesions
- Imaging is not recommended in patients considered to have low risk MGUS

5.2 Cost Reimbursement Status in Australia and New Zealand

Currently Medicare Australia reimbursement in multiple myeloma is limited to whole body plain radiograph skeletal survey. Whole body low dose CT is readily available however access may be limited by local reimbursement issues. PET-CT and WBMRI are not specifically reimbursed for the indication of plasma cell disorders, except for specific situations such as spinal cord compression.

The evidence presented in this national guideline together with international practice guidelines on myeloma imaging is compelling and endorsed by MSAG. Reimbursement of these imaging modalities must be urgently addressed by Medicare Benefits Scheme.

Imaging Modality	Clinical Uses	Advantages	Disadvantages	Radiation Exposure
Whole Body X-Ray	<ul style="list-style-type: none"> Assessing for lesions at impending risk of fracture. Where other imaging modalities are unavailable. 	<ul style="list-style-type: none"> Currently reimbursed Wide availability Large field of view Good yield in ribs and skull Relatively low radiation burden 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Higher sensitivity than WBXR for detecting osteolytic lesions Readily available Quick acquisition time Ability to reconstruct 3D images 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 	<ul style="list-style-type: none"> 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 Increased length of time and expertise to report findings 	5.7 mSV
MRI	<ul style="list-style-type: none"> To screen for myeloma bone disease To upstage smouldering myeloma To further evaluate for cauda equina in symptomatic patients. 	<ul style="list-style-type: none"> 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 Ability to assess response to treatment 	<ul style="list-style-type: none"> 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.
PET-CT	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Highest cost Higher radiation dose 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)	<ul style="list-style-type: none"> Assessment of bone disease at diagnosis Treatment response Prognostication 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Radiation exposure Limited availability outside metropolitan area Longer acquisition time compared to WBLDCT 	11 mSV

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