Cancer Imaging (2010) **10,** 20–31
DOI: 10.1102/1470-7330.2010.0013

REVIEW

Multiple myeloma

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Date accepted for publication 25 January 2010

Abstract

Advances in the imaging and treatment of multiple myeloma have occurred over the past decade. This article summarises the current status and highlights how an understanding of both is necessary for optimum management.

Keywords: *Multiple myeloma; imaging.*

Introduction

Multiple myeloma is the second most common form of haematological malignancy in the western World after non-Hodgkin lymphoma, accounting for approximately 10% of haematological malignancies and 1% of all malignancies[1]. Multiple myeloma is characterised by uncontrolled proliferation of plasma cells within the marrow (mature antibody producing B cells).

Diagnosis is based on laboratory and radiographic findings and depends on 3 abnormal results:

- Bone marrow containing more than 10% plasma cells (normally no more than 4% of the cells in the bone marrow are plasma cells)
- Generalised osteopaenia and/or lytic bone deposits on plain film radiography
- Blood serum and/or urine containing an abnormal protein.

In about 75% of all cases of multiple myeloma the paraprotein present (M protein) will correspond with one type of immunoglobulin. In about 60% of cases an abnormal protein, known as Bence–Jones protein may also be found in the urine. Measuring the amount of paraprotein in the blood or urine is of value in the diagnosis of myeloma and in monitoring the response to treatment. A full list of criteria for diagnosis issued by the International Myeloma Working Group can be found elsewhere[2].

Staging

The clinical staging system devised by Durie and Salmon[3] distinguishes different patient subgroups in terms of tumour mass and disease aggression and still often determines management. Patients with at least 2 lytic foci are classified in advanced disease subgroups and aggressive systemic treatment is usually indicated. Subsequently, the scientific advisers of the International Myeloma Foundation proposed a new staging system called Durie and Salmon PLUS based on the traditional Durie and Salmon system integrated by [^{18}F]fluorodeoxyglucose (FDG)-positron emission tomography (PET) or magnetic resonance imaging (MRI) of the spine[4] (Table 1). This system attributes an equal relevance to [^{18}F]FDG-PET and MRI of the spine, which can be used, as suggested by the guidelines, in a flexible fashion. This staging system has recently been replaced by one based entirely on serum β2 microglobulin and serum albumin levels[5] (Table 2). However, this system cannot be used for therapeutic risk stratification and does not provide a good estimate of tumour burden[6]. Its prognostic role in the era of new drugs is also not yet established. Despite the new system many physicians still find that information regarding imaging status influences their management so the Durie and Salmon PLUS is a more relevant system for radiologists.

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Table 1 Durie–Salmon PLUS staging system for symptomatic multiple myeloma[4]

Stage	Imaging findings (including MR and FDG PET)
Stage I clinical criteria	<5 focal spine lesions ± mild diffuse spine disease
Stage II clinical criteria	5-20 focal lesions ± moderate diffuse spine disease
Stage III clinical criteria	>20 focal lesions ± severe diffuse spine disease

Table 2 New international staging system[5]

Stage I	Serum β2 microglobuli <3.5 mg/l (average survival 62 months), serum albumin >3.5 g/dl
Stage II	Not I or III[a] (average survival 44 months)
Stage III	Serum β2 microglobulin >5.5 mg/l (average survival 29 months)

[a]There are 2 categories for stage II: serum β2 microglobulin <3.5 mg/l but serum albumin <3.5 g/dl or serum β2 microglobulin 3.5–5.5 mg/l irrespective of the serum albumin level.

Therapy

The International Myeloma Foundation and UK Myeloma Forum (with the support of the British Committee for Standards in Haematology) should be regarded as the preferred source of detailed guidance on treatment[4,7,8]. Treatment strategy is directed towards adequate analgesia, rehydration, management of hypercalcaemia and renal impairment, and treatment of infection. The response categories (complete, near complete, partial, minimal, stable and progressive) are determined primarily by the level of M protein present. M protein is the level of monoclonal protein measured by protein electrophoresis in serum or 24-h urine.

Chemotherapy is indicated for management of symptomatic myeloma. High-dose therapy using melphalan and prednisolone can produce complete remission in up to 75% of patients[9,10]. In recent years thalidomide (and its more potent immunomodulatory analogue lenalidomide) has been recognised as a valuable drug for the treatment of myeloma[11]. A newer class of drug, bortezomib (a proteasome inhibitor), is effective for treatment of relapsed refractory myeloma and is superior to dexamethasone in progression-free and overall survival[12]. Other new agents entering clinical trials include conventional drugs (doxorubicin, Doxil), cytokines (bevacizumab, Avastin), biological agents (β-alanyl cystreamine disulfide, Betathine) and agents such as arsenic trioxide[11,13,14]. Animal studies using the novel recombinant vesicular stomatitis virus have proved encouraging and point to the likely direction of future therapies[15].

The most serious morbidity in these patients arises from destructive bone deposits which cause severe intractable pain and pathological fractures often resulting in deformity and disability. A recently published retrospective review of outcome data from 67 myeloma patients treated with vertebroplasty showed significant improvement in rest pain, activity pain, narcotic use and mobility[16]. The bisphosphonate group of drugs bind to bone at sites of active bone remodelling and can therefore inhibit myelomatous bone damage arresting the destructive cycle described above[17,18]. These agents (used in conjunction with cytotoxic chemotherapy) have been found to be superior to chemotherapy alone in decreasing the incidence of pathological fractures and bone pain and may lead to prolonged survival[19].

Autologous transplantation has an established place in the treatment of myeloma. It is the treatment of choice for patients aged under 65 years and can be considered in older age groups (with good performance status) carrying a procedure-related mortality of less than 5%[11]. At present the added benefit of double or tandem transplantation versus a single autologous transplant is not known.

Radiation therapy is reserved for patients with spinal cord compression secondary to vertebral body collapse associated with a soft tissue mass or pathological fractures elsewhere associated with a soft tissue mass. It can be very effective but permanently destroys normal bone marrow stem cells in the treatment field.

Myeloma is generally considered incurable. It is a slowly progressing disease with long periods of relative inactivity. Relapse occurs in virtually all cases. On current treatment regimens patients younger than 70 years can expect a median survival of 5 years (depending on stage)[9,14]. Death results from bacterial infection, renal insufficiency and thromboembolism.

Radiology and cross-sectional imaging

Radiology plays an important role in staging, monitoring treatment response, detection of relapse and assessing complications. The various imaging techniques used and their associated findings are described more fully below.

Conventional radiography (skeletal survey)

Almost 80% of patients with multiple myeloma have radiological evidence of skeletal involvement at diagnosis

manifest in 4 different appearances: solitary deposit (plasmacytoma), diffuse skeletal involvement (myelomatosis), generalised osteopaenia and sclerosing myeloma[20]. Views acquired should be posterior-anterior chest, anterior-posterior (AP) and lateral views of cervical spine (including an open mouth view), thoracic spine, lumbar spine, humeri and femora, AP and lateral views of skull and AP view of pelvis[21]. Additional views of any symptomatic area should also be acquired. The most common sites include the vertebrae, ribs, skull and pelvis; involvement of the distal bones is unusual. In early stage disease the role of the plain radiograph is limited with myeloma deposits often not visualised.

Myeloma lesions are sharply defined, small lytic areas (average size 20 mm) of bone destruction with no reactive bone formation. At post mortem these lesions are due to nodular replacement of marrow and bone by plasma cells. Although myeloma arises within the medulla, disease progression may produce infiltration of the cortex, invasion of the periosteum and large extraosseous soft tissue masses. The pattern of destruction may be geographic, moth eaten or permeated. Pathological fractures are common.

When the skeletal survey has been obtained any further imaging should be discussed in the context of a multidisciplinary setting that includes an appropriately experienced radiologist, haemato-oncologist and possibly an orthopaedic surgeon[22]. The expertise of the latter is useful in deciding if surgical stabilisation of any bones is required. A major disadvantage of the skeletal survey is its relatively low sensitivity with lytic deposits only becoming visible once 30% of the trabecular bone substance has been lost. Particular difficulty may arise in the sternum, sacrum, scapulae and ribs. In addition, accurate assessment of osteopaenia is not possible.

Generalised osteopaenia may be the only bone manifestation of myeloma in up to 15% of patients. At post mortem these patients show diffuse replacement of marrow with plasma cells but have less severe bone resorption compared with lytic deposits[23]. Vertebral body collapse is the usual manifestation of this subtype which should not be confused with non-myelomatous osteoporosis that occurs in many older patients.

Radionuclide imaging

In multiple myeloma the osteoblastic response to bone destruction is negligible and the bone scan (using technetium-99m labelled diphosphonate) is often therefore normal or may show areas of decreased uptake (photopaenia). As a result its routine use is not recommended[24]. However, skeletal scintigraphy may be helpful in evaluating areas not well visualised on plain film radiographs such as the ribs, sacrum, scapulae and sternum.

PET using the glucose analogue [^{18}F]FDG has the functional and morphological capacity to identify the extent and activity of multiple myeloma for staging and monitoring purposes. The ability of PET to perform whole-body examinations is a major advantage over conventional imaging techniques. In one series comprising 28 patients PET was true positive in almost 93% of the radiographically documented osteolytic deposits and showed a greater extent of disease than plain film radiography in 61% of patients[25]. Another study confirmed its reliability in detecting active myeloma within bone and at extramedullary sites and its ability to differentiate between new active disease and inactive (treated) sites[26,27]. It is extremely useful in the evaluation of non-secretory myeloma and in identifying patients with a poor prognosis (residual myeloma after stem cell transplantation and extramedullary myeloma). A negative [^{18}F]FDG-PET strongly supports the diagnosis of monoclonal gammopathy of uncertain significance (MGUS)[26,28]. In a recent study of 49 patients with plasma cell malignancies only 5% relapsed after a negative FDG-PET scan after therapy[28]. In a study involving 239 untreated patients the presence of more than 3 FDG avid focal lesions was the leading independent parameter associated with inferior overall and event-free survival[29]. The more recently available technology of PET/computed tomography (CT) is now being used in the assessment of multiple myeloma. In a small study of 16 patients comparing FDG-PET/CT with the skeletal survey, CT scans and MRI scans, it was shown that FDG-PET/CT led to management changes in 9 patients but that MRI revealed diffuse bone involvement in 5 patients not evident on PET/CT[30]. A larger study of 46 patients comparing FDG-PET/CT with MRI of spine and pelvis and skeletal survey revealed that in 30% of patients PET/CT failed to show abnormalities visible on the MRI scan[31]. However, PET/CT identified deposits outside the spine and pelvis in 35% of patients. Combining both techniques enabled identification of 92% of medullary and extramedullary sites of active disease. In a comparative study of 24 patients FDG-PET/CT and MRI were concordant in 62%; when concordant and positive, the positive predictive value was 100%[32]. FDG-PET/CT is likely to be particularly useful for restaging after chemotherapy and stem cell transplantation[33]. False-positive PET scans using FDG may arise from inflammatory changes due to active infection, chemotherapy within the previous 3–4 weeks or radiotherapy within the previous 2–3 months[34,35].

Cross-sectional imaging

A wide range of findings have been described in CT of myeloma. These include sharp, lytic foci of small and relatively homogeneous size with no sclerotic rim, diffuse faint osteolysis fan angioma-like appearance due to the presence of thickened vertical trabeculae and expansile deposits[36]. CT can accurately depict the extent of associated soft tissue masses and can direct needle biopsy for histological diagnosis. Multidetector CT (MDCT) provides more detailed information on the risk of

vertebral fractures compared with conventional radiography and MRI[37]. In patients who are severely disabled or who are unable to undergo MRI examination this is a useful alternative imaging technique[38].

A study using MDCT in patients with stage III myeloma provided more detailed information on the risk of vertebral fractures compared with plain film radiography and MRI. Upward stage migration occurred in 17% of patients[37]. More recently, a study comparing MDCT (64×0.6 mm collimation) with conventional radiography showed a significant increase in detection of myelomatous deposits in spine, pelvis and ribs ($p \leq 0.001$) necessitating a change in management in 18% of patients[39]. A large study comparing whole-body low-dose unenhanced MDCT in 131 patients with multiple myeloma with conventional haematological parameters showed that the combination provided significantly greater diagnostic accuracy compared with laboratory testing alone particularly in monitoring patients after therapy[40]. MDCT also allows for improved imaging of patients with scoliosis due to its ability to adapt the data set to the individual patient's features. As most patients are elderly, dose considerations are not a major drawback and its ability to image well the ribs, sternum, scapulae and sacrum in addition to the fact that intravenous contrast is not necessary makes it a realistic alternative in the clinical scenarios outlined above. MDCT has an important role in evaluating suspected spinal cord compression in cases where MRI is contraindicated (e.g. cardiac pacemaker, intraorbital metallic foreign body) or not possible due to patient intolerance. Although MDCT may replace the skeletal survey due to its speed and superior patient tolerance, the most recent consensus statement continues to favour conventional radiography[24].

Magnetic resonance imaging

MRI is used routinely in many centres because of its high sensitivity and its ability to directly visualise bone marrow. The role of MRI (and PET imaging) is acknowledged by their inclusion in the Durie–Salmon PLUS staging system[4]. Utilising this system the number of lytic lesions is counted leading to possible upstaging and altered therapy[41]. In patients with suspected cord compression MRI is the examination of first choice[24]. Bone deposits have been shown by MRI in about 50% of asymptomatic myeloma patients with normal plain radiographs. In a recent study of over 600 patients it was shown that focal deposits detected by MRI (but not on skeletal survey) independently affected survival[42]. Resolution of MRI focal lesions also conferred superior survival. MRI can detect bone marrow infiltration in 29–50% of patients with Durie–Salmon stage I disease and negative conventional radiographs[43].

Sagittal studies of the spine enable screening of a high proportion of haematopoietic marrow in a limited time and detection of any potential threat to the spinal cord. Additional coronal images of the pelvis and proximal femora enable evaluation of about an extra one-third of red marrow in an adult. These images may enable detection of deposits potentially at risk of fracture. Whole-body MRI (WB-MRI) can be performed although its clinical benefit has not yet been fully evaluated in myeloma[44–47]. In one study comparing whole-body MRI and the skeletal survey in 54 patients (47 myeloma, 7 MGUS) WB-MRI correctly revealed marrow deposits in 74% of patients versus 55% for the skeletal survey[48]. WB-MRI also showed greater extent of infiltration in 90% of concordant deposits. In a recent study of 100 untreated patients (73 myeloma, 27 MGUS) using WB-MRI, almost 50% of all observed deposits would have been missed using spinal MRI only[49].

The imaging patterns in multiple myeloma can be classified as normal, focal, diffuse and variegated[50,51]. Others have added a further classification of combined diffuse and focal infiltration[52]. Normal marrow is present on MRI at diagnosis in 50–75% of patients with early untreated (stage I) myeloma and in about 20% of patients with advanced and treated (stage III) disease. Fast and complete assessment can be achieved using a combination of a T1-weighted sequence and a fat suppression technique[43]. The focal pattern consists of localised areas of decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images. Myelomatous deposits are generally sharply demarcated on a background of an otherwise normal-appearing bone marrow. Homogeneous enhancement occurs on T1-weighted images following intravenous contrast injection. Dynamic contrast-enhanced MRI has been shown to correlate with vessel density and paraprotein level[53]. In a recent study using WB-MRI in 23 patients the highest sensitivity and reliability was achieved using a T2-weighted inversion recovery sequence[54].

The diffuse pattern is characterised by a diffuse and homogeneous decrease in marrow signal intensity, which becomes identical to or lower than that of adjacent intervertebral discs on a T1-weighted image and on a T2-weighted image by a diffuse or patchy increase in signal intensity. Marked enhancement is usually seen on T1-weighted images following intravenous contrast. The increased contrast between enhancing marrow and the lower signal intervertebral discs allows more subtle forms of infiltration to be identified[55].

The variegated pattern is characterised by the presence of multiple foci of low signal intensity on T1-weighted images, intermediate to high signal intensity on T2-weighted images and enhancement following intravenous contrast T1-weighted images. This pattern is seen almost exclusively in an early stage of the disease[56].

The lack of specificity of the MRI patterns should be noted. The focal and diffuse patterns may be observed in both metastatic disease from primary solid tumours and in other haematological malignancies, especially lymphoma and leukaemia. Differentiation between red

marrow hyperplasia secondary to anaemia, infection, malignant or treated marrow infiltration can be extremely difficult. Normal marrow heterogeneities may mimic the variegated pattern although in most cases high signal intensity on T2-weighted images and contrast enhancement help distinguish relevant small marrow abnormalities from normal haematopoietic foci that generally show intermediate signal intensity on T2-weighted images and no contrast enhancement on T1-weighted images. The advent of diffusion-weighted imaging promised an effective method for differentiating benign from malignant compression fractures[57,58]. However, only variable success has been reported since then and as a result it is not used routinely[59,60].

Functional MRI

Analysis of enhancement patterns following intravenous contrast has enabled a functional component to MRI studies. Changes in microcirculation patterns using MRI circulation parameters (amplitude A, exchange rate constant k_{ep}) reflecting vascular volume and permeability allow this to be visualised.

Bone marrow angiogenesis is increased in multiple myeloma and has prognostic importance[61]. Patients with newly diagnosed multiple myeloma have higher microvessel density at bone marrow biopsy than do control subjects[62]. In a study of 110 patients with newly diagnosed multiple myeloma lower microvessel density was observed in complete responders and patients with rapid disease progression post-therapy had higher levels of angiogenesis pre-treatment. Induction of angiogenesis by normal and malignant plasma cells analysed by DNA microassay (300 untreated multiple myeloma patients), in vivo microcirculation by dynamic contrast-enhanced (DCE)-MRI and in vitro angiogenesis found that 97% of CD 138 purified myeloma cells aberrantly expressed at least one of a number of known angiogenic factors[63]. Supernatants of multiple myeloma cells and human myeloma cell lines induce significantly higher in vitro angiogenesis compared with normal bone marrow cell lines.

In 2003, DCE-MRI of the thoraco-lumbar spine in 42 patients with documented marrow infiltration from myeloma and lymphoma using time enhancement curves revealed significant differences in enhancement ($p < 0.001$) and washout ($p = 0.005$) between healthy subjects and those with documented malignant marrow infiltration[64]. Receiver operating characteristic (ROC) analysis showed enhancement patterns had a high level of diagnostic accuracy in assessing the degree of marrow infiltration and also in differentiating responders from non-responders.

Bone marrow microcirculation in the lumbar spine was analysed in 65 patients with relapsed or progressive myeloma (median follow-up 56 months)[65]. Contrast uptake was quantified using the output variables amplitude A and exchange rate constant k_{ep}. Using a multivariate Cox regression model, β2 microglobulin ($p = 0.01$) and amplitude A of DCE-MRI ($p = 0.02$) were identified as statistically significant prognostic variables of event-free survival.

A recent study using an 18 channel 1.5-T WB-MRI scanner (with dynamic contrast enhancement) in 3 healthy volunteers and 21 patients with plasma cell disorders showed that the examination could be completed in 28 min[66]. Diffuse and focal enhancement could be assessed with enhancement being greater in patients with 10% or higher plasma cell infiltration.

A large study using DCE-MRI of the lumbar spine in 222 persons (healthy controls, MGUS, asymptomatic and symptomatic multiple myeloma) showed significant differences in microcirculation parameters between the different groups[67]. MGUS and asymptomatic multiple myeloma patients with increased microcirculation patterns showed significantly higher bone marrow plasmacytosis compared with patients with a low microcirculation pattern. Pathological DCE-MRI findings correlate with adverse prognostic factors and also identify patients with MGUS and asymptomatic multiple myeloma who have increased microcirculation parameters.

Compression fractures in multiple myeloma

Compression fractures arise from extensive osteoclastic bone resorption or replacement of bone by a growing plasma cell tumour mass. Several criteria exist for differentiating benign from malignant vertebral body compression fractures[68]. However, these should be applied with caution to patients with multiple myeloma as normal signal intensity within a compressed vertebral body on spinal MR images does not preclude the diagnosis of multiple myeloma. In a study of 224 vertebral fractures in patients with known multiple myeloma Lecouvet *et al.* found that 67% appeared benign on MRI and 38% of their 37 patients had benign fractures only at diagnosis[69].

In patients with osteoporotic or post-traumatic vertebral compression of recent onset MRI will usually show signal alteration that parallels one of the end plates, involves less than half of the vertebral body, does not extend to the pedicles and enhances homogenously following intravenous contrast. Diffusion-weighted MRI may also prove to be a useful method to apply to the differential diagnosis of compression fractures[57].

Patients being treated for multiple myeloma may suffer acute back pain secondary to vertebral body collapse even after effective chemotherapy. This is due to resolution of the tumour mass that was supporting the bony cortex. Conversely, progression of disease may also be responsible for a new compression fracture and MRI may be useful in differentiating between these 2 clinical settings.

Side effects of therapy and complications: the role of radiology

Drug therapy

Infection is the single most dangerous complication for myeloma patients with the patient most at risk in the first 3 months of front-line therapy and is a recognised cause of bone pain in its own right[4,70]. Myeloma is associated with a higher incidence of infective discitis and cerebritis in part due to cytotoxic therapy-induced immunosuppression associated with corticosteroid therapy[71–73]. Central venous catheters represent a potential source of bacteraemia[74]. MRI enables early identification followed by percutaneous needle aspirate using CT to confirm the diagnosis and provide information regarding choice of antibiotic[75]. Melphalan is associated with increased risk of pancytopaenia, mucositis and pulmonary complications[76–79]. Conventional radiography and CT scanning are the appropriate imaging investigations. High doses of corticosteroids may cause spinal fractures and avascular necrosis of the femoral heads (amongst other bones). MRI is useful for assessing both these conditions. When thalidomide is used in combination with dexamethasone it carries a 16% incidence of deep vein thrombosis (DVT)[80,81]. Abdominal discomfort resulting from constipation is also a well-recognised side effect of thalidomide and can be readily assessed radiologically using a supine plain radiograph of abdomen. A reported side effect is interstitial pneumonitis which can be identified on high-resolution CT[82]. The drug bortezomib is associated with cytopaenia and a decrease in platelet count to $<50{,}000$ mm^3 occurs in almost 30% of patients increasing the risk of haemorrhage[83]. This drug has not been associated with an increased incidence of DVT in trials reported to date[14]. Other reported adverse effects are sensory neuropathy and pseudomembranous colitis[84]. Chronic bisphosphonate use is associated with renal damage (monitored with regular serum creatinine levels) and osteonecrosis of the mandible[85–88]. Regular dental check-ups in association with an orthopantomogram and a CT scan enable early diagnosis of the latter[89].

Marrow transplantation

Allogeneic transplant is a high-risk procedure with reported encephalopathic changes (reversible) that may develop as result of cyclosporin therapy[90]. In patients undergoing non-myeloablative or 'mini' allogeneic transplants there is a high risk of acute (32–39%) and chronic (32–46%) graft versus host disease in reported series[11]. Autologous stem cell transplantation is also available but it is not curative with a median relapse time of 3 years[91]. Imaging depends on symptomatology and consists of plain film radiography, CT and MRI as required.

Spinal cord compression

Spinal cord compression resulting from vertebral body collapse may occur in up to 25% of patients and has been described as the presenting feature in 12% of patients[92–94]. Early recognition of back pain and neurological symptoms is essential. Magnetic resonance is the imaging investigation of choice. Fractures of the tubular bones heal readily with normal amounts of callus but extensive fractures may require insertion of intramedullary nails. Myelofibrosis manifest by diffuse low signal on both T1-weighted and short time inversion recovery (STIR) sequences and amyloidosis manifest by focal areas of decreased signal on T1-weighted and STIR sequences are other recognised complications[20].

Osteopaenia

Osteopaenia in myeloma may be confined to bones where myeloma is active leaving the remaining bony skeleton unaffected. Insufficiency fractures may arise in the sacrum, pubic rami or acetabular roof with the latter having a characteristic appearance[95]. Although dual energy X-ray absorptiometry (DEXA) is the best technique for diagnosing osteoporosis and for fracture risk assessment, no reliable data exist currently to differentiate between benign osteoporosis and myeloma-induced osteoporosis. Newer scanners allow estimation of vertebral bone mineral density from a lateral view (with the patient supine) but accuracy of the analysis is affected if spinal osteophytes, pre-existing vertebral body compression or spondylosis are present precluding its use routinely. A further complicating factor is the widespread use of bisphosphonates in symptomatic myeloma patients.

Patients being treated for multiple myeloma may suffer acute back pain secondary to vertebral body collapse even after effective chemotherapy. This is due to resolution of the tumour mass that was supporting the bony cortex. In one study, 131 vertebral compression fractures appeared in 37 patients with multiple myeloma after the onset of therapy[57].

The most sensitive and specific imaging technique for the diagnosis of avascular necrosis of the femoral head is MRI which is manifest by a characteristic double-line sign on T2-weighted images[96]. This condition may result from high-dose steroid therapy or radiotherapy and its early recognition before the development of subchondral fractures is important for the success of conservative management.

Renal impairment is common in myeloma and affects up to half of all patients at some stage in their illness. This is usually a consequence of amyloisosis rather than plasma cell infiltration[97]. Other possible causes include hypercalcaemia, dehydration, hyperuricaemia, infection or the action of nephrotoxic drugs. Unfortunately several of the drugs that are used to treat myeloma have an adverse effect on kidney function. Secondary amyloid occurs in approximately 10% of cases and in the early

stages ultrasound demonstrates enlarged kidneys with increased cortical reflectivity. Amyloid protein is deposited mainly in the cortex so that corticomedullary differentiation is preserved and the pyramids are normal in size[98]. Radiolabelled serum amyloid P component scintigraphy is a non-invasive and quantitative method for imaging amyloid deposits although it is less effective in myeloma-associated amyloid than other forms of amyloid[99]. Cardiac involvement is difficult to demonstrate due to motion artefact and blood pooling in addition to proximity of the spleen[100]. Unfortunately, this examination is only available in a few specialist centres.

Radiology of responding/relapsing disease

The role of radiology in the assessment of treatment response is limited and sequential quantification of biological markers of disease (monoclonal protein levels and bone marrow plasmacytosis) are usually sufficient to assess response to chemotherapy[19]. In 2006 the International Myeloma Working Group proposed new criteria for disease response in order to allow more accurate comparison between new therapies and different treatment strategies[101]. The new criteria incorporate new categories of stringent complete response and very good partial response (whilst maintaining existing categories of complete response, partial response and stable disease). Imaging studies are not required to satisfy these response requirements. However, all categories also require no known evidence of progressive or new bone deposits if imaging studies were performed. The choice of imaging technique depends on the findings from the initial work-up and treatment received.

Conventional radiography

A repeat skeletal survey is not routinely indicated as lytic bone deposits often show little evidence of healing radiographically (manifest by shrinkage or sclerosis) even in those patients achieving a complete remission[21,41]. The addition of bisphosphonate compounds as antiosteoclast agents leads to bone strengthening, which may further accentuate these features. New or enlarging deposits signify disease progression. New vertebral body compression fractures on conventional radiography do not necessarily indicate disease progression as they may arise due to resolution of the tumour mass formerly supporting the bony cortex. Persistence of radiological abnormalities should not be considered evidence of active disease, since they may represent residual osteolysis in the absence of plasma cell proliferation. There is insufficient evidence to recommend routine skeletal surveys in untreated asymptomatic patients in the absence of any evidence of disease progression[21]. If this situation changes, the skeletal survey should be repeated with targeted views of any symptomatic region.

Computed tomography

Current evidence does not support using CT scans for routine follow-up assessment. However, in selected cases, particularly those with a substantial soft tissue component, it is reasonable to use CT scanning to monitor treatment response. In these cases there is disappearance of extraosseous or extramedullary masses and the reappearance of a continuous cortical outline with fatty marrow content[51]. CT scanning should also be considered if there are persistent unexplained symptoms, concern about a risk of fracture or lack of response to therapy.

Magnetic resonance imaging

There is insufficient evidence to recommend routine MRI for the follow-up of treated disease[21]. Interpretation of post-treatment MRI changes can be difficult as there is a wide spectrum of possible treatment-induced changes on MRI depending on the pattern of bone marrow infiltration. Although MRI is more sensitive than the skeletal survey, it is often difficult to differentiate inactive from active disease. Focal marrow lesions may remain identical or decrease in size[102,103]. Changes in contrast enhancement between the pre- and post-treatment MR examinations have been studied[104]. The lack of lesion enhancement or only a peripheral rim enhancement seen after treatment can be indicative of responsive deposits. Other features suggestive of a good response include decreased signal intensity on T2-weighted images[43]. Local radiation therapy of focal complex deposits induces a rapid decrease in the soft tissue extension and appearance of presumably necrotic, avascular central areas within the deposit on T1-weighted images with a later decrease in lesion size[105]. In diffuse marrow abnormalities, increased marrow signal is usually observed on post-treatment T1-weighted images due to reappearance of fat cells within more hydrated cellular components. Conversion of a diffuse to a focal or variegated pattern is also frequent[102]. Post-treatment MRI of the bone marrow may provide important information for patients with equivocal clinical and laboratory results as well as for patients with non-secretory myeloma.

In contrast to patients with advanced disease stages treated with conventional chemotherapy, patients with normal MR findings at diagnosis have better response to treatment and a longer survival than those with focal or diffuse marrow abnormalities at MR imaging[55]. This feature has not yet been assessed in patients treated with marrow transplantation. Patients undergoing therapy with thalidomide have more favourable outcomes (better overall survival rate and prolonged event-free survival) with a normal post-treatment MRI than those with persistent focal deposits[106].

In patients with clinical relapse, new focal deposits or an increase in size of deposits previously present can be identified with MRI. Conversion of a normal or

variegated pattern to a diffuse pattern indicates severe relapse on follow-up MRI scans. MRI is also useful in assessing status of leptomeninges as abnormal enhancement representing tumour spread has been reported in 18 out of 1856 treated patients in one series[107]. In patients with a solitary bone plasmacytoma, MR screening of the spine and pelvis will usually reveal radiographically unsuspected deposits in up to 80% of patients thus suggesting true myeloma from the outset. This finding is associated with a poor response to localised radiotherapy and an earlier development of systemic disease than in patients with a negative MRI survey[108].

MRI has been useful in the assessment of patients following transplantation. The bone marrow evolution index based on comparison of pre- and post-transplant MRI scans combines findings related to the number of deposits, deposit size, contrast enhancement and marrow background[109]. A score of 0, 1 or 2 is given depending on whether there is improvement, stability or deterioration. A score below 4 had superior treatment response and was more successful than evaluating each parameter individually. However, diffuse or focal marrow changes following granulocyte colony-stimulating factor (GCSF) treatment may mimic active disease and limit its effectiveness[110].

High levels of serum β2 microglobulin correlate with a poor prognosis and remain the single most powerful determinant of outcome[111]. A recent study used MRI in 170 patients (144 active myeloma) to quantify disease burden and validate staging by correlating it with common clinical and laboratory parameters[112]. Significant association between MRI and Durie–Salmon stage ($p = 0.0006$), international staging system ($p = 0.0001$) and β2 microglobulin levels was shown. Significant association was also shown between MRI and overall survival in the untreated myeloma patient group (univariate $p = 0.013$; multivariate $p = 0.045$). This would indicate accurate correlation of MRI with other conventional parameters of disease burden and an ability to independently predict survival at time of diagnosis. Further studies are likely to confirm the significance and prognostic value of the different MRI patterns of marrow involvement and their correlation with various laboratory values particularly in patients undergoing transplantation.

Functional imaging

Conventional scintigraphy

Although abnormal tracer uptake has been shown to indicate residual activity on conventional skeletal scintigraphy, osteoblastic activity due to healing vertebral body fractures, fractures elsewhere in bony skeleton and drug therapy (particularly bisphosphonates) also give rise to increased isotope uptake[17,18,113]. As a result it is not used routinely. Despite the volume of published work supporting methoxyisobutylisonitrile (MIBI) scintigraphy, it will be superseded by PET/CT in major oncology centres in the coming years.

FDG-PET and PET/CT

Studies have shown the reliability of FDG-PET in detecting active myeloma both within bone and at extramedullary sites and its ability to differentiate between new active disease and inactive (treated) sites[26,114,115]. In a study involving 13 patients using FDG-PET, 9 of whom had undergone therapy, PET proved superior to anatomical imaging in identifying sites of active residual disease[27]. Patients showing no abnormal or decreased FDG uptake showed clinical improvement. In a recent study of 49 patients with plasma cell malignancies only 5% relapsed after a negative FDG-PET scan after therapy[28]. False-negative results may occur due to limitations with spatial resolution resulting in deposits less than 0.5 cm not being detected. If relapse is suspected, PET may identify new sites of disease and unsuspected sites of extramedullary disease. If FDG uptake is present in medullary or extramedullary compartment following high-dose therapy and stem cell transplantation then prognosis is adversely affected[26]. GCSF can cause changes mimicking active disease on PET scans which can last for up to 1 month following discontinuation of treatment[116]. In many centres, PET/CT is becoming the imaging study of choice for post-transplant patients. Deposits in the range of 0.5–1 cm (standardized uptake value (SUV_{max}) > 2.5) can be identified[53]. FDG-PET/CT has an advantage over MRI in the post-transplantation patient by more accurately reflecting disease status[31,33,117]. Given the range of newer therapies now available the identification of occult active disease may allow for targeted multimodal therapy. Non-secretory myeloma patients should get PET/CT scans during their initial staging because PET/CT will be the imaging study of choice after treatment[47]. Despite much anecdotal evidence for its success, PET is not yet recommended for use in routine follow-up in treated myeloma patients on the basis of current evidence[21].

Uncommon variants of myeloma

Extraosseous myeloma

Clinical manifestations of extraosseous myeloma are rare, occurring in less than 5% of patients with multiple myeloma. Extraosseous myeloma deposits have been reported at multiple sites with the breast, lymph nodes and spleen most frequently involved. It may also occur in the epidural region causing cord compression[118]. Extraosseous myeloma is more aggressive, occurs in a younger age group (average age 50 years) and is associated with worse survival than conventional myeloma[119].

Sclerotic myeloma

Primary sclerotic manifestations are rare and occur only in 3% of patients. It may take the form of diffuse osteosclerosis, patchy sclerotic areas throughout the skeleton or very small numbers of focal sclerotic lesions[120].

Conclusion

The recent consensus statement from the International Myeloma Working Group summarises all the available data and recommends conventional radiography as the preferred imaging examination for newly diagnosed and relapsed patients[24]. MRI should be performed in all patients with a normal skeletal survey and apparently solitary plasmacytoma of bone. Suspected cord compression should be evaluated by MRI (or MDCT if MRI is contraindicated or not available). Neither PET/CT nor DEXA are recommended for use on a routine basis. There is no role for conventional bone scintigraphy.

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