Guidelines for the use of imaging in the management of myeloma

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Summary

In 2001, reference to the use of imaging in the British Committee for Standards in Haematology guidelines for the diagnosis and management of myeloma was confined to the standard use of plain X-rays in the diagnostic skeletal survey and emergency use of computed tomography (CT) and magnetic resonance (MR) imaging in the setting of cord compression. Since then, there has been a steady rise in interest in the use of various imaging techniques in the management of myeloma. The purpose of imaging in the management of myeloma includes the assessment of the extent and severity of the disease at presentation, the identification and characterisation of complications, and the assessment of response to therapy. Plain radiography, CT, and MR imaging are generally established examination techniques in myeloma whilst positron emission tomography (PET) and Technetium sestamibi (MIBI) imaging are promising newer scanning techniques under current evaluation. These stand-alone imaging guidelines discuss recommendations for the use of each modality of imaging at diagnosis and in the follow up of patients with myeloma.

Keywords: guidelines, imaging, myeloma, plasmacytoma.

1. Introduction: Context, methodology

1.1 Context

In 2001, guidelines for the diagnosis and management of myeloma were prepared by the Guidelines Working Group of the UK Myeloma Forum on behalf of the British Committee for Standards in Haematology (BCSH) (Samson, 2001). Reference to the use of imaging was confined to the standard use of plain X-rays in the diagnostic skeletal survey and emergency use of computed tomography (CT) and magnetic resonance (MR) imaging in the setting of cord compression. Since then, there has been a steady rise in interest in the use of various imaging techniques in the management of myeloma, not least due to the apparently successful application of techniques, such as positron emission tomography (PET) scanning, and developments in MR technology. It was therefore felt appropriate to develop stand-alone guidelines for the use of imaging in the management of myeloma.

Myeloma is a plasma cell tumour with an annual incidence in the UK and Scandinavian countries of approximately 50 per million and a median age at presentation of about 70 years (Turesson et al, 1984; Hjorth et al, 1992; Office for National Statistics, 2001; Phekoo et al, 2004). Clinical presentation is varied. Common presentations of myeloma include bone pain, recurrent or persistent infection, anaemia, renal impairment, symptoms of hypercalcaemia or a combination of these. Some patients are asymptomatic, abnormalities being identified on blood tests carried out for other clinical reasons. In the majority of patients, the disease is characterised by plasma cell infiltration of the bone marrow, osteolytic bone lesions and the presence of a monoclonal protein in the serum or urine. In a proportion of these, however, one or more features may be absent, giving rise to a diagnosis of solitary plasmacytoma, asymptomatic myeloma or non-secretory myeloma.

1.2 Approach to imaging in the management of myeloma

The purpose of imaging in the management of myeloma includes the assessment of the extent and severity of the disease at presentation, the identification and characterisation of complications, and the assessment of response to therapy. Plain radiography, CT, and MR imaging are generally established examination techniques in myeloma whilst PET and Technetium -2-methoxy-isobutyl-isonitrile (MIBI) imaging are promising newer scanning techniques under current evaluation. With the advent and development of these newer techniques, it is tempting to use them in the follow up of
challenging situations, such as patients with non-secretory disease (especially those who have non-contributory serum free light chain (FLC) measurements). Various studies of myeloma patients have demonstrated that more sophisticated imaging techniques, such as CT and MR, demonstrate the presence of a higher tumor burden than techniques such as plain radiography (Laroche et al., 1996; Dimopoulos et al., 2000; Mulligan, 2000). The important consideration is whether the increased costs involved and/or greater exposure to radiation is justifiable in terms of improved clinical outcome. If clinical outcome is measured by improved survival, very few imaging techniques can claim to achieve this goal, as it is the treatment intervention itself that produces this effect. If, however, successful clinical outcome is measured by an improvement in quality of life measures as well, then it can be argued that the greater sensitivity and specificity of particular imaging techniques may contribute to this goal (Hunink & Krestin, 2002). As a result of rapid advancements in diagnostic imaging techniques, comprehensive evaluation of new techniques prior to their implementation is difficult (Fryback & Thornbury, 1991). In practice, newer imaging techniques are often implemented on the basis of subjective experience with a limited number of cases and subjective expectations of their usefulness (Hunink & Krestin, 2002).

1.3 Methods

These guidelines have been compiled by the Imaging Subgroup of the Guidelines Working Group of the UK Myeloma Forum and Nordic Myeloma Study Group on behalf of the BCSH, including two UK haematologists, one Danish haematologist and two UK radiologists with specialist experience of oncological radiology. Their production involved the following steps:

- Review of key literature including Cochrane database, Medline and Internet searches updated to 28 February 2006.
- Consultation with representatives of other specialties, including surgeons and specialists in nuclear medicine.
- Recommendations made based on the literature review and consensus of expert opinion.
- Completion date 31st March 2006.

These guidelines are intended to set out the key areas of strategy in the effective use of imaging in the management of myeloma. Levels of evidence and grades of recommendation are set out in Table I and II. However, there is a distinct lack of randomised controlled trials in the use of imaging in myeloma, and the relationship between diagnostic imaging information and patient outcomes is difficult to demonstrate due to the multiple steps and confounding factors that intervene, including individual patient performance status, prognostic factors and treatment modalities undertaken (Eisenberg et al., 1989). Thus all the recommendations made are of grade B and

<table>
<thead>
<tr>
<th>Table I. Levels of Evidence.</th>
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<tbody>
<tr>
<td>Ia</td>
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<tr>
<td>Ib</td>
</tr>
<tr>
<td>IIa</td>
</tr>
<tr>
<td>IIb</td>
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<tr>
<td>III</td>
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<tr>
<td>IV</td>
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</table>

C. Detailed imaging technical protocols are not included; they are beyond the scope of this document.

1.4 Minimising radiation exposure

At all times during the investigation and follow up of a patient with myeloma, the potential usefulness of a proposed imaging investigation should be carefully considered. A useful investigation is one in which the result, positive or negative, will alter management. A significant number of radiological investigations do not fulfil these aims, may increase waiting times, waste limited resources and add unnecessarily to patient radiation exposure (Royal College of Radiologists, 2003). The extent and

<table>
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<th>Table II. Grades of Recommendation.</th>
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<tbody>
<tr>
<td>Grade A</td>
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<tr>
<td>Evidence level Ia, Ib</td>
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<tr>
<td>Grade B</td>
</tr>
<tr>
<td>Evidence level IIa, IIb, III</td>
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<tr>
<td>Grade C</td>
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<td>Evidence level IV</td>
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frequency of imaging investigations with inherent risks due to
radiation dose must be justified in terms of likely clinical
benefit; it is important to avoid unnecessary risk due to X-ray
exposure (Berrington de Gonzalez & Darby, 2004). Typical
effective doses for common diagnostic radiology procedures
are shown in Table III. These values, compiled by the UK
National Radiological Protection Board (Hart & Wall, 2002)
are based on the weighted sum of the doses to a number of
body tissues, where the weighting factor for each tissue
depends on its relative sensitivity to radiation-induced cancer
or severe hereditary defects.

**Recommendations**

- Robust systems should be in place for timely reporting
  and secure storage of X-ray films in order to avoid
  repeating investigations that have already been done.

**Table III. Typical effective doses of common diagnostic radiological procedures.**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Typical effective dose (mSv)</th>
<th>Equivalent numbers of chest X-rays</th>
<th>Approximate equivalent period of natural background radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray examinations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limbs &amp; joints (except hips)</td>
<td>&lt;0.01</td>
<td>&lt;0.5</td>
<td>&lt;1.5 d</td>
</tr>
<tr>
<td>PA film</td>
<td>0.02</td>
<td>1</td>
<td>3 d</td>
</tr>
<tr>
<td>Skull</td>
<td>0.06</td>
<td>3</td>
<td>9 d</td>
</tr>
<tr>
<td>Thoracic spine</td>
<td>0.7</td>
<td>35</td>
<td>4 months</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>1.0</td>
<td>50</td>
<td>5 months</td>
</tr>
<tr>
<td>Hip</td>
<td>0.4</td>
<td>20</td>
<td>2 months</td>
</tr>
<tr>
<td>Pelvis</td>
<td>0.7</td>
<td>35</td>
<td>4 months</td>
</tr>
<tr>
<td>Skeletal survey</td>
<td>2.5</td>
<td>125</td>
<td>12 months</td>
</tr>
<tr>
<td>CT head</td>
<td>2.0</td>
<td>100</td>
<td>10 months</td>
</tr>
<tr>
<td>CT chest</td>
<td>8</td>
<td>400</td>
<td>3-6 years</td>
</tr>
<tr>
<td>CT abdomen or pelvis</td>
<td>10</td>
<td>500</td>
<td>4-5 years</td>
</tr>
<tr>
<td>Radiouclide studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone scan (Tc-99m)</td>
<td>4</td>
<td>200</td>
<td>1.8 years</td>
</tr>
<tr>
<td>PET whole body (F-18 FDG)10</td>
<td>500</td>
<td>4.5 years</td>
<td></td>
</tr>
<tr>
<td>PET-CT</td>
<td>20</td>
<td>1000</td>
<td>9 years</td>
</tr>
</tbody>
</table>

- Accurate clinical information should be provided to the Radiology Department when the imaging request is made
to ensure that the right imaging technique is performed
at the right time, specifying whether the request pertains
to a diagnostic work up or investigation of new symptoms
in a patient who is known to have myeloma, including
details of prior therapy.

1.5 The patient’s perspective and the multidisciplinary team

Although the skeletal survey is widely accepted as a standard
and technically straightforward imaging technique in myeloma
patients, the impact that this and other imaging investigations
may have on a patient who has skeletal fractures, deformities
or lytic lesions should not be underestimated. Adequate
provision should be made for analgesia or sedation to be
administered prior to the investigation being carried out.

Following this initial investigation, any further imaging
should ideally be discussed in the setting of a multidisciplinary
team meeting that includes an experienced radiologist and
clinical oncologist. When necessary, the input of a specialist
orthopaedic surgeon may be needed to advise on the need for
surgical stabilisation of bones vulnerable to fracture. Specialist
services may be available locally or in a neighbouring hospital.
There should be clear policies and protocols for access to these
services.

2. Use of imaging at diagnosis

At diagnosis, it is important to establish the extent of disease to
permit accurate staging. This is achieved by staging investiga-
tions, including a bone marrow biopsy to assess degree of
infiltration by plasma cells, quantification of the amount of
monoclonal protein secreted in the serum (paraprotein)
and/or urine (Bence–Jones protein) and imaging the skeleton
for evidence of osteolytic lesions. This section discusses the
recommended use of each imaging modality in turn; a
summary of the recommendations is shown in Fig. 1.

2.1 Skeletal survey

The skeletal survey remains the standard method for radiolo-
gical screening at diagnosis; there is a clear association between
the extent of disease (in terms of the number of lytic lesions at
presentation) and tumour load at diagnosis (Durie & Salmon,
1975). Plain radiography is universally available, allows large
areas of the skeleton to be visualised and may identify long
bones at risk of impending fracture. Almost 80% of patients
with myeloma will have radiological evidence of skeletal
involvement on the skeletal survey, most commonly affecting
the following sites: vertebrae in 66% of patients, ribs in 45%,
skull in 40%, shoulder in 40%, pelvis in 30% and long bones in
25% (Collins, 1998). However, radiologically detectable lesions
distal to the elbows and knees are exceptional (Healy &
Armstrong, 1998). A scoring system based on clinical and radiological findings (Table IV) has been devised to predict the likelihood of fracture in long bones affected by metastatic disease, suggesting that patients with a high score benefit from internal fixation, whereas those with a lower score can receive radiotherapy alone (Mirels, 1989). Patients who are clinically asymptomatic but have radiological evidence of bone disease (at least one lytic lesion) are at high risk of progression with a median time to progression of 8 months (Wisloff et al, 1991; Dimopoulos et al, 1993). Note that, in the new International Classification (International Myeloma Working Group, 2003), patients with bone disease are classified as “symptomatic” and requiring treatment even in the absence of clinical symptoms.

Fig 1. Algorithm of suggested recommendations. CT, computed tomography; MR(I), magnetic resonance (imaging); PET, positron emission tomography; R/T, radiotherapy.
Normal fatty replacement of red marrow begins in the changes with age, particularly during the second decade. and relative proportions of trabecular bone; fat and water and time to perform. The MR appearance depends on the presence of haematological malignancies (Moulopoulos & Dimopoulos, 1997). Depending on the technical specification and set up of numerous MR imaging techniques, such as computed tomography, and certain parts of the skeleton are difficult to assess accurately, such as the sternum and ribs and scapulae. The skeletal survey has been found to provide more accurate staging of bone involvement in myeloma than limited MR imaging (Lecouvet et al, 1999).

**Recommendations**

- As part of the staging procedure of newly diagnosed myeloma, the skeletal survey should include a postero-anterior (PA) view of the chest, antero-posterior (AP) and lateral views of the cervical spine (including an open mouth view), thoracic spine, lumbar spine, humeri and femora, AP and lateral views of the skull and AP view of the pelvis. In addition, any symptomatic areas should be specifically visualised with appropriate views (Grade C recommendation; level IV evidence).

### Table IV. Scoring system for diagnosing impending pathological fractures.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td></td>
<td>Upper limb</td>
<td>Lower limb</td>
<td>Peritrochanteric</td>
</tr>
<tr>
<td>Pain</td>
<td>Mild</td>
<td>Moderate</td>
<td>Functional</td>
<td></td>
</tr>
<tr>
<td>Lesion</td>
<td>Blastic</td>
<td>Mixed</td>
<td>Lytic</td>
<td></td>
</tr>
<tr>
<td>Size</td>
<td>&lt;1/3 diameter</td>
<td>1/3–2/3</td>
<td>&gt;2/3 diameter</td>
<td></td>
</tr>
</tbody>
</table>

A major disadvantage of plain radiography is the relatively low sensitivity, only demonstrating lytic disease when at least 30% of trabecular bone substance has been lost (Snapper & Khan, 1971). In addition, this technique also provides an inadequate assessment of generalised osteopenia (Scane et al, 1994) and has low specificity. Plain radiographs may show non-specific abnormalities that require further characterisation by other techniques, such as computed tomography, and certain parts of the skeleton are difficult to assess accurately, such as the sternum and ribs and scapulae. The skeletal survey has been found to provide more accurate staging of bone involvement in myeloma than limited MR imaging (Lecouvet et al, 1999).

#### 2.2 MR imaging

In the event of suspected cord compression (refer to section 3.1), MR imaging is the technique of choice (Joffe et al, 1988). The potential for its use in other contexts is considerable. Owing to its ability to visualise large volumes of bone marrow without radiation exposure, magnetic resonance (MR) imaging has become a favoured imaging method for evaluating disease within the bone marrow. Numerous MR imaging techniques have been developed to aid the assessment of bone marrow in haematological malignancies (Moulopoulos & Dimopoulos, 1997). Depending on the technical specification and set up of the MR scanner, this technique can take a varying length of time to perform. The MR appearance depends on the presence and relative proportions of trabecular bone; fat and water and changes with age, particularly during the second decade. Normal fatty replacement of red marrow begins in the periphery of the appendicular skeleton and proceeds centrally, reaching adult proportions around the age of 20 years. However, there is continued replacement of red marrow throughout adult life, and this may occur in a diffuse or focal pattern (Ricci et al, 1990).

Typical myeloma lesions have a low signal intensity on T1-weighted images and a high signal intensity on T2-weighted and STIR (short time inversion recovery) images (Libshitz et al, 1992) and generally show enhancement on gadolinium-enhanced images. Four MR imaging patterns of marrow involvement in myeloma have been recognised. A normal marrow appearance is present at diagnosis in 50–75% of untreated Durie–Salmon stage I myeloma and in 20% of untreated Durie–Salmon stage III disease (Moulopoulos et al, 1992; Stabler et al, 1996). Other marrow appearances of untreated disease include the focal pattern, diffuse pattern and variegated appearance. Low tumour burden is usually associated with a normal MR pattern, but a high tumour burden is usually suspected when there is diffuse hypointense change on T1-weighted images, diffuse hyperintensity on T2-weighted images and enhancement with gadolinium injection. Thus the main methodological consideration with MR imaging is the lack of specificity of the findings. Focal or diffuse changes may exist at diagnosis, may be variations of the norm, or reflect an alternative pathological or physiological process such as iron loading (Isoda et al, 2001), amyloid deposition (Baur et al, 1998) or reactive marrow hyperplasia.

The prognostic value of bone marrow MR images has been evaluated in different studies. Patients with a single lytic lesion on plain radiography, who are found to have further lesions on MR imaging have a significantly shorter interval before they demonstrate disease progression and the need for therapy compared to those with a normal MR study (Wisloff et al, 1991; Moulopoulos et al, 1995; Van de Berg et al, 1996; Weber et al, 1997). MR can detect bone marrow infiltration in 29–50% of patients with Durie–Salmon stage I disease and negative plain radiographs (Baur-Melnyk et al, 2005). Patients with advanced disease who have normal MR findings and receive conventional dose chemotherapy respond better to treatment and have a longer survival compared to those with diffuse or focal abnormalities on MR imaging (Lecouvet et al, 1998a). The finding of more than 10 lesions on spinal MR images in patients with advanced stage myeloma was associated with a 6–10-fold higher risk of fracture than patients who had normal appearances or fewer than 10 lesions on MR imaging (Lecouvet et al, 1997). MR imaging does not predict the level of fracture (Lecouvet et al, 1998b).

The pattern of MR bone marrow involvement in myeloma also has prognostic significance, with both focal and diffuse patterns being associated with a higher tumour burden (Moulopoulos et al, 1992, 2005; Carlson et al, 1995; Lecouvet et al, 1998a; Stabler et al, 1996). MR consistently demonstrates more numerous spinal and pelvic marrow lesions than corresponding conventional radiographs in patients with marrow involvement (Ludwig et al, 1987; Fruehwald et al, 1992).
Guideline

1988; Tertti et al, 1995; Lecouvet et al, 1999). Given the significance of detecting occult disease on the rate of progression of the disease, the use of MR imaging in selected patients may contribute to the decision-making process. The other setting in which MR imaging has significance is in the staging of apparently solitary bone plasmacytoma. MR screening of the spine and pelvis reveals lesions that are radiographically occult in up to 80% of patients. Such patients, if treated with local radiotherapy alone, show earlier progression to systemic disease than those with a negative MR imaging survey at diagnosis (Moulopoulos et al, 1993; Soutar et al, 2004).

Approximately 1–2% of patients have non-secretory myeloma, i.e. they do not have a detectable serum or urine monoclonal protein. A proportion of these patients may in fact have detectable free light chains in their serum, which can be serially monitored, but most patients are usually followed up by sequential bone marrow biopsies. The use of MR imaging may be a useful tool for monitoring of non-secretory patients in the future, once appropriate studies that examine serial MR imaging in parallel with bone marrow histology have been performed. As yet, there is insufficient evidence to recommend the use of MR imaging in the follow up of non-secretory patients.

Technological advances in MR imaging is leading to an increase in the potential use of this imaging modality in the staging of myeloma. In fact, MR imaging contributes to the Durie–Salmon Plus staging system, in which the staging suffix B is applied in the event that additional lytic lesions on imaging studies such as plain radiographs or PET scanning and/or mild, moderate or severe diffuse spinal involvement on MR imaging are present (Durie et al, 2003). In this system, the number of lytic lesions is quantified as is the degree of diffuse marrow involvement and their presence can lead to an upstaging of the classical Durie-Salmon staging system and may alter management (Mulligan, 2005). In another study of the redistribution of contrast agent from the interstitial to the intravascular compartment in the bony pelvis and comparing this with bone marrow biopsy of the same region, dynamic contrast-enhanced MR has been shown to correlate with vessel density and paraprotein level (Nosas-Garcia et al, 2005). These imaging correlates, once confirmed by further study, may contribute to the assessment of newly diagnosed myeloma patients in the future.

Recently, whole body STIR MR imaging has gained popularity for the detection of occult malignant disease in the skeleton (Eustace et al, 1997, 1999; Walker & Eustace, 2001; Hargaden et al, 2003; Kavanagh et al, 2003). With ongoing technical advancements, such as the moving table, use of multicoil elements and sophisticated image processing technology, this technique is becoming more feasible and quicker to perform (Schmidt et al, 2005). MR sequences that are employed include STIR, T1-weighting with or without contrast enhancement and T2-weighting. Although the use of more sequences improves the specificity of the images, this increases acquisition time. In addition, false positive findings remain a problem, and current research is ongoing to improve on the sensitivity and specificity of the technique for reliable and reproducible detection of malignant disease. The potential application of this technique to myeloma patients is attractive, with inclusion of sites such as the sternum, skull and ribs, which are usually excluded from standard MR imaging protocols. Studies comparing MR and PET-CT imaging are underway, but MR imaging, if equivalent in sensitivity and specificity, would prove to be advantageous in terms of the lack of radiation exposure. Current disadvantages of whole body STIR MR imaging include lack of widespread availability of specialised scanning facilities, as well as how to manage the detection of unexpected and possibly irrelevant abnormalities. In addition, the clinical experience of this imaging modality as a screening tool in myeloma patients is yet to be established.

Recommendations

- Urgent MR imaging is the diagnostic procedure of choice to assess suspected cord compression in myeloma patients even in the absence of vertebral collapse (Grade B recommendation; level IIB evidence).
- MR imaging of the whole spine should be performed in addition to the skeletal survey as part of staging in all patients with an apparently solitary plasmacytoma of bone irrespective of site of index lesion (Grade B recommendation; level IIB evidence).
- MR imaging should be used to clarify the significance of ambiguous CT findings, as these two imaging techniques can give complementary information (Grade C recommendation; level IV evidence).

Recommendation on use of MR imaging in follow up of non-secretory disease removed.

2.3 Computed tomography

Computed tomography (CT) provides an excellent tool in selected situations. Thus far, owing to the high levels of radiation exposure, CT cannot be used for screening purposes, although low dose CT techniques are being developed as a possible alternative to plain radiography (Horger et al, 2005). Conventional CT has higher sensitivity than plain radiographs for detecting small lytic lesions and can accurately depict the presence and extent of associated extra-osseous extension of the disease. It can provide a high predictive value in the clarification of suspicious areas on plain films or symptomatic areas that do not show abnormalities on plain films and provides important information about vital organ (e.g. cord) compression. In addition, CT can be used to assess areas of the skeleton that are of clinical concern or that cannot be accurately visualised by plain radiography, e.g. scapulae, CT of chest for rib and sternal lesions. CT has the practical advantage of guiding needle biopsy for histological diagnosis (Kyle, 1985) and forms the basis for radiotherapy and surgery.
planning (Walker et al, 2003). CT may also identify bone destruction in cases where MR is negative, and hence may provide complementary imaging information (Lecouvet et al, 2001).

**Recommendations**

- **Urgent CT** may be used to establish the presence of suspected cord compression in cases where MR imaging is unavailable, impossible due to patient intolerance or contraindicated e.g. intraorbital metallic foreign bodies or cardiac pacemakers (Grade B recommendation; level III evidence).
- **CT of the spine** may be considered to clarify the presence or absence of bone destruction in cases of clinical concern where MR is negative (Grade B recommendation; level III evidence).
- **CT should be used to clarify the significance of ambiguous plain radiographic findings**, such as equivocal lytic lesions, especially in parts of the skeleton that are difficult to visualise on plain radiographs, such as ribs, sternum and scapulae (Grade B recommendation; level III evidence).
- **CT may identify lesions that are negative on plain radiography**, and should be considered in patients who remain symptomatic despite having no evidence of osteolysis on the skeletal survey (Grade B recommendation; level III evidence).
- **CT is indicated to delineate the nature and extent of soft tissue disease**, and where appropriate, tissue biopsy may be guided by CT scanning (Grade B recommendation; level IIB evidence).

### 2.4 Bone scintigraphy

Bone scintigraphy is a radionuclide technique, using a technetium 99-phosphorus compound, which is incorporated into bone areas of increased mineralisation. Owing to the excessive bone resorption/lack of osteoblastic activity that characterises the lytic lesions of myeloma, bone scintigraphy has lower sensitivity than conventional radiographs in the detection of osteolytic lesions in myeloma (Bataille et al, 1982; Ludwig et al, 1982; Nilsson-Ehle et al, 1982; Tamir et al, 1983). However, bone scintigraphy may be helpful in evaluating areas of the skeleton that are not well demonstrated on plain radiography, such as the ribs and sternum (Ludwig et al, 1982; Nilsson-Ehle et al, 1982; Otuka et al, 1993). In reality though, the bone scintigraph is typically normal in myeloma, or may show areas of decreased uptake representing bone destruction and replacement of bone by myeloma cells without an osteoblastic reaction, and is therefore of little value in evaluating myeloma lesions.

**Recommendation**

- **Bone scintigraphy has no place in the routine staging of myeloma.**

### 2.5 DEXA scanning

Dual energy X-ray absorptiometry (DEXA) scanning has been declared by the World Health Organisation to be the gold standard procedure for diagnosing osteoporosis (Kanis & Gluer, 2000), for fracture risk assessment in benign osteoporosis (Marshall et al, 1996) and for longitudinal monitoring to assess changes of bone mineral density (BMD) over time. The technique, which involves assessment of BMD in the lumbar spine, hip and distal radius, is a quick, non-invasive investigation that uses a small dose (<1 μSv) of radiation (Lewis et al, 1994). However, the estimated BMD can be influenced by spondylitis and spinal osteophytes (Masud et al, 1993) and the presence of vertebral collapse, giving rise to methodological difficulties in using DEXA scanning in myeloma patients. Newer scanners are more sophisticated and can estimate vertebral BMD from a lateral view with the patient in a supine position, with improved visualisation of the vertebral column. A recent study has demonstrated that reduced lumbar spine BMD at diagnosis is correlated with an increased risk of early vertebral collapses (Abildgaard et al, 2004), but this remains to be confirmed by further studies. With regard to using DEXA to distinguish between benign osteoporosis and myeloma-induced osteoporosis, there are no reliable data available at present. A large deviation in BMD between individual vertebrae may indicate local osteolysis due to myeloma, but there are no published data to confirm this. It is important to remember that osteopenia in myeloma is not necessarily universal, but often restricted to haematopoietically active bone. Though examination of the distal radius would be easy to perform in myeloma patients, with reduced chance of confounding abnormalities, it would not allow examination of “myeloma-induced” BMD changes.

**Recommendation**

- **Routine assessment of bone mineral density cannot be recommended, owing to the methodological difficulties of the technique and the universal use of bisphosphonates in all symptomatic myeloma patients.**

### 2.6 PET and MIBI Scanning

Positron emission tomography (PET) is a tomographic nuclear imaging procedure that uses positrons as radiolabels and positron–electron annihilation reaction gamma rays to locate the radiolabels. A low dose of a radiopharmaceutical labelled with a positron emitter, such as 18F is injected into the patient, who is scanned by a tomographic system; the scan takes 10–40 min to perform. The most widely used labelled radiopharmaceutical is 18Fluorine-fluoro-deoxyglucose (FDG), and numerous studies of this imaging technique applied to patients with plasma cell dyscrasias have been published. These studies have ranged from single case reports to prospective studies of up to 66 patients, in which PET findings were compared to other simultaneously
performed imaging techniques such as plain radiography, MR and CT.

At the present time, it is fair to conclude that clinical experience of PET imaging in patients with plasma cell dyscrasias is in evolution. PET imaging may detect early bone marrow involvement in patients with apparently solitary plasmacytoma (Kato et al, 2000; Schirrmieister et al, 2002), can usefully assess the extent of active disease, detect extramedullary involvement or evaluate treatment response (Jadvar & Conti, 2002; Orchard et al, 2002; Schirrmieister et al, 2003; Bredella et al, 2005). The presence of extramedullary uptake due to involvement by myeloma at diagnosis is a poor prognostic factor (Durie et al, 2002). A study by Schirrmieister et al (2002) demonstrated a 93% sensitivity for focal lesions and a 84–92% sensitivity for diffuse lesions when verified against plain radiography, MR, CT and clinical evaluation. The specificity ranged from 83–100% in patients with diffuse FDG uptake and 60% of patients with known focal osteolytic lesions on plain radiography were upstaged as a result of PET imaging. PET imaging appears to reliably predict active myeloma by virtue of FDG uptake, and supports the diagnosis of monoclonal gammopathy of undetermined significance (MGUS) by virtue of negative scans (Durie et al, 2002).

The main limitation of PET scanning is limited spatial resolution; subcentimetre lytic lesions seen on plain radiographs may not be detectable on PET scanning, resulting in a negative scan (Bredella et al, 2005). The advent of fusion scanning combining both PET and CT addresses the issue of limited spatial resolution. In PET/CT fusion scanning, the patient receives an injection of FDG about 1 h before image acquisition. After the patient is positioned on the scanner bed, an initial topogram is acquired to define the examination range for the PET/CT image acquisition (usually from the ears to the hips). A spiral CT is then performed after which the scanner bed is moved back to the starting position and the PET scan commenced. Reconstruction of the image, incorporating PET and CT data is completed soon after PET image acquisition. The actual scanning time is shorter for PET/CT (approximately 30 min) than a PET scan alone (approximately 1 h) because CT data are used to perform attenuation correction. Although impressive 3-dimensional images are available on completion of the investigation, this occurs at the expense of greater cost and radiation exposure (Kluetz et al, 2000). It is worth bearing in mind that false positive PET scans may arise from inflammatory changes due to active infection (Mahfouz et al, 2005), chemotherapy within the previous 4 weeks or radiotherapy within the previous 2–3 months (Juweid & Cheson, 2006). Studies of PET scanning and fusion PET-CT scanning in myeloma are currently early in development and it is too early to conclude what role this investigation will play in the management of the disease.

99mTechnetium sestamibi (MIBI) imaging is an alternative nuclear imaging procedure that uses Tc-99m-2-methoxy-isobutylisonitrile (Tc-99m sestamibi) as a tumour-seeking tracer to identify areas of active disease in a variety of tumours including plasma cell dyscrasias. There are more published data available on the utility of MIBI than PET imaging in myeloma, but the technique has not been adopted widely into clinical practice. The evidence from various studies of MIBI imaging in myeloma suggests that the uptake of the Tc-99m sestamibi correlates with the extent of disease (el-Shirbiny et al, 1997; Alexandrakis et al, 2001), and this can be correlated with other measurable parameters of disease activity such as lactate dehydrogenase, C-reactive protein and β2microglobulin (Alexandrakis et al, 2001). In addition, this technique has a high sensitivity (90–100%) and specificity (88–93%) for the detection of myeloma bone lesions and good negative predictive value in MGUS (Ballearei et al, 2001; Svaldi et al, 2001; Martin et al, 2005). The pattern (diffuse or focal plus diffuse rather than normal or focal) of Tc-99m sestamibi uptake has added value in relation to known prognostic variables, such as C-reactive protein (Pace et al, 2001), with focal uptake being more predictive of active myeloma than diffuse uptake (Nandurkar et al, 2006).

While MIBI imaging can detect additional lesions compared to the radiological skeletal survey (Alper et al, 2003), it has been shown to underestimate the extent of spinal involvement by myeloma compared to MR imaging of the spine (Mirzaei et al, 2003). In a comparative study of MIBI versus PET imaging in myeloma patients, MIBI imaging detected additional disease sites compared with the skeletal survey, and more sites of disease activity than PET imaging, and correlated better with the degree of bone marrow biopsy infiltration than PET imaging (Mileskin et al, 2004). More recently, in a study of 12 myeloma patients at diagnosis, PET was found to compare favourably with MIBI imaging, detecting 100% of the cases with marrow involvement compared to 80% detected by MIBI, 89.5% of soft tissue lesions (vs. 68.4% for MIBI) and 93.3% of skeletal lesions (vs. 80% for MIBI) (Hung et al, 2005).

Recommendations

• Based on currently available evidence, neither PET nor MIBI imaging can be recommended for routine use in the management of myeloma patients.

• Either technique may be useful in selected cases that warrant clarification of previous imaging findings, but such an approach should ideally be made within the context of a clinical trial (Grade C recommendation; level IV evidence)

• The evidence for the sensitivity of PET scanning is most convincing in the setting of extramedullary disease. It is therefore reasonable to consider PET scanning in this setting, to clarify the extent of extramedullary disease, in cases where other imaging techniques have failed to clarify the situation (Grade B recommendation; level III evidence)

• If the decision to perform PET scanning has been taken, it is advisable to avoid undertaking the procedure within 4 weeks of chemotherapy or 3 months of radiotherapy (Grade B recommendation; level III evidence)

Guideline
2.7 Serum amyloid P component scintigraphy

AL amyloidosis in association with monoclonal gammopathies is the most common and serious type of systemic amyloidosis and is the cause of death in about one in 1500 people in the UK (Bird, 2004). Owing to the poor diagnostic yield from biopsies of uninvolved tissues, the considerable risk of haemorrhage from biopsies of involved tissues or organs and the lack of information regarding extent of disease and response to therapy, alternative methods of confirming the diagnosis of suspected amyloidosis have been sought. Radio-labelled serum amyloid P (SAP) component localises rapidly and specifically to amyloid deposits in proportion to the quantity of amyloid present. This enables the diagnosis and quantification of deposits by whole body scintigraphy (Hawks, 2002). The diagnostic yield is >90% in AL amyloidosis, with reliable demonstration of deposits in the liver, spleen, kidneys, adrenal glands and bones, but insufficient spatial resolution for gut, nerve and skin involvement. Cardiac involvement is difficult to demonstrate due to motion artifact and blood pool content as well as proximity to the spleen, which is frequently involved (Hachulla et al, 1996). SAP scintigraphy permits both the quantification of whole body amyloid load, which correlates with risks of high dose therapy in AL amyloidosis as well as providing information about response to therapy (Gillmore et al, 1999). The major drawback of SAP scintigraphy is that it is only available in a few specialist centres.

Recommendations

- A diagnostic SAP scan should be requested if possible in any patient suspected of having AL amyloidosis as a complication of their plasma cell dyscrasias in addition to obtaining tissue biopsy evidence whenever possible (Grade B recommendation; level IIB evidence).
- Follow up SAP scans should be performed every 6–12 months in accordance with specialist centre policy, to assess response to therapy or to monitor a patient with confirmed amyloidosis on a watchful waiting programme (Grade B recommendation; level IIB evidence).

3. Use of imaging in the management of vertebral collapse

3.1 Acute vertebral collapse

Up to 70% of patients with myeloma experience vertebral collapse during the course of their disease due to osteopaenia and the predilection for vertebral body destruction (Carson et al, 1955), with involvement most frequent in the lower thoracic and lumbar vertebrae, although this figure may become lower with the universal use of bisphosphonates in symptomatic patients. Spinal cord compression secondary to vertebral body collapse occurs in up to 25% patients with vertebral body collapse (Woo et al, 1986). It is common practice to perform a plain X-ray to confirm a suspected vertebral fracture. In the event of suspected cord compression, MR imaging is the technique of choice (Joffe et al, 1988). It provides an accurate assessment of the level and extent of cord or nerve root compression, the size of the tumour mass and the degree to which it has extended into the epidural space. Once compression or impingement of the cord has been identified, it is important to obtain the opinions of both a clinical oncologist and spinal surgeon as to the appropriate management, particularly when extensive bony destruction is present.

3.2 Vertebral collapse unresponsive to conservative measures

Recently, new interventions including percutaneous vertebroplasty (PV) and kyphoplasty have been carried out in myeloma patients with vertebral body collapse. PV has been shown to provide rapid and effective pain relief in acute osteoporotic vertebral fractures, and may improve subsequent rehabilitation of patients (Diamond et al, 2003; Winking et al, 2004). Encouraging results have also been achieved in patients with myeloma (Fournier et al, 2003; Diamond et al, 2004; Yu et al, 2004). In the UK, National Institute for Clinical Excellence (NICE) guidance (NICE, 2003) recommends PV for the treatment of patients with vertebral collapse due to osteoporosis, haemangioma and tumours, such as myeloma, whose pain is not alleviated by more conservative analgesic measures. The following imaging investigations have been carried out prior to PV in various studies:

- Lateral and antero-posterior radiographs of the cervical, thoracic and lumbar spine.
- Cross-sectional MR imaging of affected vertebral body to define the integrity and shape of the posterior vertebral body cortex.
- STIR sequence of affected vertebrae may confirm acute nature of vertebral body fracture by virtue of local bone marrow oedema (Van Gelderen et al, 1997).
- Single photon emission computed tomography (SPECT) of the spine may help to determine how acute a fracture is, and may predict for a good clinical response (Maynard et al, 2000).
- Calculation of percentage loss of vertebral height on MR image (Diamond et al, 2004).

Unfortunately, MR imaging does not enable recognition of vertebrae that are likely to collapse, so cannot be used to predict for the use of preventive therapy at a particular level (Lecouvet et al, 1998b). Although some authors strongly advocate the use of MR evaluation prior to the procedure (Yu et al, 2004), there is no consensus regarding the optimum imaging protocol that should be undertaken prior to PV.
4. Assessment of response to therapy and disease relapse

4.1 Skeletal survey

Although new or enlarging lesions undoubtedly signify disease progression, it is worth noting that lytic bone lesions seldom show evidence of healing on plain radiographs and sequential skeletal surveys have limited value (Wahlin et al, 1992). New vertebral compression fractures on plain radiographs do not always signify disease progression and may occur even after effective therapy, due to resolution of the tumour mass that was supporting the bony cortex (Collins, 2005). Furthermore, a skeletal survey is an exhausting and potentially painful experience for myeloma patients and the justification for further radiation exposure should be assessed. Logistical considerations may intervene when previous radiographs are misplaced, making sequential comparison impossible.

Recommendations

- There is insufficient evidence of benefit to recommend routine follow up skeletal surveys in untreated asymptomatic patients in the absence of signs of disease progression.
- In the event of clinical or laboratory evidence of disease progression in treated or untreated patients, the skeletal survey should be repeated as part of the restaging process. Any newly 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 (Grade C recommendation; level IV evidence).

4.2 MR imaging

Following treatment, there is a wide spectrum of treatment-induced changes seen on MR for each pattern of marrow involvement. In some cases, MR images fail to demonstrate evidence of regression of myeloma infiltration in the marrow (Ishibashi et al, 1998). Focal lesions may shrink or remain unchanged in size; a fatty halo may appear following treatment (Lecouvet et al, 2001). Contrast enhancement may be advantageous in evaluating response to treatment (Rahmouni et al, 1993). A change in MR pattern may correlate with response to therapy, including complete response shown by complete resolution of the preceding marrow abnormality, and partial response demonstrated by conversion of a diffuse to a variegated or focal pattern (Moulopoulos et al, 1994). Other features suggestive of a good response to treatment include a reduction in signal intensity on T2-weighted spin echo images and the absence of contrast-induced rim-enhancement that was previously present (Baur-Melnyk et al, 2005). Unfortunately, focal osteolytic lesions may remain hyperintense in both responders and non-responders to treatment due to treatment-induced marrow repopulation following treatment. Following stem cell transplantation, the marrow typically becomes replaced by fat, due to the effect of the high dose chemotherapy, and thus is seen as high signal on T1-weighted images but focal residual lesions may persist (Agren et al, 1998). Residual marrow MR imaging abnormalities such as these may be associated with a poorer outcome (Antuguaco et al, 2004), but this remains to be confirmed by other studies.

Paragraph on use of MR in follow up of non-secretory disease has been removed. Some patients have persistent pain despite evidence for a good response to therapy on laboratory parameters. Such patients may benefit from further imaging to identify further deterioration in the skeleton, which can be ongoing despite adequate disease reduction. In such situations, careful interpretation is required, including correlation of the images with the nature and timing of the treatment received (Lecouvet et al, 2001).

MR imaging is the most sensitive and specific imaging modality for the diagnosis of avascular necrosis of the femoral head that may result from high dose steroid therapy or radiotherapy, as demonstrated by the presence of the characteristic double-line sign on T2-weighted MR images (Lafforgue et al, 1993). Early recognition of avascular necrosis before the development of a subchondral fracture is important for the success of conservative management.

Recommendations

- There is insufficient evidence to recommend routine MR imaging for the follow up of treated disease.
- In selected cases, where there are persisting unexplained symptoms, it is reasonable to discuss the potential usefulness of follow up MR imaging with the radiologist (Grade C recommendation; level IV evidence)
• MR imaging is the investigation of choice for suspected avascular necrosis of the femoral head (Grade B recommendation; level III evidence)

4.3 Computed Tomography

In the follow up of treated disease, CT is more discriminating than plain radiography when pre- and post-treatment films are compared. The disappearance of extrasosseous or extramedullary masses and the reappearance of a continuous cortical outline and fatty marrow content may be seen in treated lytic disease in selected cases (Lecouvet et al, 2001).

Recommendations
• Routine follow up CT scanning of treated disease cannot be recommended on current evidence and concern regarding radiation exposure.
• In selected cases, however, it is reasonable to use CT scanning in the monitoring of the response of soft tissue masses to therapy (Grade B recommendation; level III evidence).
• In selected cases, where there are persistent unexplained symptoms or there is concern about on-going fracture risk, or a lack of response to therapy, it is reasonable to discuss the potential usefulness of performing a CT scan in treated patients (Grade B recommendation; level III evidence).

4.4 PET and MIBI scanning

The results of serial PET scans in treated patients have been reported in a few patients with myeloma. Evidence of early relapse was identified in 60% of patients including some with non-secretory disease, permitting prompt therapeutic intervention with radiotherapy (Durie et al, 2002). PET scanning has also been shown to be useful in evaluating response to therapy, particularly when other imaging techniques, such as MR and CT, have remained abnormal, but the number of patients evaluated was small (Bredella et al, 2005). In the setting of relapse, PET imaging may identify new sites of disease, and unsuspected sites of extramedullary disease; patients appear to have a particularly poor prognosis if FDG uptake is present following high dose therapy and stem cell transplantation in either the medullary or extramedullary compartment (Durie et al, 2002). In the era of newer therapies, including thalidomide analogues and proteasome inhibitors, the identification of occult residual disease may open up the possibility of multimodal or maintenance therapy, but further diagnostic and therapeutic studies remain to be done.

MIBI scanning has shown some utility in the follow up of treated myeloma, including following the use of high dose therapy, but concordance between response determined by scintigraphic criteria and by conventional criteria (including bone marrow examination and paraprotein measurement) was around 90% (Balleari et al, 2001; Pace et al, 2001; Svaldi et al, 2001). MIBI has also been found to be predictive of disease relapse with a correlation between the pattern of extension and intensity of 99mTc-MIBI uptake and disease activity (Fallahi et al, 2005).

Despite the plethora of reports of the use of MIBI in the assessment of myeloma patients, the main limiting factor remains its limited sensitivity and specificity, the relatively low numbers of patients included and the heterogeneity of clinical situations described. With the increasing use of PET scanning in the management of oncological diseases, the tendency for PET-based studies to be carried out in major myeloma treatment centres and technological advancements, such as fusion PET-CT scanning, it is likely that PET-CT will overtake MIBI as the nuclear medicine tool of choice in myeloma.

Recommendations
• Neither PET nor MIBI scanning can be recommended on the basis of current evidence for use in routine follow up of treated myeloma patients.
• It would be reasonable to consider either technique for the follow up of selected patients, such as those with predominant extramedullary or non-secretory disease, but this would be best performed in the context of a clinical trial (Grade C recommendation; level IV evidence).

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References


Guideline


