Guidelines for the use of imaging in the management of patients with myeloma

Andrew Chantry,[1,*] Majid Kazmi,[2,*] Sally Barrington,[3,4] Vicky Goh,[3,5] Nicola Mulholland,[6] Matthew Streetly,[2] Maggie Lai[7], Guy Pratt,[8] and on behalf of the British Society for Haematology Guidelines

[1]Department of Haematology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, [2]Department of Haematology, Guys and St Thomas's NHS Foundation Trust, [3]Division of Imaging Sciences & Biomedical Engineering, King's College London Department of Cancer Imaging, [4]The PET Centre, Guy's and St Thomas' NHS Foundation Trust, [5]Department of Radiology, Guy's and St Thomas' NHS Foundation Trust, [6]Department of Radiology, Kings College Hospital NHS Foundation Trust, London, [7]Myeloma UK, Edinburgh, and [8]Department of Haematology, University Hospital Birmingham NHS Foundation Trust, Birmingham, UK

Summary

The role of imaging in myeloma has gained increasing importance over the past few years. The recently revised definition of myeloma from the International Myeloma Working Group (IMWG) includes cross sectional imaging as a method to define bone disease and also incorporates its use in the disease definition for patients with suspected smouldering myeloma. The National Institute for Health and Care Excellence myeloma guidelines also recommend cross sectional imaging for patients with suspected myeloma. There is also increasing use of imaging in disease assessments and the International Myeloma Working Group has recently incorporated imaging in defining new response categories of minimal residual disease negativity, with or without imaging-based evidence of disease. Plain X-rays have previously been the standard imaging modality included in a myeloma work up at presentation but evidence is mounting for use of cross-sectional modalities such as computed tomography (CT), magnetic resonance imaging (MRI) and ^{18}fluoro-deoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT. Funding and therefore availability of newer imaging techniques remains a barrier. Here, we propose an evidence-based approach to the use and technical application of the latest imaging modalities at diagnosis and in the follow-up of patients with myeloma and plasmacytoma.

Keywords: myeloma, imaging, magnetic resonance imaging, CT scan, positron emission tomography.

Methodology

The guideline was compiled according to the British Society for Haematology (BSH) process. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at the website http://www.gradeworkinggroup.org.

Literature review

The literature search entailed a systematic search of MEDLINE and PUBMED for publications that included an abstract and were published in English between 1980 and 2015 using the following key words: myeloma, plasmacytoma, imaging, CT, PET, MRI.

Review of the manuscript

Review of the manuscript was performed by the BSH Guidelines Committee Haemato-Oncology Task Force, Myeloma UK, the BSH Guidelines Committee and the Haemato-Oncology sounding board of BSH.

Myeloma is a haematological malignancy that is characterised by the clonal proliferation of plasma cells and is commonly associated with bone disease. Typically, myeloma presents as multiple focal lesions or a diffuse infiltrate throughout the bone marrow or both, and occasionally with extramedullary disease. Myeloma is preceded by a premalignant asymptomatic stage known as monoclonal gammopathy of undetermined significance (MGUS) (Landgren *et al*, 2009; Weiss *et al*, 2009). Smouldering myeloma is an intervening phase between MGUS and myeloma but is not a single entity; there is a biological spectrum ranging from a stable state resembling MGUS, which does not progress, to a condition where progression to symptomatic disease is inevitable.

One of the defining criteria for multiple myeloma is the unequivocal presence of myeloma bone disease (Kyle & Rajkumar, 2009; Dimopoulos *et al*, 2011). The new International Myeloma Working Group (IMWG) definition of

Correspondence: BSH Administrator, British Society for Haematology, 100 White Lion Street, London N1 9PF, UK.
E-mail: bshguidelines@b-s-h.org.uk
*Joint first authors.

First published online 5 July 2017
doi: 10.1111/bjh.14827

myeloma incorporates cross sectional imaging and now includes patients with more than one unequivocal focal bone lesion as a defining myeloma-related event indicating the need for treatment (Rajkumar *et al*, 2014). Cross sectional imaging has also been incorporated into disease assessment in the recently revised IMWG consensus criteria for response assessment (Kumar *et al*, 2016) and is likely to be increasingly used for disease assessment in clinical trials.

This guideline reviews the evidence available for the role of imaging techniques in multiple myeloma, diagnosis, management of vertebral collapse, evaluation of treatment response and evaluation at relapse; the role of imaging techniques in the assessment of plasmacytomas is similarly considered. In addition we provide guidance, where possible, on the technical considerations around image acquisition and reporting.

Use of imaging for diagnosis

Skeletal survey

A full skeletal survey has for many years been the standard for assessing the presence of myeloma bone disease for any patient with suspected myeloma. Approximately 80% of multiple myeloma patients will have radiological evidence of skeletal involvement using plain radiography (vertebrae in 66% of patients, ribs in 45%, skull in 40%, shoulder in 40%, pelvis in 30% and long bones in 25%) (Collins, 1998). Sites distal to the elbows and knees are rarely affected (Healy & Armstrong, 1994). A clear association exists between the extent of disease on the skeletal survey in terms of the number of lytic lesions at presentation and tumour load at diagnosis (Durie & Salmon, 1975). Their presence represents a criterion that defines treatment-requiring myeloma even in the absence of symptoms (IMWG, 2003; Kyle & Rajkumar, 2009; Bird *et al*, 2011). The skeletal survey is widely available at a relatively low cost, is simple to use and interpret, allows large areas of the skeleton to be visualised and only exposes patients to relatively low doses of radiation. Careful documentation of the extent of myeloma bone disease is important to provide a baseline for future monitoring.

The major disadvantage of plain X-rays is the significantly lower sensitivity compared to advanced imaging. Lytic lesions are only demonstrated when at least 30–50% of the trabecular bone has been lost (Snapper & Khan, 1971) and around 20% of myeloma patients have no abnormal findings by plain X-ray. Plain X-rays cannot distinguish osteopenia or vertebral collapse caused by myeloma from more common causes such as early osteoporosis or corticosteroid use.

A recent systematic review confirmed that computed tomography (CT) and magnetic resonance imaging (MRI) are significantly superior to plain X-ray for the detection of skeletal lesions, apart from those of the ribs and skull (Regelink *et al*, 2013).

Skeletal surveys can be difficult to tolerate for patients with pain and poor mobility due to the duration of the assessment and the need to adopt various positions (D'Sa *et al*, 2007; Dimopoulos *et al*, 2009).

Method

If being performed as part of the staging procedure of newly diagnosed myeloma, a skeletal survey should include:

- Postero-anterior (PA) view of the chest
- Antero-posterior (AP) and lateral views of the whole spine, humera and femora
- Lateral views of the skull
- AP view of the pelvis
- Views of any symptomatic areas.

The dose will vary depending on patient size and equipment used, typically 1·5–2·5 mSv for an average 70 kg patient.

Skeletal survey has widespread availability and is well established as an assessment tool in myeloma, but has poor sensitivity and should be superseded by low-dose CT scan, PET-CT and whole body (WB)-MRI. Issues remain relating to lack of capacity and health economic consequences, but performing both a skeletal survey and cross sectional imaging will be the least cost-effective approach.

Computed tomography

CT offers improved sensitivity over plain X-rays in detecting lytic lesions and high resolution three-dimensional images generated by CT provide a more detailed evaluation of the bone. Small lytic lesions (<5 mm) that would otherwise be missed by X-ray imaging are detectable by CT, especially in the vertebrae (Mahnken *et al*, 2002; Hur *et al*, 2007). Therefore, bone changes can be identified earlier and potential instabilities and fracture risks estimated with greater reliability (Horger *et al*, 2005; Zamagni & Cavo, 2012), particularly in areas where it is difficult to survey by plain X-ray, e.g. scapulae and sternum. Given the recently revised classification of multiple myeloma, CT scanning is a suitable option for patients with suspected smouldering myeloma, but is not necessary in straightforward MGUS patients, unless they have skeletal symptoms.

From a practical point of view, CT has the advantage of being quick to perform and allows patients to lie on their back, without the need to change position. CT is also helpful for visualising soft tissue involvement, assessing spinal fracture stability, depicting spinal cord and cauda equina compression (although MRI is superior for this), guiding needle biopsies and surgical interventions and planning radiotherapy.

Despite a number of advantages, conventional CT uses higher doses of radiation (20 mSv for CT of the neck, chest, abdomen and pelvis) than skeletal survey (1·5–2·5 mSv). This has led to the introduction of whole body low-dose CT

(WBLDCT), which uses a lower tube voltage (kV) and current (mAS) to reduce the energy delivered to the patient to an effective dose of approximately 4–7 mSv. Dose reduction comes at a cost of reduced image resolution, but this can be partly offset by new iterative reconstruction techniques so that WBLDCT can now be performed at a similar dose to skeletal survey. WBLDCT is recommended as first line novel imaging investigation in European Myeloma Network guidelines (Terpos *et al*, 2015). Studies have shown that low dose CT accurately assesses the extent of bone destruction and remains more sensitive than plain X-rays. In one study, the level of confidence in 48 ambiguous plain X-ray findings was raised when WBLDCT from skull base to knees was used, increasing the detection of osteolytic lesions in the spine seven-fold (Kropil *et al*, 2008), whilst in another it could accurately exclude findings in MGUS patients being related to myeloma bone disease (Spira *et al*, 2012). Studies have shown WBLDCT outperforms radiographs even in traditionally difficult to assess areas, such as skull and ribs (Princewill *et al*, 2013). Modern scanners routinely use 1 mm resolution, thus reducing partial volume artefacts, which previously hindered evaluation of ribs. New post-processing software shows promise, such as the ability to review unfolded ribs (Homann *et al*, 2015 Bier *et al*, 2016) and the skull (Ringl *et al*, 2010), although this is not in routine practise. Dual energy CT is a further development in which the calcium containing bony structures can be mathematically subtracted to reveal medullary lesions. Thomas *et al* (2015) have shown increased detection of non-osteolytic myeloma bone lesions in a series of 32 patients although it was found to be less sensitive than MRI. Current IMWG guidelines require demonstration of an osteolytic lesion so this technique is not currently recommended.

Whole body low-dose CT is capable of demonstrating extramedullary disease (Surov *et al*, 2014) and correlates with whole-body MRI findings (Wolf *et al*, 2014). As well as extramedullary myeloma, WBLDCT demonstrates clinically significant non-osseous incidental findings (NOIF), such as occult carcinoma and infection, so careful extra skeletal review is mandated. Surov *et al* (2014) retrospectively reported an average of 3·2 NOIF per patient which were clinically significant in 36·6% of 93 patients with myeloma undergoing WBLDCT.

Other limitations of CT must also be recognised: For example, it may underestimate bone marrow disease, particularly if it is diffuse, and cortical bone damage with a homogeneous appearance may be mistaken for osteoporosis or osteopenia (Mahnken *et al*, 2002; Horger *et al*, 2007). Furthermore, traditionally CT has not been used to measure treatment response or provide prognostic information (Durie, 2006). However, recently simplified new CT response monitoring criteria have been proposed. Changes in measurement of 2–4 medullary lesions in the limbs have been shown to correlate to change in lytic lesions and haematological indices in a series of 78 patients (Schabel *et al*, 2016).

Method

Low-dose CT as an alternative to skeletal survey should incorporate red marrow in adults because this includes the predominant sites of disease. Body coverage proposed in the literature is variable but larger series suggest WBLDCT to include roof of skull to proximal tibial metaphysis (Ippolito *et al*, 2013). Low-dose CT algorithms optimised for attenuation correction on positron emission tomography (PET/CT) are suitable for WBLDCT and should be optimised locally. Low dose CT is given without IV contrast. As a guide, diagnostic images can be achieved with parameters such as 120 kV, <100 mAs, dose modulation and iterative reconstruction.

Recommendations

- Whole body low-dose computed tomography (WBLDCT; roof of skull to proximal tibial metaphyses) is an alternative to skeletal survey where facilities exist. It is a more sensitive technique for initial screening for lytic lesions in myeloma than skeletal survey but less sensitive than magnetic resonance inamging (MRI) at detection of medullary infiltration (1C).
- WBLDCT is superior to skeletal survey but less sensitive than MRI for the detection of medullary infiltration and should be considered in asymptomatic patients with either 10–60% plasma cells on their trephine biopsy or bone marrow aspirate or an M-protein of >30 g/l as the detection of more than one definite focal lesions is diagnostic of multiple myeloma and an indication for treatment (1B).
- WBLDCT is recommended, if MRI is not feasible, for assessing disease in patients with suspected myeloma who remain symptomatic despite having no evidence of osteolysis on the skeletal survey, or to clarify the significance of ambiguous plain radiographic findings, such as vertebral compression fracture or equivocal lytic lesions, especially in parts of the skeleton that are difficult to visualise on plain X-rays, such as sternum and scapulae, or to delineate the nature and extent of soft tissue disease. WBLDCT is, however, less sensitive than WB-MRI for assessing medullary infiltration (1C).

Magnetic resonance imaging

Magnetic resonance imaging has emerged as a valuable imaging modality in myeloma because of its ability to directly visualise the disease within the bone marrow rather than its secondary effects on cortical bone. It is the most sensitive tool available for detecting marrow infiltration at an early stage, before bone destruction occurs, as well as offering

improved detection of lesions, particularly in the axial skeleton (Dimopoulos *et al*, 2015). Several studies have compared MRI (limited or whole body) to skeletal survey at diagnosis (see Table I) and have shown that MRI may detect up to 50% more lesions, although the skeletal survey continues to outperform it at certain sites, e.g. ribs (Walker *et al*, 2007). Comparison of MRI with CT also indicates that MRI outperforms CT (Laroche *et al*, 1996; Baur-Melnyk *et al*, 2008) with a pooled sensitivity of 91% [95% confidence interval (CI): 88–94%] and pooled specificity of 41% [95% CI: 26–58%] for MRI in a recent systematic review (Regelink *et al*, 2013).

Magnetic resonance imaging is useful for confirming a diagnosis of solitary plasmacytoma, by ruling out additional disease (Moulopoulos *et al*, 1993; Liebross *et al*, 1998; Dimopoulos *et al*, 2000), for detecting lesions in symptomatic patients with myeloma whose skeletal surveys are normal, for assessing disease burden in patients diagnosed with nonsecretory or oligosecretory myeloma, and for evaluation of extramedullary disease (Dimopoulos *et al*, 2011). It is the technique of choice for suspected spinal cord compression (Joffe *et al*, 1988).

Magnetic resonance imaging provides greater contrast resolution than CT and has the advantage that it does not expose patients to radiation. Established MRI protocols include T1-weighted turbo spin echo, T2-weighted turbo spin echo and short tau inversion recovery (STIR) sequences. T1- and T2-weighted signal intensity provides the ratio between cellular and fatty components in the bone marrow, and in myeloma the increased cellular and decreased fatty components give rise to a hypointense signal on T1-weighted images, and a hyperintense signal T2-weighted images and STIR sequences. On the whole, published studies have utilised whole body techniques with STIR and T1 sequences. MRI limited to the spine and pelvis may be performed, but optimal methods need to be defined for evaluation of the skull and for determining the preferred extent of coverage of the appendicular skeleton (as approximately 10% of patients present with extra-axial disease only) (Bauerle *et al*, 2009).

Magnetic resonance imaging can demonstrate patterns of bone marrow involvement that are generally described as normal, focal, diffuse (homogeneous or heterogeneous), variegated (also known as salt and pepper) or a combination of these. Normal or variegated marrow patterns have been associated with lower disease burden, whereas focal or diffuse marrow patterns have been associated with higher disease burden (Baur-Melynk *et al*, 2005). A focal or diffuse pattern of bone marrow involvement is not unique to myeloma and may be present in other haematological malignancies and in metastatic disease (Vogler & Murphy, 1988).

Magnetic resonance imaging has prognostic value. One study showed that patients with more than seven focal lesions on initial spinal MRI and cytogenetic abnormalities had a poorer five-year overall survival than patients without these features (37% vs. 76%) (Walker *et al*, 2007). The presence of at least one focal lesion or the presence of a diffuse infiltration pattern on WB- MRI is related to a higher risk of progression of patients previously labelled as having asymptomatic disease (Hillengass *et al*, 2010). The two-year progression rate for such patients with ≤1 focal lesion was 20% compared to 70% for patients with >1 focal lesion (Hillengass *et al*, 2010), and patients with lesions required systemic treatment at an earlier time point than patients without lesions (16 months vs. 46 months) (Hillengass *et al*, 2014), similarly to the Greek study group (median 15 months, $P = 0{\cdot}001$) (Kastritis *et al*, 2013). The IMWG revised classification is currently restricted to focal involvement where a lesion of diameter >5 mm is regarded as positive; any equivocal lesions should be imaged again after three to 6 months. Symptomatic patients with a diffuse pattern of marrow involvement at staging have a poorer outcome (Lecouvet *et al*, 1998; Moulopoulos *et al*, 2005, 2012; Song *et al*, 2014). Although recognised as a prognostic factor, diffuse marrow involvement was not included as an indication to start treatment in patients with suspected smouldering myeloma and this reflects not only the need for greater evidence but also that assessment of marrow infiltration can be challenging and subjective. False positives can occur, e.g. following

Table I. Studies investigating MRI in the diagnostic setting with a skeletal survey or CT as the reference standard.

Imaging method	Reference standard	Patients (*n*)	Whole body imaging	MM stage	Reference
MRI	SS	60	Yes	SD I–III	Dinter *et al* (2009)
MRI	SS	45	Yes	SD I–III	Ghanem *et al* (2006)
MRI	SS	611	No	SD II–III	Walker *et al* (2007)
MRI	SS	77	No	SD I–III	Baur *et al* (2002)
MRI	SS	18	No	SD I–III	Mahnken *et al* (2002)
MRI	SS	80	No	SD I–III	Lecouvet *et al* (1999)
MRI	SS	55	No	SD I	Mariette *et al* (1999)
MRI	SS	23	No	SD I	Dimopoulos *et al* (1993)
MRI	CT	41	Yes	SD I–III	Baur-Melnyk *et al* (2008)
MRI	CT	48	No	SD I–III	Laroche *et al* (1996)

CT, computed tomography; MM, multiple myeloma; MRI, magnetic resonance imaging; SD, stable disease; SS, skeletal survey.

administration of granulocyte-colony stimulating factor (G-CSF), and both focal or diffuse bone marrow patterns may represent other malignant infiltrations, or be caused by a previous bone marrow biopsy (Hanrahan *et al*, 2010).

Image enhancement with contrast agents, such as gadolinium-diethylene triamine pentaacetic acid (DTPA), may not always be possible as these agents should be avoided in patients with renal dysfunction because of the risk of nephrogenic systemic fibrosis (Nicholas *et al*, 2012). The main limitation of MRI is the long acquisition time (up to 1 h) which may be difficult to tolerate for those with severe back pain, or those who suffer from claustrophobia. It is also contraindicated in patients with cardiac pacemakers and metallic prostheses.

At present, there is no evidence to indicate that MRI is necessary for patients with MGUS, although a recent study suggested it might be useful to help identify MGUS and the various stages of myeloma (Kloth *et al*, 2014).

Newer MRI protocols enable whole-body T1 ± gadolinium contrast agent administration, T2 ± fat saturation and diffusion-weighted sequences to be performed. Quantification of skeletal apparent diffusion co-efficient, vascularity and marrow fat fraction may be possible with diffusion-weighted, dynamic contrast-enhanced and T1 DIXON sequences (Koutoulidis *et al*, 2017). These sequences capture the physiological changes that may occur with plasma cell infiltration in addition to the morphological changes, including a higher signal on high *b*-value diffusion weighted sequences, a higher apparent diffusion co-efficient compared to normal bone marrow on diffusion-weighted sequences; a higher vascularisation compared to normal bone marrow on contrast enhanced sequences and a lower fat fraction compared to normal marrow. For example at initial staging diffusion sequences are highly sensitive to diffuse marrow infiltration in comparison to standard TSE and STIR sequences. Nevertheless, although these techniques have the potential to improve the specificity of MRI, good quality WB-MRI evidence remains limited as to their usefulness at diagnosis; instead they may better serve in other settings, e.g. response monitoring, where a change in quantitative parameters such as apparent diffusion co-efficient may be warranted, until there is further high quality evidence from multi-centre prospective trials (Huang *et al*, 2012; Messiou *et al*, 2012; Messiou & Kaiser, 2015).

Method

WB-MRI (typically from the vertex to knees) is recommended. Increasing coverage to below knees improves sensitivity but is offset by increased time for the examination. WB-MRI should include fast T1- and T2-weighted imaging with fat suppression (e.g. STIR) in either the axial or coronal plane. With MRI scanners capable of diffusion-weighted imaging, the acquisition should be performed with at least two *b* values (e.g. *b* 50 and 900 s/mm^2). An additional T1-weighted sagittal spine sequence should be incorporated to facilitate assessment of vertebral collapse and cord compression. Where WB-MRI cannot be performed, STIR and T1-weighted sagittal spine and axial pelvis sequences should be performed.

Recommendation

- MRI is the gold standard for the detection of bone marrow infiltration by plasma cells in patients with suspected myeloma (2B).
- MRI has superior detection of lesions compared to skeletal survey and should be considered in asymptomatic patients with either 10–60% plasma cells on a trephine biopsy or bone marrow aspirate or an M-protein of >30 g/l as the detection of more than one definite focal lesions is diagnostic of multiple myeloma and an indication for treatment (1B).
- MRI is the recommended technique in patients with suspected myeloma who remain symptomatic despite having no evidence of osteolysis on the skeletal survey and to clarify the significance of ambiguous plain radiographic findings, such as vertebral compression fracture or equivocal lytic lesions, especially in parts of the skeleton that are difficult to visualise on plain X-rays, such as sternum and scapulae, and to delineate the nature and extent of soft tissue disease (2C).
- Where whole body (WB)-MRI is not possible, MRI of the spine and pelvis may be performed but may not detect up to 10% of lesions located in the appendicular skeleton (2C). Where MRI cannot be performed, WBLDCT is an alternative but has lower sensitivity and specificity for marrow infiltration (2C).

Positron emission tomography/computed tomography

Positron emission tomography uses ^{18}Fluorine-fluoro-deoxy-glucose (^{18}F-FDG) as a radiotracer to detect glucose metabolism throughout the body, making use of the fact that tumour cells have a higher metabolic rate than normal cells and, therefore, higher ^{18}F-FDG uptake. Uptake can be estimated by calculating the standardised uptake value (SUV), which is the uptake of ^{18}F-FDG corrected for administered dose and patient weight.

Fluoro-deoxy-glucose PET imaging has limited spatial resolution but combining it with CT imaging addresses this issue and enables areas of active disease to be identified with exact anatomical localisation (Zamagni & Cavo, 2012; Agarwal *et al*, 2013; Nakamoto, 2014). This type of information is valuable in myeloma and FDG PET/CT has a potential role in initial diagnosis (Walker *et al*, 2012), particularly in extramedullary disease and non secretory myeloma (Durie *et al*, 2002; Orchard *et al*, 2002; Dimopoulos *et al*, 2009; Agarwal *et al*, 2013).

Several studies have shown that FDG PET/CT identifies more lesions than plain X-rays in 40–60% of cases and can also detect lesions in patients with negative skeletal surveys (Nanni *et al*, 2006). FDG PET/CT is useful for investigating equivocal cases when skeletal survey has not detected clear evidence of lytic bone damage, but patients remain symptomatic (Dimopoulos *et al*, 2009). It is also useful for assessing patients with smouldering myeloma and is a recommended imaging technique for evaluating such cases (Rajkumar *et al*, 2014). There is little evidence for a role for FDG PET/CT in stable MGUS patients who are at low risk of progression to multiple myeloma. Durie *et al* (2002) performed FDG PET/CT scans in a series of 66 patients with myelomatous and monoclonal disease. Fourteen patients had MGUS. All had normal PET/CT scans and only one patient progressed to multiple myeloma after 8 months (Durie *et al*, 2002).

The sensitivity of FDG PET/CT in detecting focal lesions in the spine and pelvis is broadly similar to MRI, but the latter is thought to be superior in detecting diffuse and variegated bone marrow infiltration (Breyer *et al*, 2006; Fonti *et al*, 2008; Mesguich *et al*, 2014). In one study, FDG PET/CT was used to detect bone marrow involvement at initial diagnosis. Sensitivity for the detection of bone marrow involvement shown on trephine biopsy was 90% while specificity was 100%, but, interestingly, a significant correlation was observed between ^{18}F-FDG SUV_{max} on PET/CT and bone marrow cellularity and plasma cell ratios on biopsy samples (Sager *et al*, 2011). This led to the suggestion that it may be possible to replace bone marrow biopsy with FDG PET/CT as a marker of disease extent, but further studies are needed to confirm this, particularly in patients with nonsecretory myeloma.

Fluoro-deoxy-glucose PET/CT can provide prognostic information in newly diagnosed myeloma patients. The presence of three or more lesions was shown initially to be an independent predictor of overall survival (OS) (Bartel *et al*, 2009) and, in a follow-up study of 429 newly diagnosed myeloma patients in the same institution, PET was the only independent predictor of OS (Usmani *et al*, 2013). In a European study, the presence of three or more focal lesions at baseline, a SUV_{max} greater than 4·2 and the presence of extramedullary disease adversely affected both progression-free survival (PFS) and OS (Zamagni *et al*, 2011).

The level of FDG uptake on PET/CT may predict pathological fractures. A SUV_{max} greater than 3·2 was shown in one study to differentiate between old and new vertebral fractures, and SUV_{max} greater than 3·5 when combined with MRI, showing that vertebral body involvement predicted fracture in 5/7 patients either at the time of imaging or within 10 weeks of the scan (Mulligan *et al*, 2011). It should be noted, however, that this retrospective study was limited by small patient numbers (Mulligan *et al*, 2011). Fractures are known to adversely affect survival (Sonmez *et al*, 2008) so the ability to predict fracture risk with FDG PET/CT is of potential significance, allowing patients to be managed appropriately and, possibly, improve outcome.

Fluoro-deoxy-glucose PET/CT must be interpreted with care as it has a high rate of false positives compared to other imaging techniques. False positives can occur in areas of inflammation or infection, as a result of post-surgical or vertebroplasty changes or because of the presence of other malignant conditions. On the other hand, false negatives may occur with concurrent use of corticosteroids and in diabetic patients with raised blood glucose. To overcome these potential problems, other radiotracers such as ^{11}C methionine and ^{18}F-fluorodeoxy-L-thymidine (^{18}F-FLT) have been investigated (Dankerl *et al*, 2007) but these are not widely available and more studies are needed to confirm their clinical value in myeloma. Until then, ^{18}F-FDG remains the radiotracer of choice. The radiation dose is similar to that of conventional WB-CT.

Whole body imaging from vertex to toes is recommended using methods published in European guidelines for performing ^{18}F-FDG tumour imaging (Boellaard *et al*, 2015). No standardised criteria currently exist for the interpretation of myeloma imaging, but recommendations for PET/CT reporting in myeloma are suggested, based on published experience in the field (Mesguich *et al*, 2014). Table II shows recommendations for myeloma imaging and reporting using PET/CT and Table III shows criteria for the interpretation of FDG bone and bone marrow uptake in patients with myeloma.

Further recommendations are anticipated in 2017 from an international working group, involving experts from clinical trials groups and cancer centres, which critically aim to provide standardisation of PET/CT methods.

Recommendations

- FDG PET/CT has superior detection of lesions compared to skeletal survey and should be considered in asymptomatic patients with either 10–60% plasma cells on their trephine biopsy or bone marrow aspirate or an M-protein of >30 g/l as the detection of more than one definite focal lesions is diagnostic of multiple myeloma and an indication for treatment (1B).
- FDG PET/CT may be considered for patients with newly diagnosed nonsecretory or oligosecretory myeloma and for evaluation of extramedullary disease. (2C) Although FDG PET/CT has some prognostic value when used in the initial diagnosis of myeloma, there is currently insufficient evidence to justify the routine use of FDG PET/CT in all cases of newly diagnosed myeloma (2C).

Use of imaging in the management of vertebral collapse/spinal cord compression

Vertebral compression fractures are common in myeloma and affect up to 70% of patients during the course of their disease (Lecouvet *et al*, 1997). Vertebral collapse causes

Table II. Recommendations for myeloma imaging and reporting using PET/CT.*

Whole body imaging should be performed from vertex to toes, if tolerated, using European guidelines for tumour imaging with FDG 60 m post-FDG administration (Boellaard *et al*, 2015)

The following should be reported:

1. **Number** of FL with increased FDG uptake (>3 FL shown to be prognostic at diagnosis and during treatment) and **distribution and SUV $_{max}$ as appropriate** Note MM lesions may have focal uptake with no CT abnormality, osteolytic change or soft tissue density within marrow spaces
2. Presence of **associated CT findings** e.g. osteolytic lesions, osteoblastic lesions, acute and chronic fractures, pathological fractures
3. Presence of **extramedullary disease** to be differentiated from 'break-out lesions' where the lesion involves bone with cortical disruption and soft tissue extension. Size of soft tissue mass/es may be helpful.
4. Risk of cord compression or invasion of base of skull
5. Presence of diffuse bone marrow uptake > liver
6. Sites for possible biopsy if appropriate
7. Other relevant findings such as infection- or disease-related complications e.g. avascular necrosis, osteonecrosis
8. Previous surgical interventions e.g. vertebroplasty, prostheses and orthopaedic devices

CT, computed tomography; FDG, fluoro-deoxyglucose; FL, focal lesions; MM, multiple myeloma; PET, positron emission tomography; SUV_{max}, maximum standardised uptake value.

*Modified from Modified from Mesguich *et al* (2014), Copyright (2014), with permission from Elsevier.

Table III. Interpretation of FDG bone and bone marrow uptake in patients with myeloma* (given the limited evidence it is not possible to give a consensus on the interpretation of extramedullary disease).

Uptake pattern	Pre-treatment	Post-treatment	Other causes of 'false positive' FDG uptake
Focal bone uptake	Positive: intensity > uptake in normal bone marrow and/or normal liver with or without lytic changes on CT (although lytic changes needed for IMWG definition†) Negative: uptake that corresponds to another cause of FDG uptake e.g. degenerative joint disease Equivocal: uptake corresponding to rib fracture or bone lesions with sclerotic change on CT	Positive: intensity > normal liver with stable or new lytic lesion or without CT abnormality [Note for local RT treatment increased uptake may occur due to inflammation if scanned within 3 months of treatment] Negative: intensity < normal liver Equivocal: FDG uptake associated with previous lytic lesion with development of sclerosis could represent treatment response	Trauma Osteoporotic fracture (especially vertebral body, ribs, sacrum) Stress fracture, Bone infarcts (especially femoral head) Degenerative joint disease Orthopaedic devices and surgical interventions
Diffuse bone marrow uptake	Positive: intensity > normal liver but reactive changes can give similar appearances Correlation with MRI or bone marrow biopsy advised as appropriate Negative: intensity ≤ normal liver	Positive: heterogeneous uptake > normal liver Equivocal: Homogenous uptake should be correlated with MRI and laboratory data	Bone marrow colony stimulation (though not commonly used in MM)

CT, computed tomography; FDG, fluoro-deoxyglucose; IMWG, International Myeloma Working Group; MM, multiple myeloma; MRI, magnetic resonance imaging; PET, positron emission tomography; RT, radiotherapy.

*Modified from Mesguich *et al* (2014), Copyright (2014), with permission from Elsevier.

†The revised IMWG definition (Rajkumar *et al*, 2014) states that increased uptake on PET-CT alone is not adequate evidence for the diagnosis of a bone lesion due to multiple myeloma; evidence of underlying osteolytic bone destruction is needed on the CT portion of the examination.

severe pain and can lead to significant spinal deformity, loss of total body height, impaired mobility, respiratory compromise and gastro-intestinal discomfort. Of greatest concern, however, is the risk of spinal cord compression secondary to vertebral collapse. Plain X-rays are the initial diagnostic modality to confirm a suspected vertebral fracture, but urgent additional imaging is essential to accurately characterise spinal disease. Importantly, cord compression can be due to soft tissue disease. CT scans can accurately identify unstable vertebra at risk of fracture (Horger *et al*, 2005; Kropil *et al*, 2008; Touzeau & Moreau, 2013), identify a soft tissue component, provide better images of more complex fractures and help determine the degree of vertebral compression (Alexandru & So, 2012).

Magnetic resonance imaging is the most sensitive and specific imaging modality to assess spinal lesions (Carlson *et al*, 1995; Dimopoulos *et al*, 2015). It enables the morphological detection of vertebral compression fractures and provides an accurate assessment of the level and extent of cord or nerve root compression (Joffe *et al*, 1988; Moulopoulos *et al*, 1999; Dimopoulos *et al*, 2009). Thus, in the event of suspected cord compression, whole spine MRI including a STIR sequence is the imaging modality of choice (Dimopoulos *et al*, 2009; Brooks *et al*, 2014). Additional CT imaging may be required to assess spinal instability more accurately both at diagnosis and in pre-treated patients (particularly as MRI signal intensity and MRI changes may normalise with treatment). The spinal instability neoplastic score (SINS) classification (Fourney *et al*, 2011) is useful for evaluating the stability of the spine at the involved levels. This evidence-based classification helps to determine stability/instability in a spine affected by tumour, by taking into account the location in the spine, pain, lytic nature, alignment, percentage vertebral body height loss and the presence of posterior bony elements: a score between 0 and 6 denotes stability, a score of 7–12 denotes indeterminate (possibly impending) instability and a score of 13–18 signifies instability.

Recommendation

- Urgent MRI is the diagnostic procedure of choice to assess suspected cord compression in myeloma patients (2B).
- Urgent CT may be used to establish the presence of suspected cord compression in cases where MRI is either unavailable, not suitable due to patient intolerance or contraindicated, e.g., intraorbital metallic foreign bodies or cardiac pacemakers (2C).
- Where there is a suggestion of spinal instability on MRI, spinal surgeons may recommend a CT scan with sagittal and coronal reconstructions to assess for vertebral body fracture and any involvement of the pars, facet joints and pedicles. The SINS classification (Fourney *et al*, 2011) is useful for evaluating the stability of the spine at the involved levels (2C).

Use of imaging in the assessment of treatment response and disease relapse

Assessment of treatment response, monitoring during follow-up and detection of disease relapse in myeloma patients is predominantly based on paraprotein and serum free light chain measurement. Imaging is important for reassessing bone disease at suspected relapse in patients with new bony symptoms and in assessing disease in patients with nonsecretory, oligosecretory or extramedullary disease. With modalities that now enable bone marrow infiltration and disease activity to be measured, imaging has, in fact, the potential to play a wider role in assessing treatment response and disease relapse. The IMWG has recently incorporated imaging into disease response assessment (Kumar *et al*, 2016) and this will lead to imaging being increasingly incorporated into disease assessment in future clinical trials although it is unclear how practical this will be in the UK.

Skeletal survey and CT scan

Plain X-ray assessment is of limited use in assessing treatment response and in monitoring, as lytic bone lesions seldom show evidence of healing on plain X-rays (Wahlin *et al*, 1982). Its role is more restricted to helping define progressive disease by providing evidence of new bone lesions but caution is needed, as new vertebral compression fractures on plain X-rays do not necessarily signify disease progression and may represent structural weakness (Collins, 2005).

Similarly, CT is not felt to be particularly useful for assessing treatment response or for following up bony lesions, but further studies are needed to evaluate its use in this setting. It may be used to demonstrate resolution of extramedullary disease, following treatment and may help in response assessment of medullary involvement at some sites, e.g., pelvic bones and appendicular skeleton (Horger *et al*, 2007).

Recommendations

- There is insufficient evidence of benefit to recommend routine follow-up skeletal survey in untreated asymptomatic patients in the absence of signs of disease progression (1B).
- Any new symptomatic areas of the skeleton should be specifically targeted. However, if disease progression occurs within 3 months of the previous skeletal survey, in the absence of new skeletal symptoms, a new skeletal survey is unlikely to provide additional information (1B).

Magnetic resonance imaging

In the treatment response setting, there is a wide spectrum of treatment-induced changes with conventional MRI.

In some cases, complete resolution of initial marrow abnormalities is observed in patients achieving a complete response, while conversion from diffuse to focal or variegated pattern of infiltration is seen in those achieving a partial response (Moulopoulos *et al*, 1994). A good response to treatment can also be demonstrated by an increase in focal lesion signal intensity on T2-weighted spin echo images, probably related to necrosis, and the disappearance of contrast-induced rim-enhancement (Baur-Melynk *et al*, 2005). In the post-autologous transplant setting, one study showed that MRI had 79% concordance with laboratory tests for detection of persistent disease and a sensitivity of 64% for detection of remission (Bannas *et al*, 2012). Another study demonstrated that MRI findings of both focal and diffuse

patterns correlated with treatment response, with there being an inverse correlation between the number of focal lesions observed at follow-up and OS (Hillengass *et al*, 2012).

In other cases, MRI fails to show evidence of regression of marrow infiltration; focal lesions may shrink, remain unchanged in size (Lecouvet *et al*, 2001) or remain hyperintense as a result of treatment-induced necrosis and inflammation (Rahmouni *et al*, 1993). Furthermore, marrow changes can occur following G-CSF and erythropoietin treatment that cannot be easily distinguished from active disease (Hartman *et al*, 2004). In this setting, PET/CT has an advantage over MRI (see later).

Recently, more specialised MRI techniques have been developed. Of these, whole body diffusion weighted MRI (WB-DWI) shows great potential as a technique for assessing response to treatment. WB-DWI provides information on the difference between normal and diseased bone marrow architecture, based on differences in the motion of water at the cellular level (Messiou *et al*, 2011). Significant differences in measured marrow apparent diffusion coefficient (ADC) are observed between non-myeloma and myeloma patients, and between myeloma patients with active and non-active disease (Hillengass *et al*, 2011; Messiou *et al*, 2011, 2012), offering a means to quantify both disease burden and response to treatment. ADC is typically higher for myeloma than normal bone marrow. An increase in ADC may be seen initially after treatment, presumably due to plasma cell death increasing extracellular space, followed by normalisation of values when normal marrow architecture is restored (Messiou & Kaiser, 2015). Whilst showing significant promise, particularly in quantifying response to treatment, further studies are warranted before WB-DWI can become fully established as a mainstream imaging tool in the management of myeloma patients.

Recommendation

- Conventional MRI may be performed to assess response to treatment but whole-body diffusion weighted MRI (WB-DWI) should be considered where available (2C).

Positron emission tomography/computed tomography

Fluoro-deoxy-glucose PET/CT, due to its ability to distinguish between active and non-active disease in myeloma, is a potentially powerful modality to assess response to treatment, predict outcome and guide treatment decisions.

Successful treatment is accompanied by a reduction or resolution of ^{18}F-FDG uptake and allows for earlier evaluation as metabolic changes precede morphological changes (Caldarella *et al*, 2012). Conversely, detection of increasing focal uptake of ^{18}F-FDG, either in old lytic sites or in new areas, is an early indicator of relapse. The usefulness of FDG PET/CT in the assessment of treatment response was confirmed in a meta-analysis of 10 studies involving 690 myeloma patients, based on its ability to differentiate between metabolically active and inactive lesions (Caldarella *et al*, 2012). It is particularly useful for the approximately 1% of myeloma cases that are truly nonsecretory and the up to 5% of cases who have oligosecretory disease with discrepantly low intact monoclonal product or serum free light chain compared with tumour load, measured either by bone marrow biopsy or imaging. Nonsecretory and oligosecretory disease become more common with disease progression, with loss of secretory capacity of some tumours at relapse (Larson *et al*, 2012). Current practice in such cases often relies on serial bone marrow biopsies, which are painful and distressing for patients. FDG-PET (Durie *et al*, 2002; Larson *et al*, 2012) and diffusion weighted MRI (Messiou & Kaiser, 2015) are particularly attractive options for monitoring nonsecretory or oligosecretory myeloma, either as a standalone measure of disease, or in conjunction with less frequent bone marrow biopsies. Furthermore, whole body imaging is less prone to anatomical sampling error than bone marrow biopsy.

Response assessment by FDG-PET has prognostic value with negative FDG PET/CT after treatment correlated well with improved outcome (Zamagni *et al*, 2007) including following autologous stem cell transplantation (ASCT) (Bartel *et al*, 2009; Zamagni *et al*, 2011; Lapa *et al*, 2014a). The presence/absence of minimal residual disease by flow cytometry following initial treatment is prognostic for both PFS and OS (Rawstron *et al*, 2015) and FDG-PET assessment will improve this further (Zamagni *et al*, 2015).

Recommendation

- Whole body MRI/diffusion weighted MRI or FDG – PET/CT (at clinician discretion) is recommended for serial monitoring of disease burden of patients with nonsecretory myeloma, oligosecretory myeloma (1B) (which can occur at relapse in patients with previously secretory disease) and extramedullary disease (1B).

Use of imaging in the assessment of solitary plasmacytoma

Solitary plasmacytoma is a single lesion (bone more commonly than soft tissue) that on biopsy shows infiltration by clonal plasma cells with there being no features of myeloma i.e. no CRAB (**c**alcium elevated, **r**enal failure, **a**naemia, **b**one lesions) features, absence of abnormal plasma cells in random sampling of bone marrow and normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion).

MRI was previously recommended to assess patients with a solitary bone plasmacytoma in order to exclude other sites of disease, evidence of which would alter the diagnosis to that of multiple solitary plasmacytomas or multiple myeloma (D'Sa *et al*, 2007; Hughes *et al*, 2009) and change treatment decisions. Moulopoulos *et al* (1993) showed additional foci

in a third of patients when MRI of the thoracic and lumbosacral spine was used, indicating that some patients would be under staged if an MRI was not performed. This was supported by Liebross *et al* (1998), who demonstrated that a skeletal survey was too insensitive to diagnose a solitary plasmacytoma. However, where available, whole-body MRI should now be considered to allow more thorough assessment of disease sites elsewhere.

Due to its ability to identify active disease in both medullary (Kannivelu *et al*, 2014) and extramedullary sites (Mulligan *et al*, 2011; Kim *et al*, 2014; Lapa *et al*, 2014b), FDG PET/CT is also a useful modality for the assessment of suspected solitary plasmacytoma (Lu *et al*, 2012; Yi *et al*, 2013). In several studies, FDG PET/CT allowed the detection of additional lesions in 30–50% of cases, which had been missed by plain X-ray or MRI of the spine (Schirrmeister *et al*, 2003; Nanni *et al*, 2008; Salaun *et al*, 2008). The current definition of solitary plasmacytoma requires the absence of disease outside the primary lesion by bone marrow examination and MRI (or CT) of spine and pelvis, There is thus lack of clarity, both in terminology and management, of those cases of solitary plasmacytoma defined according to existing criteria, but which have evidence of PET positivity. There is a lack of data on performing imaging routinely during follow-up, and decisions should be guided by the presence of new symptoms or biochemical progression.

Recommendations

- Either FDG PET/CT or whole body MRI should be performed to exclude additional sites of disease, and help to confirm a diagnosis of solitary plasmacytoma (1C).
- Repeat imaging should be performed when there is clinical suspicion of relapse or biochemical progression (1C).

Summary

Although it is clear that newer imaging techniques are replacing skeletal surveys for assessing myeloma-related bone disease in people with newly diagnosed myeloma, funding and availability for these techniques remains a barrier in most healthcare systems. The comparative effectiveness of whole-body MRI, diffusion weighted MRI, FDG PET/CT and whole-body low-dose CT is not clear. Defining patients with suspected myeloma is extremely difficult, but it is clear that imaging is not necessary for patients with an obvious diagnosis of MGUS. Future research outcomes of interest are the cost effectiveness, lesion detection, sensitivity and specificity for myeloma-related bone disease, patient acceptability, incremental upstaging, radiation exposure, risk of second primary cancer, value in monitoring and the impact of additional information for predicting PFS, OS and skeletal-related events.

Conflicts of interest

None of the authors had conflicts of interest to declare.

Review process

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BSH current guidelines website (http://www.b-s-h.org.uk/guidelines/) if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website. If minor changes are required due to changes in level of evidence or significant additional evidence becomes available to support current recommendations a new version of the guidance will be issued on the BSH website.

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

Acknowledgements

This guideline was compiled by a writing group that included Consultant haematologists (AC, MK, MS and GP), Consultant Radiologists (SB, VG, NM) and representation from the patient charity Myeloma UK (ML). ML reviewed the literature and all authors contributed to writing the guideline. Guideline development was led by AC, MK and GP. The authors would like to thank Myeloma UK, the BSH haemato-oncology task force and the BSH sounding board.

References

Agarwal, A., Chirindel, A., Shah, B.A. & Subramaniam, R.M. (2013) Evolving role of FDG PET/CT in multiple myeloma imaging and management. *AJR American Journal of Roentgenology*, **200**, 884–890.

Alexandru, D. & So, W. (2012) Evaluation and management of vertebral compression. *The Permanente Journal*, **16**, 46–51.

Bannas, P., Hentschel, H.B., Bley, T.A., Treszl, A., Eulenburgh, C., Derlin, T., Yamamura, J., Adam, G., Stubig, T., Kroger, N. & Weber, C. (2012) Diagnostic performance of whole-body MRI for the detection of persistent or relapsing disease in multiple myeloma after stem cell transplantation. *European Radiology*, **22**, 2007–2012.

Bartel, T.B., Haessler, J., Brown, T.L., Shaughnessy, J.D. Jr, van Rhee, F., Anaissie, E., Alpe, T., Angtuaco, E., Walker, R., Epstein, J., Crowley, J. & Barlogie, B. (2009) F18-fluorodeoxyglucose

positron emission tomography in the context of other imaging techniques and prognostic factors in multiple myeloma. *Blood*, **114**, 2068–2076.

Bauerle, T., Hillengass, J., Fechtner, K., Zechmann, C.M., Grenacher, L., Moehler, T.M., Christiane, H., Wagner-Gund, B., Neben, K., Kauczor, H.U., Goldschmidt, H. & Delorme, S. (2009) Multiple myeloma and monoclonal gammopathy of undetermined significance: importance of whole-body versus spinal MR imaging. *Radiology*, **252**, 477–485.

Baur, A., Stabler, A., Nagel, D., Lamerz, R., Bartl, R., Hiller, E., Wendtner, C., Bachner, F. & Reiser, M. (2002) Magnetic resonance imaging as a supplement for the clinical staging system of Durie and Salmon? *Cancer*, **95**, 1334–1345.

Baur-Melnyk, A., Buhmann, S., Becker, C., Schoenberg, S.O., Lang, N., Bartl, R. & Reiser, M.F. (2008) Whole-body MRI versus whole-body MDCT for staging of multiple myeloma. *AJR American Journal of Roentgenology*, **190**, 1097–1104.

Baur-Melynk, A., Buhmann, S., Durr, H.R. & Reiser, M. (2005) Role of MRI for the diagnosis and prognosis of multiple myeloma. *European Journal of Radiology*, **55**, 56–63.

Bier, G., Mustafa, D., Kloth, C., Weisel, C., Ditt, H., Nikolaou, K. & Horger, M. (2016) Improved follow- up and response monitoring of thoracic cage involevement of multiple myeloma using a novel CT postprocessing software: the lessions we learned. *AJR American Journal of Roentgenology*, **206**, 57–63.

Bird, J.M., Owen, R.G., D'Sa, S., Snowden, J.A., Pratt, G., Ashcroft, J., Yong, K., Cook, G., Feyler, S., Davies, F., Morgan, G., Cavenagh, J., Low, E., Behrens, J. & Haemato-oncology Task Force of British Committee for Standards in Haematology (BCSH) and UK Myeloma Forum (2011) Guidelines for the diagnosis and management of multiple myeloma 2011. *British Journal of Haematology*, **154**, 32–75.

Boellaard, R., Delgado-Bolton, R., Oyen, W.J., Giammarile, F., Tatsch, K., Eschner, W., Verzijlbergen, F.J., Barrington, S.F., Pike, L.C., Weber, W.A., Stroobants, S., Delbeke, D., Donohoe, K.J., Holbrook, S., Graham, M.M., Testanera, G., Hoekstra, O.S., Zijlstra, J., Visser, E., Hoekstra, C.J., Pruim, J., Willemsen, A., Arends, B., Kotzerke, J., Bockisch, A., Beyer, T., Chiti, A. & Krause, B.J. & European Association of Nuclear Medicine (EANM) (2015) FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. *European Journal of Nuclear Medicine and Molecular Imaging* **42**, 328–354.

Breyer, R.J. 3rd, Mulligan, M.E., Smith, S.E., Line, B.R. & Badros, A.Z. (2006) Comparison of imaging with FDG PET/CT with other imaging modalities in myeloma. *Skeletal Radiology*, **35**, 632–640.

Brooks, F.M., Ghatahora, A., Brooks, M.C., Warren, H., Price, L., Brahmabhatt, P., De Vauvert, S., John, C., Farnworth, E., Sulaiman, E. & Ahuja, S. (2014) Management of metastatic spinal cord compression. *European Journal of Orthopaedic Surgery and Traumatology*, **24**, S255–S259.

Caldarella, C., Treglia, G., Isgro, M.A., Treglia, I. & Giordana, A. (2012) The role of fluorine-18-fluorodeoxyglucose positron emission tomography in evaluating the response to treatment in patients with multiple myeloma. *International Journal of Molecular Imaging*, **2012**, 175803.

Carlson, K., Astrom, G., Nyman, R., Ahlstrom, H. & Simonsson, B. (1995) MR imaging of multiple myeloma in tumour mass measurement at diagnosis and during treatment. *Acta Radiologica*, **36**, 9–14.

Collins, C. (1998) Multiple myeloma. In: Imaging in Oncology (ed. by J.E. Husband & R.H. Resnik), Vol. **2**, Boca, Raton, Taylor and Francis, London.

Collins, C.D. (2005) Problems monitoring response in multiple myeloma. *Cancer Imaging*, **23**, S119–S126.

Dankerl, A., Liebisch, P., Glatting, G., Friesen, C., Blumstein, N.M., Kocot, D., Wendl, C., Bunies, D. & Reske, S.N. (2007) Multiple myeloma: molecular imaging with 11C-methionine PET/CT – initial experience. *Radiology*, **242**, 498–508.

Dimopoulos, M.A., Moulopoulos, L.A., Maniatis, A. & Alexanian, R. (2000) Solitary plasmacytoma of bone and asymptomatic multiple myeloma. *Blood*, **96**, 2037–2044.

Dimopoulos, M.A., Moulopoulos, A., Smith, T., Delasalle, K.B. & Alexanian, R. (1993) Risk of disease progression in asymptomatic multiple myeloma. *Am J Med*, **94**, 57–61.

Dimopoulos, M., Terpos, E., Comenzo, R.L., Tosi, P., Beksac, M., Sezer, O., Siegel, D., Lokhorst, H., Kumar, S., Rajkumar, S.V., Niesvizky, R., Moulopoulos, L.A. & Durie, B.G. & IMWG (2009) International myeloma working group consensus statement and guidelines regarding the current role of imaging techniques in the diagnosis and monitoring of multiple myeloma. *Leukemia*, **23**, 1545–1556.

Dimopoulos, M., Kyle, R., Fermand, J.P., Rajkumar, S.V., San Miguel, J., Chanan-Khan, A., Ludwig, H., Joshua, D., Mehta, J., Gertz, M., Avet-Loiseau, H., Beksac, M., Anderson, K.C., Moreau, P., Singhal, S., Goldschmidt, H., Boccadoro, M., Kumar, S., Giralt, S., Munshi, N.C. & Jagannath, S. & International Myeloma Workshop Consensus Panel 3 (2011) Consensus recommendations for standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3. *Blood*, **117**, 4701–4705.

Dimopoulos, M.A., Hillengass, J., Usmani, S., Zamagni, E., Lentzsch, S., Davies, F.E., Raje, N., Sezer, O., Zweegman, S., Shah, J., Badros, A., Shimizu, K., Moreau, P., Chim, C.S., Lahuerta, J.J., Hou, J., Jurczyszyn, A., Goldschmidt, H., Sonneveld, P., Palumbo, A., Ludwig, H., Cavo, M., Barlogie, B., Anderson, K., Roodman, G.D., Rajkumar, S.V., Durie, B.G. & Terpos, E. (2015) Role of magnetic resonance imaging in the management of patients with multiple myeloma: a consensus statement. *Journal of Clinical Oncology*, **33**, 657–664.

Dinter, D.J., Neff, W.K., Klaus, J., Bohm, C., Hastka, J., Weiss, C., Schoenberg, S.O. & Mezgeroth, G. (2009) Comparison of whole-body MR imaging and conventional X-ray examination in patients with multiple myeloma and implications for therapy. *Annals of Hematology*, **88**, 457–464.

D'Sa, S., Abildgaard, N., Tighe, J., Shaw, P. & Hall-Craggs, M. (2007) Guidelines for the use of imaging in the management of myeloma. *British Journal of Haematology*, **137**, 49–63.

Durie, B.G. (2006) The role of anatomical and functional staging in myeloma: description of the Durie/Salmon PLUS staging system. *European Journal of Cancer*, **42**, 1539–1543.

Durie, B.G. & Salmon, S.E. (1975) A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment and survival. *Cancer*, **36**, 842–854.

Durie, B.G., Waxman, A.D., D'Agnolo, A. & Williams, C.M. (2002) Whole-body (18)-FDG PET identifies high-risk myeloma. *Journal of Nuclear Medicine*, **43**, 1457–1463.

Fonti, R., Salvatore, B., Quarantelli, M., Sirignano, C., Segreto, S., Petruzziello, F., Catalano, L., Liuzzi, R., Rotoli, B., Del Vecchio, S., Pace, L. & Salvatore, M. (2008) 18F-FDG PET/CT, 99mTc-MIBI and MRI in evaluation of patients with multiple myeloma. *Journal of Nuclear Medicine*, **49**, 195–200.

Fourney, D.R., Frangou, E.M., Ryken, E.M., Dipaola, C.P., Shaffrey, C.I., Berven, S.H., Bilsky, M.H., Harrop, J.S., Fehlings, M.G., Boriani, S., Chou, D., Schmidt, M.H., Polly, D.W., Biagini, R., Burch, S., Dekutoski, M.B., Ganju, A., Gerszten, P.C., Gokaslan, Z.L., Groff, M.W., Liebsch, N.J., Mendel, E., Okuno, S.H., Patel, S., Rhines, L.D., Rose, P.S., Sciubba, D.M., Sundaresan, N., Tomita, K., Varga, P.P., Vialle, L.R., Vrionis, F.D., Yamada, Y. & Fisher, C.G. (2011) Spinal instability neoplastic score: an analysis of reliability and validity from the spine oncology study group. *Journal of Clinical Oncology*, **29**, 3072–3077.

Ghanem, N., Lohmann, C., Engelhardt, M., Pache, G., Uhl, M., Saueressig, U., Kotter, E. & Langer, M. (2006) Whole-body MRI in the detection of bone marrow infiltration in patients with plasma cell neoplasms in comparison to the radiological skeletal survey. *European Radiology*, **16**, 1005–1015.

Hanrahan, C.J., Christensen, C.R. & Crim, J.R. (2010) Current concepts in the evaluation of multiple myeloma MR imaging and FDG PET/CT. *Radiographics*, **30**, 127–142.

Hartman, R.P., Sundaram, M., Okuno, S.H. & Sim, F.H. (2004) Effect of granulocyte-stimulating factors on marrow of adult patients with musculoskeletal malignancies: incidence and MRI findings. *AJR American Journal of Roentgenology*, **183**, 645–653.

Healy, J.C. & Armstrong, P. (1994) Radiology of myeloma. In: Myeloma: Biology and Management (ed. by J.S. Malpas, D.E. Bergsagel & R.A. Kyle), pp. 222. Oxford Medical Publications, New York.

Hillengass, J., Fechtner, K., Weber, M.A., Bauerle, T., Ayyaz, S., Heiss, C., Hielscher, T., Moehler, T.M., Egerer, G., Neben, K., Ho, A.D., Kauczor, H.U., Delorme, S. & Goldschmidt, H. (2010) Prognostic significance of focal lesions in whole-body magnetic resonance imaging in patients with asymptomatic multiple myeloma. *Journal of Clinical Oncology*, **28**, 1606–1610.

Hillengass, J., Bauerle, T., Bartl, R., Andrulis, M., McClanahan, F., Laun, F.B., Zechmann, C.M., Shah, R., Wagner-Gund, B., Simon, D., Heiss, C., Neben, K., Ho, A.D., Schlemmer, H.P., Goldschmidt, H., Delorme, S. & Stieltjes, B. (2011) Diffusion-weighted imaging for non-invasive and quantitative monitoring of bone marrow infiltration in patients with monoclonal plasma cell disease: a comparative study with histology. *British Journal of Haematology*, **153**, 721–728.

Hillengass, J., Ayyaz, S., Kilk, K., Weber, A., Hielscher, T., Shah, R., Hose, D., Delorme, S., Goldschmidt, H. & Neben, K. (2012) Changes in magnetic resonance imaging before and after autologous stem cell transplantation correlate with response and survival in multiple myeloma. *Haematologica*, **97**, 1757–1760.

Hillengass, J., Weber, M.A., Kilk, K., Listl, K., Wagner-Gund, B., Hillengass, M., Hiescher, T., Farid, A., Neben, K., Delorme, S., Landgren, O. & Goldschmidt, H. (2014) Prognostic significance of whole-body MRI in patients with monoclonal gammopathy of undetermined significance. *Leukemia*, **28**, 174–178.

Homann, G., Weisal, K., Mustafa, D., Ditt, H., Nikolaou, K. & Hoerger, M. (2015) Improvement of diagnostic confidence for detection of multiple myeloma involvement of the ribs by a new CT software generating rib unfolded images: comparison with 5- and 1-mm axial images. *Skeletal Radiology*, **44**, 971–979.

Horger, M., Claussen, C.D., Bross-Bach, U., Vonthein, R., Trabold, T., Heuschmid, M. & Pfannenberg, C. (2005) Whole-body low dose multidetector row-CT in the diagnosis of multiple myeloma: an alternative to conventional radiography. *European Journal of Radiology*, **54**, 289–297.

Horger, M., Kanz, L., Denecke, B., Vonthein, R., Pereira, P., Claussen, C.D. & Driessen, C. (2007) The benefit of using whole-body, low-dose, nonenhanced, multidetector computed tomography for follow-up and therapy response monitoring in patients with multiple myeloma. *Cancer*, **109**, 1617–1626.

Huang, S.Y., Chen, B.B., Lu, H.Y., Lin, H.H., Wei, S.Y., Hsu, S.C. & Shih, T.T. (2012) Correlation among DCE-MRI measurements of bone marrow angiogenesis, microvessel density, and extramedullary disease in patients with multiple myeloma. *American Journal of Hematology*, **87**, 837–839.

Hughes, R., Soutar, R., Lucraft, R., Owen, R. & Bird, J. & UKMF Guidelines Working Group (2009) Guidelines on the diagnosis and management of solitary plasmacytoma of bone, extramedullary plasmacytoma and multiple solitary plasmacytomas: 2009 update. *Addendum 19/1/2009 to the original guideline – Soutar R et al 2004 British Journal of Haematology*, **124**, 717–726.

Hur, J., Yoon, C.S., Ryu, Y.H., Yun, M.J. & Suh, J.S. (2007) Efficacy of multidetector row computed tomography of the spine in patients with multiple myeloma: comparison with magnetic resonance imaging and fluorodeoxyglucose-positron emission tomography. *Journal of Computer Assisted Tomography*, **31**, 342–347.

International Myeloma Working Group (2003) Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *British Journal of Haematology*, **121**, 749–757.

Ippolito, D., Besostri, V., Bonaffini, P., Rossini, F., Di Lelio, A. & Sironi, S. (2013) Diagnostic value of whole-body low-dose computed tomography (WBLDCT) in bone lesions detection in patients with multiple myeloma (MM). *European Journal of Radiology*, **82**, 2322–2327.

Joffe, J., Williams, M.P., Cherryman, G.R., Gore, M., McElwain, T.J. & Selby, P. (1988) Magnetic resonance imaging in myeloma. *Lancet*, **1**, 1162–1163.

Kannivelu, A., Loke, K.S., Kok, T.Y., Osmany, S.Y., Ali, S.Z., Suat-Jin, L. & Ng, D.C. (2014) The role of PET/Ct in the evaluation of skeletal metastases. *Seminars in Musculoskeletal Radiology*, **18**, 149–165.

Kastritis, E., Terpos, E., Moulopoulos, L., Spyropoulou-Vlachou, M., Kanellias, N., Eleftherakis-Papaiakovou, E., Gkotzamanidou, M., Migkou, M., Gavriatopoulou, M., Roussou, M., Tasidou, A. & Dimopoulos, M.A. (2013) Extensive bone marrow infiltration and abnormal free light chain ratio identifies patients with asymptomatic myeloma at high risk for progression to symptomatic disease. *Leukemia*, **27**, 947–953.

Kim, D.W., Kim, W.H., Kim, M.H., Choi, K.H. & Kim, C.G. (2014) Detection of extramedullary multiple myeloma in liver by FDG-PET/CT. *Nuclear Medicine and Molecular Imaging*, **48**, 166–168.

Kloth, J.K., Hillengass, J., Listl, K., Kilk, K., Hiescher, T., Landgren, O., Delorme, S., Goldschmidt, H., Kauczor, H.U. & Weber, M.A. (2014) Appearance of monoclonal plasma cell diseases in whole-body magnetic resonance imaging and correlation with parameters of disease activity. *International Journal of Cancer*, **135**, 2380–2386.

Koutoulidis, V., Fontara, S., Terpos, E., Zagouri, F., Matsaridis, D., Christoulas, D., Panourgias, E., Kastritis, E., Dimopoulos, M.A. & Moulopoulos, L.A. (2017) Quantitative diffusion-weighted imaging of the bone marrow: an adjunct tool for the diagnosis of a diffuse MR imaging pattern in patients with multiple myeloma. *Radiology*, **282**, 484–493.

Kropil, P., Fenk, R., Fritz, L.B., Blondin, D., Kobbe, G., Modder, U. & Cohnen, M. (2008) Comparison of whole-body 64-slice multidetector computed tomography and conventional radiography in staging of multiple myeloma. *European Radiology*, **18**, 51–58.

Kumar, S., Paiva, B., Anderson, K.C., Durie, B., Landgren, O., Moreau, P., Munshi, N., Lonial, S., Bladé, J., Mateos, M.V., Dimopoulos, M., Kastritis, E., Boccadoro, M., Orlowski, R., Goldschmidt, H., Spencer, A., Hou, J., Chng, W.J., Usmani, S.Z., Zamagni, E., Shimizu, K., Jagannath, S., Johnsen, H.E., Terpos, E., Reiman, A., Kyle, R.A., Sonneveld, P., Richardson, P.G., McCarthy, P., Ludwig, H., Chen, W., Cavo, M., Harousseau, J.L., Lentzsch, S., Hillengass, J., Palumbo, A., Orfao, A., Rajkumar, S.V., San Miguel, J. & Avet-Loiseau, H. (2016) International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *The Lancet Oncology*, **17**, e328–e346.

Kyle, R.A. & Rajkumar, S.V. (2009) Criteria for diagnosis, staging, risk stratification and response assessment for multiple myeloma. *Leukemia*, **23**, 3–9.

Landgren, O., Kyle, R.A., Pfeiffer, R.M., Katzmann, J.A., Caporaso, N.E., Hayes, R.B., Dispenzieri, A., Kumar, S., Clark, R.J., Baris, D., Hoover, R. & Rajkumar, S.V. (2009) Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood*, **113**, 5412–5417.

Lapa, C., Luckerath, K., Malzahn, U., Samnick, S., Einsele, H., Buck, A.K., Hermann, K. & Knop, S. (2014a) 18FDG-PET/CT for prognostic stratification of patients with multiple myeloma relapse after stem cell transplantation. *Oncotarget*, **15**, 7381–7391.

Lapa, C., Knop, S. & Luckerath, K. (2014b) FDG PET/CT depicts cutaneous plasmacytoma. *Clinical Nuclear Medicine*, **39**, 910–911.

Laroche, M., Assoun, J., Sixou, L. & Attal, M. (1996) Comparison of MRI and computed tomography in the various stages of plasma cell disorders: correlations with biological and histological findings. Myelome-Midi-Pyrenees Group. *Clinical and Experimental Rheumatology*, **14**, 171–176.

Larson, D., Kyle, R.A. & Rajkumar, S.V. (2012) Prevalence and monitoring of oligosecretory myeloma. *New England Journal of Medicine*, **367**, 580–581.

Lecouvet, F.E., Vande Berg, B.C., Maldague, B.E., Michaux, L., Laterre, E., Michaux, J.L., Ferrant, A. & Malghem, J. (1997) Vertebral compression fractures in multiple myeloma. Part 1. Distribution and appearance at MR imaging. *Radiology*, **204**, 195–199.

Lecouvet, F.E., Vande-Berg, B.C., Michaux, L., Malghem, J., Maldague, B.E., Jamart, J., Ferrant, A. & Michaux, J.L. (1998) Stage III multiple myeloma: clinical and prognostic value of spinal

bone marrow MR imaging. *Radiology*, **209**, 653–660.

Lecouvet, F.E., Malghem, J., Michaux, L., Maldague, B., Ferrant, A., Michaux, J.L. & Vande Berg, B.C. (1999) Skeletal survey in advanced multiple myeloma: radiologic versus MR imaging survey. *British Journal of Haematology*, **106**, 35–39.

Lecouvet, F.E., Vande-Berg, B.C., Malghem, J. & Maldague, B.E. (2001) Magnetic resonance and computed imaging in multiple myeloma. *Seminars in Musculoskeletal Radiology*, **5**, 43–55.

Liebross, R.H., Ha, C.S., Cox, J.D., Weber, D., Delasalle, K. & Alexanian, R. (1998) Solitary bone plasmacytoma: outcome and prognostic factors following radiotherapy. *International Journal of Radiation, Oncology, Biology, Physics*, **41**, 1063–1067.

Lu, Y.Y., Chen, J.H., Lin, W.Y., Liang, J.A., Wang, H.Y., Tsai, S.C. & Kao, C.H. (2012) FDG PET or PET/CT for detecting intramedullary and extramedullary lesions in multiple myeloma: a systematic review and meta-analysis. *Clinical Nuclear Medicine*, **37**, 833–837.

Mahnken, A.H., Wildberger, J.E., Gehbauer, G., Schmitz-Rode, T., Blaum, M., Fabry, U. & Gunther, R.W. (2002) Multidetector CT of the spine in multiple myeloma: comparison with MR imaging and radiography. *AJR American Journal of Roentgenology*, **178**, 1429–1436.

Mariette, X., Zagdanski, A.M., Guermazi, A., Bergot, C., Arnould, A., Frija, J., Brouet, J.C. & Fernaud, J.P. (1999) Prognostic value of vertebral lesions detected by magnetic resonance imaging in patients with stage I multiple myeloma. *British Journal of Haematology*, **104**, 723–729.

Mesguich, C., Fardanesh, R., Tanenbaum, L., Chari, A., Jagannath, S. & Kostakoglu, L. (2014) State of the art imaging of multiple myeloma: comparative review of FDG PET/CT imaging in various clinical settings. *European Journal of Radiology*, **83**, 2203–2223.

Messiou, C. & Kaiser, M. (2015) Whole body diffusion weighted MRI – a new view of myeloma. *British Journal of Haematology*, **171**, 29–37. https://doi.org/10.1111/bjh.13509.

Messiou, C., Collins, D.J., Morgan, V.A. & Desouza, N.M. (2011) Optimising diffusion weighted MRI for imaging metastatic and myeloma bone disease and assessing reproducibility. *European Radiology*, **21**, 1713–1718.

Messiou, C., Giles, S., Collins, D.J., West, S., Davies, F.E., Morgan, G.J. & Desouza, N.M. (2012) Assessing response of myeloma bone disease with diffusion-weighted MRI. *British Journal of Radiology*, **85**, e1198–e1203.

Moulopoulos, L.A., Dimopoulos, M.A., Weber, D., Fuller, L., Libshitz, H.I. & Alexanian, R. (1993) Magnetic resonance imaging in the staging of solitary plasmacytoma of bone. *Journal of Clinical Oncology*, **11**, 1311–1315.

Moulopoulos, L.A., Dimopoulos, M.A., Alexanian, R., Leeds, N.E. & Libshitz, H.I. (1994) Multiple myeloma: MR patterns of response to treatment. *Radiology*, **193**, 441–446.

Moulopoulos, L.A., Dimopoulos, M.A., Vourtsi, A., Gouliamos, A. & Vlahos, L. (1999) Bone lesions with soft tissue mass: magnetic resonance imaging diagnosis of lymphomatous involvement of the bone marrow versus multiple myeloma and bone metastases. *Leukemia & Lymphoma*, **34**, 179–184.

Moulopoulos, L.A., Gika, D., Anagnostopoulos, A., Delasalle, K., Weber, D., Alexian, R. & Dimopoulos, M.A. (2005) Prognostic significance of magnetic resonance imaging of bone marrow in previously untreated patients with multiple myeloma. *Annals of Oncology*, **16**, 1824–1828.

Moulopoulos, L.A., Dimopoulos, M.A., Kastritis, E., Christoulas, D., Gkotzamanidou, M., Roussou, M., Koureas, A., Migkou, M., Gavriatopoulou, M., Eleutherakis-Papaikovou, E., Gika, D., Koutoulidis, V. & Terpos, E. (2012) Diffuse pattern of bone marrow involvement on magnetic resonance imaging is associated with high risk cytogenetics and poor outcome in newly diagnosed, symptomatic patients with multiple myeloma: a single center experience on 228 patients. *American Journal of Hematology*, **87**, 861–864.

Mulligan, M., Chirindel, A. & Karchevsky, M. (2011) Characterizing and predicting pathological spine fractures in myeloma patients with FDG PET/CT and MR imaging. *Cancer Investigation*, **29**, 370–376.

Nakamoto, Y. (2014) Clinical contribution of PET/CT in myeloma: from the perspective of a radiologist. *Clinical Lymphoma, Myeloma & Leukemia*, **14**, 10–11.

Nanni, C., Zamagni, E., Farsad, M., Castellucci, P., Tosi, P., Cangini, D., Salizzoni, E., Canini, R., Cavo, M. & Fanti, S. (2006) Role of 18F-FDG PET/CT in the assessment of bone involvement in newly diagnosed multiple myeloma: preliminary results. *European Journal of Nuclear Medicine & Molecular Imaging*, **33**, 525–531.

Nanni, C., Rubello, D., Zamagni, E., Castellucci, P., Ambrosini, V., Montini, G., Cavo, M., Lodi, F., Pettinato, C., Grassetto, G., Franchi, R., Gross, M.D. & Fanti, S. (2008) 18F-FDG-PET/Ct in myeloma with presumed solitary plasmacytoma of bone. *In Vivo*, **22**, 513–517.

Nicholas, B.A., Vricella, G.J., Smith, M., Passalacqua, M., Gulani, V. & Ponsky, L.E. (2012) Contrast-induced nephropathy and nephrogenic systemic fibrosis: minimizing the risk. *The Canadian Journal of Urology*, **19**, 6074–6080.

Orchard, K., Barrington, S., Buscombe, J., Hilson, A., Prentice, H.G. & Mehta, A. (2002) Fluorodeoxyglucose positron emission tomography imaging for the detection of occult disease in multiple myeloma. *British Journal of Haematology*, **117**, 133–135.

Princewill, K., Lyere, S., Awan, O. & Mulligan, M. (2013) Multiple myeloma lesion detection with whole body CT versus radiographic skeletal survey. *Cancer Investigation*, **31**, 206–211.

Rahmouni, A., Divine, M., Mathieu, D., Golli, M., Dao, T.H., Jazaerli, N., Anglade, M.C., Reyes, F. & Vasile, N. (1993) Detection of multiple myeloma involving the spine: efficacy of fat-suppression and contrast-enhanced MR imaging. *AJR American Journal of Roentgenology*, **160**, 1049–1052.

Rajkumar, S.V., Dimopoulos, M.A., Palumbo, A., Blade, J., Merlini, G., Mateos, M.V., Kumar, S., Hillengass, J., Kastritis, E., Richardson, P., Landgren, O., Paiva, B., Dispenzieri, A., Weiss, B., Leleu, X., Zweegman, S., Lonial, S., Rosinol, L., Zamagni, E., Jagannath, S., Sezer, O., Kristinsson, S.Y., Caers, J., Usmani, S.Z., Lahuerta, J.J., Johnsen, H.E., Beksac, M., Cavo, M., Goldschmidt, H., Terpos, E., Kyle, R.A., Anderson, K.C., Durie, B.G. & Miguel, J.F. (2014) International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncology*, **15**, e538–e548.

Rawstron, A.C., Gregory, W.M., de Tute, R.M., Davies, F.E., Bell, S.E., Drayson, M.T., Cook, G., Jackson, G.H., Morgan, G.J., Child, J.A. & Owen, R.G. (2015) Minimal residual disease in myeloma by flow cytometry: independent prediction of survival benefit per log reduction. *Blood*, **125**, 1932–1935.

Regelink, J.C., Minnema, M.C., Terpos, E., Kamphuis, M.H., Raijmakers, P.G., Pieters-van den Bos, I.C., Heggelman, B.G., Nievelstein, R.J., Otten, R.H., van Lammeren-Venema, D., Zijlstra, J.M., Arens, A.I., de Rooy, J.W., Hoekstra, O.S., Raymakers, R., Sonneveld, P., Ostelo, R.W. & Zweegman, S. (2013) Comparison of modern and conventional imaging techniques in establishing multiple myeloma-related bone disease: a systematic review. *British Journal of Haematology*, **162**, 50–61.

Ringl, H., Schernthaner, R.E., Schueller, G., Balassy, C., Kienzl, D., Botosaneanu, A., Weber, M., Czerny, C., Hajdu, S., Mang, T., Herold, C.J. & Schima, W. (2010) The skull unfolded: a cranial CT visualization algorithm for fast and easy detection of skull fractures. *Radiology*, **255**, 553–562.

Sager, S., Ergul, N., Ciftci, H., Cetin, G., Guner, S.I. & Cermik, T.F. (2011) The value of FDG PET/CT in the initial staging and bone marrow involvement of patients with multiple myeloma. *Skeletal Radiology*, **40**, 843–847.

Salaun, P.Y., Gastinne, T., Frampas, E., Bodet-Milin, C., Moreau, P. & Bodere-Kraeber, F. (2008) FDG-positron-emission tomography for staging and therapeutic assessment in patients with plasmacytoma. *Haematologica*, **93**, 1269–1271.

Schabel, C., Horger, M., Kum, S., Weisel, K., Fritz, J., Ioanoviciu, S. & Bier, G. (2016) Simplified response monitoring criteria for multiple myeloma in patients undergoing therapy with novel agents using computed tomography. *European Journal of Radiology*, **85**, 2195–2199.

Schirrmeister, H., Buck, A.K., Bergmann, L., Reske, S.N. & Bommer, M. (2003) Positron emission tomography (PET) for staging of solitary plasmacytoma. *Cancer Biotherapy & Radiopharmaceuticals*, **18**, 841–845.

Snapper, I. & Khan, A. (1971) Myelomatosis: Fundamentals and Clinical Features. University Park Press, Baltimore, MD, USA.

Song, M.K., Chung, J.S., Lee, J.J., Min, C.K., Ahn, J.S. & Lee, S.M. (2014) Magnetic resonance imaging pattern of bone marrow involvement as a new predictive parameter of disease progression in newly diagnosed patients with multiple myeloma eligible for autologous stem cell transplantation. *British Journal of Haematology*, **165**, 777–785.

Sonmez, M., Akagun, T., Topbas, M., Cobanoglu, U., Sonmez, B., Yilmaz, M., Ovali, E. & Omay, S.B. (2008) Effect of pathologic fractures on survival in multiple myeloma patients: a case control study. *Journal of Experimental & Clinical Cancer Research*, **27**, 11. https://doi.org/10.1186/1756-9966-27-11.

Spira, D., Weisel, K., Brodoefel, H., Schulze, M., Kaufmann, S. & Horger, M. (2012) Can whole-body low-dose multidetector CT exclude the presence of myeloma bone disease in patients with monoclonal gammopathy of undetermined significance? *Academic Radiology*, **19**, 89–94.

Surov, A., Bach, A.G., Tcherkes, A. & Schramm, D. (2014) Non-osseous incidental findings in low-dose whole-body CT in patients with multiple myeloma. *British Journal of Radiology*, **87**, 20140185.

Terpos, E., Kleber, M., Engelhardt, M., Zweegman, S., Gay, F., Kastritis, E., van de Donk, N.W., Bruno, B., Sezer, O., Broijl, A., Bringhen, S., Beksac, M., Larocca, A., Hajek, R., Musto, P., Johnsen, H.E., Morabito, F., Ludwig, H., Cavo, M., Einsele, H., Sonneveld, P., Dimopoulos, M.A. & Palumbo, A. (2015) European Myeloma Network guidelines for the management of multiple myeloma-related complications. *Haematologica*, **100**, 1254–1266.

Thomas, C., Schabel, C., Krauss, B., Weisel, K., Bongers, M., Claussen, C. & Horger, M. (2015) Dual-energy CT: virtual calcium subtraction for assessment of bone marrow involvement of the spine in multiple myeloma. *AJR American Journal of Roentgenology*, **204**, W324–W331.

Touzeau, C. & Moreau, P. (2013) Multiple myeloma imaging. *Diagnostic and Interventional Imaging*, **94**, 190–192.

Usmani, S.Z., Mitchell, A., Waheed, S., Crowley, J., Hoering, A., Petty, N., Brown, T., Bartel, T., Anaissie, E., van Rhee, F. & Barlogie, B. (2013) Prognostic implications of serial 18-fluoro-deoxyglucose emission tomography in multiple myeloma treated with total therapy 3. *Blood*, **21**, 1819–1823.

Vogler, J.B. 3rd & Murphy, M.A. (1988) Bone marrow imaging. *Radiology*, **168**, 679–693.

Wahlin, A., Holm, J., Osterman, G. & Norberg, B. (1982) Evaluation of serial bone X-ray examination in multiple myeloma. *Acta Medica Scandinavica*, **212**, 385–387.

Walker, R., Barlogie, B., Haessler, J., Tricot, G., Anaissie, E., Shaughnessy, J.D. Jr, Epstein, J., van Hemert, R., Erdem, E., Hoering, A., Crowley, J., Ferris, E., Hollmig, K., van Rhee, F., Zangari, M., Pineda-Roman, M., Mohiuddin, A., Yaccoby, S., Sawyer, J. & Angtuaco, E.J. (2007) Magnetic resonance imaging in multiple myeloma: diagnostic and clinical implications. *Journal of Clinical Oncology*, **25**, 1121–1128.

Walker, R.C., Brown, T.L., Jones-Jackson, L.B., De Blanche, L. & Bartel, T. (2012) Imaging of multiple myeloma and related plasma cell dyscrasias. *Journal of Nuclear Medicine*, **53**, 1091–1101.

Weiss, B.M., Abadie, J., Verma, P., Howard, R.S. & Kuehl, W.M. (2009) A monoclonal gammopathy precedes multiple myeloma in most patients. *Blood*, **113**, 5418–5422.

Wolf, M.B., Murray, F., Kilk, K., Hillengass, J., Delorme, S., Heiss, C., Neben, K., Goldschmidt, H., Kauczor, H.U. & Weber, M.A. (2014) Sensitivity of whole-body CT and MRI versus projection radiography in the detection of osteolyses in patients with monoclonal plasma cell disease. *European Journal of Radiology*, **83**, 1222–1230.

Yi, J., Wang, S., Ma, S., Quan, Z., Zhao, X., Yang, Z. & Wang, J. (2013) Disseninated plasmacytomas in multiple myeloma: atypical presentations on multimodality images, emphasized on PET/CT. *Annals of Hematology*, **92**, 1421–1423.

Zamagni, E. & Cavo, M. (2012) The role of imaging techniques in the management of multiple myeloma. *British Journal of Haematology*, **159**, 499–513.

Zamagni, E., Nanni, C., Patriarca, F., Englaro, E., Castellucci, P., Geatti, O., Tosi, P., Tacchetti, P., Cangini, D., Perrone, G., Ceccolini, M., Brioli, A., Buttignol, S., Fanin, R., Salizzoni, E., Baccarani, M., Fanti, S. & Cavo, M. (2007) A prospective comparison of 18F-fluorodeoxyglucose positron emission tomography-computed tomography, magnetic resonance imaging and whole-body planar radiographs in the assessment of bone disease in newly diagnosed multiple myeloma. *Haematologica*, **92**, 50–55.

Zamagni, E., Patriarca, F., Nanni, C., Zannetti, B., Englaro, E., Pezzi, A., Tacchetti, P., Buttignol, S., Perrone, G., Brioli, A., Pantani, L., Terragna, C., Carobolante, F., Baccarani, M., Fanin, R., Fanti, S. & Cavo, M. (2011) Prognostic relevance of 18F FDG PET/CT in newly diagnosed multiple myeloma patients with upfront autologous transplantation. *Blood*, **118**, 5989–5995.

Zamagni, E., Nanni, C., Mancuso, K., Tacchetti, P., Pezzi, A., Pantani, L., Zannetti, B., Rambaldi, I., Brioli, A., Rocchi, S., Terragna, C., Martello, M., Marzocchi, G., Borsi, E., Rizello, I., Fanti, S. & Cavo, M. (2015) PET/CT improves the definition of complete response & allows to detect overwise unidentifiable skel, et al. progression in multiple myeloma. *Clinical Cancer Research*, **21**, 4384–4390.