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## GUIDELINES

# British Association of Surgical Oncology Guidelines

# THE MANAGEMENT OF METASTATIC BONE DISEASE IN THE UNITED KINGDOM

**The Breast Specialty Group of the British Association of Surgical Oncology***

*British Association of Surgical Oncology, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK*

### Foreword

The Breast Specialty Group of the British Association of Surgical Oncology (BASO) has now been established for 10 years and has become the acknowledged surgical breast specialty group, with some 300 members. This evolution occurred at a time when cancer-site specific specialty working in a multi-disciplinary fashion has been directed by the report on Cancer Services to the Chief Medical Officer.

The BASO Breast Specialty Group has led the way in recommending specialization and multi-disciplinary working in a limited number of soundly established units, with all necessary expertise; in setting standards for service provision; in recommending training programmes; in establishing a high-level educational course and in providing an audit programme. Particularly notable in these respects are the publications, *Guidelines for Surgeons in Breast Cancer Screening* and *Guidelines for Surgeons in Symptomatic Breast Disease*.

The BASO Breast Specialty Group is now turning towards recommendations on certain clinical situations. *The BASO Guidelines for the Management of Metastatic Bone Disease in Breast Cancer in the United Kingdom* is the first of these. The Guidelines have been written by a multi-disciplinary group of specialists, regularly engaged in the management of advanced breast cancer. It is an appropriate moment since new treatments have recently become available.

It is the sad impression of this writer that metastatic bone disease is only too often both misdiagnosed and poorly treated. The Guidelines set high standards that are achievable with clinical interest and simple rearrangements of clinical time. Such achievement will bring about a great alleviation of the terrible effects of bone metastases in many women.

A great debt of gratitude is owed to the effective author of these Guidelines, Hugh Bishop, the Secretary of the BASO Breast Specialty Group.

**Professor R.W. Blamey**

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# The Guidelines for the Management of Metastatic Bone Disease in Breast Cancer in the United Kingdom

## Introduction

These guidelines have been initiated by the BASO Breast Specialty Group and developed by a multi-disciplinary Working Party of specialists from throughout the UK and from all the prime specialties concerned with the management of metastatic bone disease in breast cancer. This Working Party has met regularly since the beginning of 1997 to draft and refine the document to this final version.

As well as inputs from the Working Party members, additional Advisers have also provided advice on specific and general aspects of the guidelines.

To consult and involve the wider professional community concerned with this disease area, we have tried hard to publicize draft copies of these guidelines to all relevant specialties. Presentations of the guidelines at a draft stage were made at the 5th Nottingham International Breast Cancer Conference in September 1997 and at the Winter meeting of The British Breast Group in February 1998. Members of the Working Party presented at Radiology '98 (Royal College of Radiologists) in Birmingham in June 1998 and the guidelines were discussed at the Summer Meeting of the British Association of Surgical Oncology in June 1998. In addition, the document has been circulated within the Association of Cancer Physicians and to a number of clinicians working in palliative care, all of whom have provided much useful comment. In October 1998, members of the Working Party presented this work to a joint meeting of the British and Irish Orthopaedic Associations in Dublin and were pleased with the response obtained.

It is vital that, if these guidelines are to succeed in effecting an improvement in managing patients with this disease, they must reflect a consensus within the UK of what can and should be done. We are therefore very grateful to everyone who has contributed to this work and for all the enthusiastic support and encouragement the Working Party has enjoyed along the way.

## Summary

Bone metastases can present to a number of different specialties and their successful management requires a coordinated approach with good liaison between the specialists. Patients who respond to systemic therapy for their metastases have a good chance of being alive at 3 years, and 20% will be alive at 5 years. This means that it is worth palliating these patients properly. With this in mind, the intention of this document is to try and improve the process of care for women with metastatic bone disease from breast cancer.

These guidelines consider all aspects of care from diagnosis to assessment of response to treatment, and describe the Quality Objectives that should be addressed at each stage. The level of available evidence is indicated throughout the document where possible.

In considering diagnosis, the guidelines emphasize the value of having a dedicated orthopaedic surgeon specifically linked to each Cancer Unit. The attachment of a dedicated orthopaedic surgeon will ensure that mechanical problems are correctly identified, and that actual or imminent fracture is correctly managed. The latter is particularly important as the management of pathological fractures is not the same as that of traumatic fractures. The orthopaedic surgeon should also act as the liaison between his/her own Unit and the tertiary spinal or neurosurgical centres as necessary. In addition, empowering the radiologist means that the diagnostic process can be accelerated and refined. The place of different investigations in diagnosis, including tumour markers, is discussed. The guidelines emphasize the need for a definitive diagnosis before treatment in the (rare) case of a solitary metastasis.

The treatment section discusses orthopaedic management, radiotherapy and systemic treatments (endocrine therapy, chemotherapy and bisphosphonates). The guidelines emphasize the emergency nature of spinal cord compression, describing the need for fast access to assessment and for good liaison between specialists. It is essential that these are available and widely publicized to ensure effective management. The role of radiotherapy in both local pain relief and spinal cord compression is discussed, and various techniques are described.

Endocrine therapy and chemotherapy are discussed in relation to the disease-free interval, performance status, extent and site of metastatic disease, and oestrogen receptor status. Specific chemotherapy regimes are not discussed as these are subject to change and local protocols should be followed. The increasing evidence behind the role of bisphosphonates is reviewed. With many unanswered questions about the long-term use of this group of drugs, the guidelines offer a scoring system for deciding which patients might benefit most from long-term bisphosphonate therapy.

The guidelines describe the possible ways of assessing response to treatment and the difficulties that may be encountered, including a discussion of the role of tumour markers in assessment of response.

A final section looks at palliative care principles in bone pain management, acknowledging the need for continuation of good care throughout the patient's journey, from diagnosis onwards.

We very much hope these guidelines will stimulate individuals and institutions to improve the process of delivering care to this group of patients.

## Background

In the UK about 9000 women with breast cancer develop bone metastases each year. Many of these women are likely to survive for more than 2 years. Up to one-fifth of patients

**Table 1.** Complications of metastatic bone disease

| |
|---|
| Pain |
| Hypercalcaemia |
| Impending fracture |
| Pathological fracture |
| Spinal instability |
| Neurological complications |
| Marrow suppression |

with metastatic bone disease will be alive at 5 years, requiring repeated palliative treatments. The incidence of bone metastases is significantly higher with steroid receptor positive tumours and those that are well differentiated.[1,2]

Bone metastases are associated with a high level of morbidity and reduced quality of life, related to a range of complications as indicated in Table 1. These patients need well co-ordinated, specialized, multi-disciplinary care by clinicians with a special interest in metastatic bone disease.

A recent orthopaedic review of women with breast cancer and bone metastases showed that when clinical review by an orthopaedic surgeon would have been appropriate it was only requested on less than 50% of occasions.[3]

Recent improvements in the understanding of the mechanisms of bone metastases have been associated with the development of better therapeutic options. The management of metastatic bone disease requires a tailored, if not bespoke, approach. In metastatic bone disease, surgical techniques differ from those used in routine orthopaedic practice.

These guidelines have been drafted by a multi-disciplinary group of specialists who have a particular interest in metastatic bone disease in breast cancer. In the light of current knowledge, these guidelines aim to promote optimal management of women with breast cancer and bone metastases.

The report *A Policy Framework for Commissioning Cancer Services* by the Expert Advisory Group on Cancer to the Chief Medical Officers of England and Wales demands the reorganization of cancer care into Cancer Centres and Cancer Units. Breast Cancer Units are expected to cope with cancer care at all stages from early detection to the care of advanced disease at Unit level (with the exception of actual treatment with radiotherapy which would be given in the Cancer Centres). The guidelines issued by the Clinical Outcomes Group, *Improving Outcomes in Breast Cancer*, state that there must be multi-disciplinary care provided by experts specializing in the treatment of breast cancer.[4] Every Unit needs to build multi-disciplinary teams for the diagnosis and care of metastatic spread and this to a large extent in breast cancer means the diagnosis and management of bone metastases.

### *Evidence base*

Current practice is to assess the scientific quality of guidelines. There is a paucity of good randomized controlled trials in metastatic bone disease, particularly of those relating to orthopaedic operations. An attempt has been made to grade the level of evidence for each of the major areas discussed in these guidelines, according to recommendations from the United States Agency for Health Care Policy and Research (see Appendix 1).[5] Our relative inability to quote good scientific evidence only serves to emphasize the need for good quality research in this area.

**Table 2.** The role of the designated radiologist and orthopaedic surgeon

| Quality objectives | Outcome measures |
|---|---|
| Accurate assessment and appropriate management of women with bone metastases | In a Breast Cancer Unit, the breast-care team should have the regular participation of an identified orthopaedic surgeon and radiologist with an interest in metastatic breast cancer |
| | The orthopaedic surgeon to be responsible for liaison with tertiary specialist colleagues as necessary |
| Ease of access to appropriate assessment | The breast care team to provide clear details of rapid access to all members, to GPs, to patients and to local staff in related disciplines |

## The breast-care team

The diagnostic process and management of women with breast cancer and metastatic bone disease should be undertaken by a multi-disciplinary breast-care team in a Breast Cancer Unit. To ensure good management, the breast-care team as it currently exists for the initial management of patients with breast cancer will need to expand to include regular participation of additional personnel, with clear routes of access to tertiary specialists. The additional personnel should include an orthopaedic surgeon and a radiologist with an interest in metastatic breast cancer (see Table 2). Details of how to access the multi-disciplinary assessment should be widely known to all members of the team including breast-care nurses, general practitioners (GPs), consultant colleagues and appropriate junior staff.

The orthopaedic surgeon on the team should have an interest in metastatic disease, and ideally should have sessional time to attend a multi-disciplinary meeting where these patients are discussed. The orthopaedic surgeon should be responsible for liaison with tertiary specialist colleagues, and ensure that a rota and contact numbers are always available to colleagues on the breast-care team.

Orthopaedic surgeons, by the nature of their day-to-day practice and training, have skills in diagnosing mechanical problems and can make an invaluable contribution to the multi-disciplinary assessment of patients in whom the distinction between mechanical and non-mechanical pain is difficult. The participation of orthopaedic surgeons in breast-cancer teams will not only provide a definitive assessment for the individual patient, but may also improve awareness of disordered mechanical process in non-orthopaedic team members.

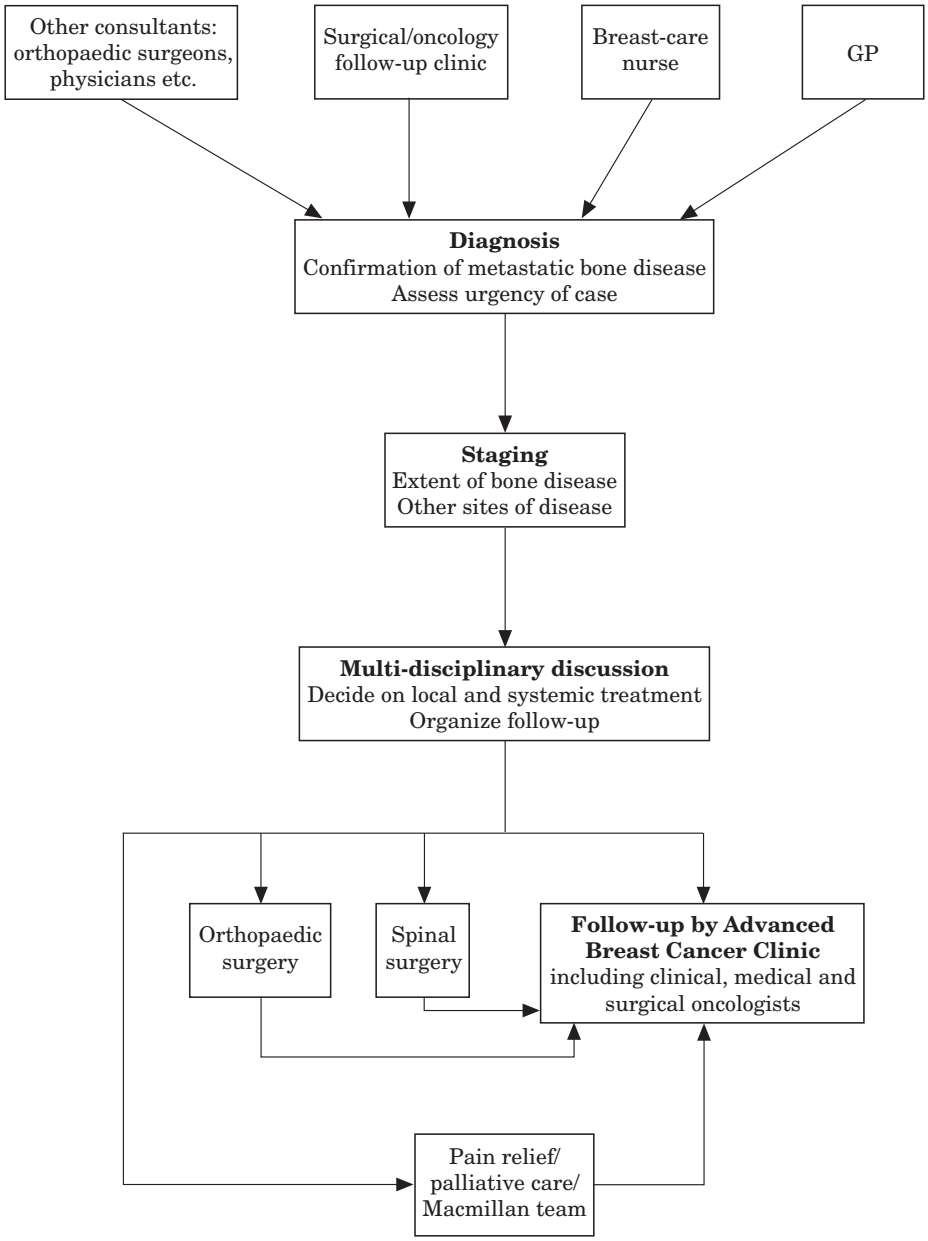



**Fig. 1.** Clinical pathway for patients with suggested/proven bone metastases.

The team approach should be considered the gold standard. The multi-disciplinary meeting should record the subsequent management pathway, which will vary from patient to patient. In the management of these patients with advanced disease, the lead role will change from time to time but should always be defined. The ideal pathway of care for the patient with metastatic bone disease is illustrated in the flow diagram (Fig. 1).

## Diagnosis

Most women with bone metastases will present with pain, and the diagnosis of bone metastases must be considered in all women with a history of breast cancer who present with musculo-skeletal pain. The degree of investigation required will depend on the level of clinical suspicion. A suggested diagnostic action plan is shown in Fig. 2.

Early detection of metastatic disease in asymptomatic women by imaging and biochemistry does not improve survival.[6,7] There is no role for routine skeletal survey or bone scan screening of asymptomatic women with a history of breast cancer.[6–8] Tumour markers may be of use for diagnostic purposes as long as the correct cut-offs are used to interpret the results. This is particularly so in confirming the diagnosis of metastatic disease in the presence of suspicious or equivocal imaging investigations.[9] (There are now two small pilot studies which report that early detection of occult metastases by blood tumour marker measurements and early therapeutic intervention resulted in prolongation of metastasis-free survival.[10,11])

| Clinical suspicion | Action |
|---|---|
| **Minimal**<br>Pain has known cause, resolving well at 2–3 weeks from onset | Normal clinic review or asked to return to GP if resolution not complete |
| **Low**<br>Probable cause of pain known, showing good resolution over 4–6 weeks | Plain radiograph<br>Negative → No further action. Patient told to contact clinic or GP if pain returns, or if pain fails to resolve completely<br>Positive → Proceed as Fig. 3 |
| **Moderate**<br>Pain has no clear cause, persisting but not progressive | Organise plain radiographs, serum calcium, skeletal scintigraphy and tumour markers* To be completed within 10 working days<br>Clinical review 1 week later<br>If all negative → Reassure. Review in 2 months if symptoms persist<br>If one or more positive → Proceed as Fig. 3 |
| **High**<br>Pain has no identifiable cause, night pain, severe and/or progressive<br>Patients with any neurological symptoms or signs | Organize plain radiographs, serum calcium, skeletal scintigraphy and tumour markers* To be completed within 10 working days<br>If all negative and clinical suspicion remains high<br>Appendicular → Clinic review 1 week later<br>Spine → MRI scan within 2 weeks → Clinic review 1 week later<br>If one or more positive → Proceed as Fig. 3 |

**Fig. 2.** A suggested diagnostic action plan. *Tumour markers (CA 15-3, CEA) are only helpful if raised.

*Computerized tomography (CT) and magnetic resonance imaging (MRI) scanning in diagnosis*

It is unusual to find positive findings on the CT scan if skeletal scintigraphy is negative. In the light of this, CT scanning is not considered to have a role in diagnosis. If plain radiographs and skeletal scintigraphy are negative but there continues to be a high level of suspicion, then the investigation of choice is an MRI scan. If MRI is contraindicated, or unavailable for geographical reasons, then skeletal scintigraphy should be repeated in 2–3 months.

**Table 3.** Rationale for referral in women with bone pain

| Quality objectives | Outcome measures | Action |
|---|---|---|
| The prompt referral of women at moderate or high clinical suspicion of bone metastases from primary care back to the Breast Cancer Unit prior to any investigation | The Breast Cancer Unit to ensure that GPs know how to refer for rapid assessment, and for urgent assessment if hypercalcaemia or spinal cord compression are suspected | The Unit to provide educational opportunities to raise GPs awareness of how to differentiate between women with minimal–low clinical suspicion of bone metastases and those with moderate–high clinical suspicion, and of the symptoms of hypercalcaemia and spinal cord compression |
| Women who are referred back to the Breast Cancer Clinic to be seen and investigated promptly | 90% to be seen within 10 working days of receipt of referral, and 90% to have had all their investigations completed within 10 working days | |

*Bone biopsy*

Where there are radiographic abnormalities of uncertain significance bone biopsy should be considered, particularly when other metastatic screening tests are negative or equivocal.

*The role of the GP or non-specialist in diagnosis*

Initial presentation is often to GPs, and occasionally to non-specialists. It is recommended that GPs should only undertake initial management where clinical suspicion is considered minimal or low (see Fig. 2). For these groups of women it is recommended that they should undertake investigation and management according to the action plan suggested in Fig. 2. It is strongly recommended that in all cases in which clinical suspicion is moderate or high, GPs should refer the patient back to the Breast Cancer Unit prior to undertaking any further investigations, including plain radiographs, as these patients require different investigations and management. To this end, it is the responsibility of the Breast Cancer Unit to make available details of access to the breast cancer clinic, and the Unit should also aim to educate GPs in the management of women with skeletal pain and a history of breast cancer (see Table 3).

Good communication is important; all changes in diagnosis and management should be communicated promptly to the GP. A suggested route for communicating details of access and some management details is through a patient-held cooperation card given to the patient at the time of primary diagnosis.

If GPs initiate plain radiographs, they should ensure that the request form details the history of breast cancer. On receipt of such a request, the radiology department should ensure that the radiograph is performed within a week and is reported promptly. Reports should not suggest further imaging. The radiologist should be empowered to initiate other appropriate imaging investigations. The radiologist should be encouraged to refer the patient back to the Breast Cancer Clinic for assessment if either:

- the radiograph shows convincing evidence of metastatic disease; or
- the radiograph shows no convincing evidence of metastatic disease, but clinical concern persists.

Any referral should include details of when and where the radiographs were taken, and copies of the radiologist's report and of the results of any other investigations should be included, to avoid duplication. The radiologist must draw the films and the request form to the breast-care team's attention.

## Diagnosis of a possible solitary bone metastasis

**All cases of an *apparently* solitary bone metastasis must be discussed at the multi-disciplinary meeting prior to treatment**

Results of radiographs and skeletal scintigraphy may show an apparently solitary lytic bone lesion in the absence of other metastatic disease outside the skeleton. In this case, it is very important to ensure that this is indeed a metastasis from breast cancer. Observation may be used as a management tool in some situations. However, prior to commencement of treatment, all such cases should have unequivocal confirmatory evidence of the diagnosis.

- Significantly raised tumour markers. Over 30% of patients with one or two lesions will have elevation of the CA15-3.[12] In such patients an elevated CA15-3 may be regarded as confirmatory of metastatic disease. Unfortunately, this leaves over 60% of such patients who are CA 15-3 'negative'.

Examination and investigation to exclude other likely primaries must be included in the patient's work-up. It is appropriate for the patient to receive other staging investigations (e.g. chest radiograph (CXR), ultrasound scan (USS) of liver and kidneys; see section on Staging, page 9) prior to the bone biopsy to look for evidence of non-bone metastases and thus see if the 'solitary' lesion is truly solitary.

- MRI (CT where not available). Where the management team are still uncertain about the diagnosis of a solitary lesion after initial staging investigations, MRI (or CT) should be performed.
- Bone biopsy. A Breast Cancer Unit must be in a position to provide a rapid bone biopsy when necessary (see Table

**Table 4.** Standards for imaging and bone biopsy in metastatic bone disease

| Quality objectives | Outcome measures |
|---|---|
| Patients with a solitary vertebral lesion require a prompt MRI scan | Over 90% of patients with a solitary vertebral lesion requiring MRI scan to receive one within 2 weeks |
| Patients with an unconfirmed solitary metastasis must have histological proof of diagnosis before treatment | 90% of those patients who need bone biopsy must have it carried out within 2 weeks of the decision to biopsy |
| Patients with a possible solitary metastasis should receive a prompt and full work-up | Patients with a possible solitary metastasis to receive a full work-up within 4 weeks of initial presentation |

4). It is the surgeon's responsibility to ensure that the pathologist receives adequate information about the bone biopsy. The reporting pathologist should be experienced in bone pathology, including that of primary tumours, and should have rapid access to a second opinion.

*The solitary vertebral lesion without neurology*

This is a difficult situation because of the need to differentiate between osteoporosis and metastasis-related collapse, and because of a small incidence of other pathology (e.g. Paget's, myeloma). If plain radiographs and skeletal scintigraphy support a solitary lesion, MRI of the spine should be performed as it will often provide evidence that the lesion is metastatic. This could either be because it identifies that the lesion is in fact not solitary (i.e. reveals other lesions), or that the lesion is eroding bone or it has the characteristic appearance of a metastasis on imaging.

However, if MRI confirms a solitary lesion, it cannot always provide the distinction between osteoporosis and a metastasis. Women with a history of breast cancer and a confirmed single vertebral collapse should be assessed by the multi-disciplinary team and management should not be changed without confirmation from histology or possibly tumour markers. It should be remembered that:

(1) measurements of bone density are not helpful in this situation as they are not diagnostic for osteoporosis as a cause of single vertebral collapse;
(2) if a metastasis is excluded, then referral should be made to a specialist with an interest in bone metabolism for further investigation and treatment.

*The pathological fracture*

For some patients, the first presentation of bony metastases will be with a pathological fracture of the appendicular skeleton (in response to a low energy injury); the most common site of symptomatic fracture is the proximal femur. The management of such fractures is different to standard fracture management, so making the correct diagnosis is important. All patients presenting with a long-bone fracture who have a past history of breast cancer should initially be managed conservatively (rest and splintage) by the trauma team. Urgent discussion with the identified specialist orthopaedic surgeon (see also pages 10–12) should take place within 48 h or less, together with referral to the local breast-care team (see Table 5). If the pathological lesion is confirmed as a solitary metastasis, the guidelines given should be followed.

Orthopaedic management of metastases is covered in more detail below (see also pages 10–12).

## Staging

All patients with confirmed solitary or multiple metastases should receive a full clinical assessment and full set of staging investigations before treatment is planned. Haematology and biochemistry should include full blood count (FBC), creatinine and electrolytes, liver function tests, alkaline phosphatase and serum calcium. Tumour markers (CEA, CA15-3, erythrocyte sedimentation rate (ESR)) may be measured as levels can be valuable in the monitoring of therapy (see also page 18 and Appendix 2).

Radiological investigations should include plain films of abnormal sites (on scintigraphy), radiographs of chest and pelvis, and an ultrasound scan of the liver. Where hot spots on the bone scan are widespread, it is suggested that radiographs are taken of up to five key metastases, decided on at the multi-disciplinary meeting, and these are then used for ongoing assessment. Radiographs should be taken of any lesion in weight-bearing bones, to aid assessment of the risk of pathological fracture. As an increasing amount of bone cortex is lost the risk of fracture rises steeply and, once 50% of the bone cortex is lost in any radiological projection, fracture should be regarded as inevitable[13,14] (see also above). In cases where the degree of cortical destruction is difficult to assess, CT may be of value.

**Orthopaedic referral is always indicated when plain radiographs show genuine erosion of a weight-bearing bone**

In spinal metastatic disease, those who are most likely to benefit from surgery, and thus in most need of a specialist orthopaedic opinion, are those who have one or more of:

- pain exacerbated by movement and relieved on rest (spinal instability);
- 50% of vertebral body destruction;
- moderate deformity and collapse.[15]

(Spinal cord compression is an emergency and is dealt with separately; see pages 13–14).

Review of the radiology should always include a review of previous imaging.

CXR and USS of liver are recommended as the presence of significant soft-tissue metastases may affect management decisions. If liver function tests are abnormal but USS normal, a CT of the liver may also be appropriate.

The precise pathway of radiological investigations should be agreed with the radiologist liaising with the breast-care team. All referrals to the radiology department for staging should be clearly marked, and the arrangement supervised by a radiologist with a special interest in the relevant

**Table 5.** Care standards for patients with a pathological fracture

| Quality objectives | Outcome measures | Action |
|---|---|---|
| To ensure that all patients with a history of breast cancer presenting with a pathological fracture of the appendicular skeleton are initially managed conservatively but receive prompt specialist orthopaedic assessment | Arrangements for urgent discussion with the identified orthopaedic specialist associated with the breast-care team to be made clear to all local trauma teams | The Breast Cancer Unit to provide education for junior trauma staff on the importance of initial conservative management, but urgent referral, of women with a pathological fracture and a history of breast cancer. |
| | In 90% of cases this discussion to take place within the next working day | |

**Table 6.** Expected standards for diagnostic imaging

| Quality objectives | Outcome measures |
|---|---|
| Appropriate staging investigations for every patient with bone metastases | Breast-care team to agree protocol for staging investigations, with the designated radiologist. All referrals to the radiology department for staging to be clearly marked, and the planning of these investigations to be supervised by the designated radiologist |
| To minimize the number of hospital visits required for staging | All radiographs and liver USS to be done at one visit if possible, within a maximum two visits |
| To minimize delay between the diagnosis of bone metastases and the decision, made with the results of staging investigations, on management | Staging investigations to be completed within 10 working days of request and follow-up clinic appointment within 1 week of completion |
| All patients with lesions at high risk of fracture receive prompt specialist orthopaedic assessment prior to initiation of treatment | Over 90% of patients with lesions in the weight-bearing long bones in which there is clear cortical destruction to be referred for specialist orthopaedic opinion which is to be obtained within 1 week, with a view to prophylactic fixation prior to radiotherapy |
| | Patients with pain and destruction of >50% of the vertebral body should receive an immediate neurological examination and in the absence of neurological signs should be seen by the orthopaedic member of the team within 48 h for a surgical opinion prior to consideration of radiotherapy |

pathology and area examined. The number of visits required should be minimized (see Table 6).

## Treatment of bone metastases

Treatment of the bone metastases should always be considered as part of overall management of the patient.

In this document we have chosen to consider local treatment first, then systemic therapy. We shall thus first discuss orthopaedic management and radiotherapy, and then proceed to discuss endocrine and cytotoxic systemic treatments, and bisphosphonates.

### *Orthopaedic management*

The role of the orthopaedic surgeon in the management of bone metastases falls into three principal categories:

- prophylactic fixation of metastatic deposits where there is a risk of fracture;
- stabilization or reconstruction following pathological fracture; and
- decompression of spinal cord and nerve roots, followed by stabilization of the affected vertebra.

Optimum treatment must, wherever possible, be aimed at identifying patients who are, or may be, at risk of fracture and identifying prophylactic treatment. This should be performed as part of the multi-disciplinary team approach.

The axial skeleton is the commonest site for bony metastases although the great majority of those in which surgical intervention is carried out involve the femur, humerus or acetabulum. There is a trend in modern surgical practice, however, towards increasing intervention for spinal metastases.

### *Appendicular skeleton*

*Mechanisms of fracture and risk assessment* As a general rule, wherever 50% of the cortex has been destroyed, pathological fracture should be regarded as inevitable[13,14] and prophylactic fixation should be performed prior to the administration of radiotherapy. In addition to this general rule, avulsion of the lesser tuberosity is an indication of imminent hip fracture.

Where there is less than 50% cortical erosion, radiotherapy may be considered without prophylactic fixation, the exception being the femoral neck where any degree of cortical erosion should be considered as an indication for prophylactic fixation. Non-weight-bearing bones such as the ribs, fibula and much of the pelvis can safely be treated with radiotherapy alone in almost all cases.

In an effort to provide a more reliable and reproducible measure of the risk of pathological fracture, Mirels devised a scoring system which is now widely used in the USA and is regarded as a useful aid to management.[16] The system

**Table 7.** Mirels' scoring system

| Variable | Score 1 | Score 2 | Score 3 |
|---|---|---|---|
| Site | Upper limb | Lower limb | Peritrochanter |
| Pain | Mild | Moderate | Functional |
| Lesion | Blastic | Mixed | Lytic |
| Size | <1/3* | 1/3–2/3* | >2/3* |

*Refers to the proportion (on radiograph) of a single cortical layer destroyed.

gives each of four features of the metastasis a score out of three (see Table 7).

Mirels assessed 78 cases. He found that for scores of 7 or less the risk of fracture was less than 5%, and for these cases conservative management is appropriate and radiotherapy can be given without prior fixation. For scores of 9 or above the risk of fracture was high, and in such cases prophylactic fixation should be carried out. Lesions scoring 8 were intermediate, having a 15% risk of fracture, and these should be assessed and a decision taken on clinical grounds. The system can be readily applied by non-orthopaedic specialists and so is a useful guide as to whether a referral is indicated.

*Axial skeleton*

*Mechanisms of fracture and risk assessment* In the axial skeleton, destruction of more than 50% of a vertebral body, with associated pain, represents an impending fracture.[15] Historically, women with limited disease were more likely to be offered surgery. Surgical instrumentation and techniques are evolving at a rapid rate. Women with involvement at multiple levels should not be denied the possibility of surgical palliation without being assessed by a surgeon with current understanding of modern spinal oncological practice.

**Evidence level: Grade C Level IV**

Certain sites are at particular risk of fracture in the presence of bone metastases and disease progression. For example, there is a 28% risk of a pathological fracture occurring through a given cervical spine metastasis in any 4-week period in which there is no response to either systemic or local treatment.[3]

*General orthopaedic principles*

Three assumptions underlie the management of metastasis-related fractures:

- the procedure should provide immediate stability;
- the surgeon must assume that the fracture will not unite; and
- the fixation should aim to last the lifetime of the patient.

*Surgical techniques* Load-bearing devices are always preferred, and, in the diaphysis of long bones, intramedullary nailing is advised. Defects in the bone should be filled with methylmethacrylate bone cement, inserted via a cement gun or syringe where appropriate. Filling of defects will prevent telescoping, and the use of locking screws also aids stability. Load-sharing devices such as plate and screws are rarely indicated in lower limbs as failure due to fracture of the plate or screws, or pulling out of screws, is almost inevitable within a short period of time. In the upper limbs, particularly the forearm, where stresses are less, plate and screws with cement augmentation can be utilized.

Fractures about the hip are the most frequent to present to the orthopaedic surgeon, and management differs significantly from that of purely traumatic fractures. The dynamic hip screw is not recommended as failure is almost inevitable due to cutting out of the screws or implant fracture. Where a case of suspected pathological fracture is admitted to a trauma unit, a full assessment should be made, speed of surgery being less important than planning and use of the appropriate implant. Where destruction is limited to the femoral neck or head, a cemented total joint replacement or cemented hemi-arthroplasty is recommended as a primary procedure. Radiographs of the entire femur must be obtained pre-operatively to exclude more distant disease. Long stem implants are frequently employed to reduce the risk of sub-prosthetic fracture. Acetabular lesions are filled with bone cement with threaded pins driven into the remaining good bone—a type of 'reinforced concrete'. This technique is referred to as the Harrington procedure.[17] Where there is more extensive destruction of the proximal femur (or the proximal humerus), endoprosthetic reconstruction is the technique of choice. Referral to a recognized centre for orthopaedic oncology should be urgently considered for these complex techniques to be carried out.

The management of spinal cord compression is discussed separately later (pages 13–14). Surgery for metastasis-related problems of the axial skeleton, including SCC, should only be undertaken in specialist centres (see Table 8).

Where life expectancy is assumed to be less than 6 weeks, the multi-disciplinary team should give careful consideration before embarking on any major surgical procedure. Against that, it must be borne in mind that a patient immobilized by bone metastases will have an extremely poor quality of life, and will not improve or regain mobility without surgery.

An algorithm for the orthopaedic assessment of symptomatic bone metastases is shown in Fig. 3.

*Cost benefit: appendicular skeleton* We believe that appropriate surgical management of bony metastases is highly cost-effective, although controlled prospective trials to demonstrate this are difficult to construct.

The cost of surgery and even specialized implants is recovered within days if a previously immobile patient can mobilize, or if a previously dependent patient becomes self-caring.

Furthermore, inadequate orthopaedic treatment frequently leads to a requirement for costly revision surgery, causing suffering and potential complications in addition to the financial cost.

*Orthopaedic service delivery* The mechanism for delivery of an effective service for the orthopaedic management of bony metastases need not be complex or costly. We believe that

**Table 8.** Institutional requirements for the provision of spinal oncology services

| |
|---|
| Imaging |
| Radiography |
| MRI (24 h) |
| CT |
| Staging facilities |
| Ultrasound scans |
| Isotope scans |
| Interventional radiology |
| Embolization |
| Biopsy |
| Multi-disciplinary planning |
| Surgery |
| Radiology |
| Oncology |
| Pathology |
| Nursing |
| Spinal-trained |
| Spinal beds |
| Anaesthetic |
| Consultant |
| Biluminal intubation |
| HDU/ITU |
| Operative |
| Surgical expertise |
| Instrumentation |
| Radiolucent tables |
| Biplanar imaging |
| Rehabilitation |
| Physiotherapy |
| Hydrotherapy |
| Occupational therapy |
| Adjuvent therapy |
| Community care/hospice |
| Oncology nurse specialist |
| Social services |

one surgeon within the trauma team should be identified as the 'lead clinician' with responsibility for metastatic bone disease.

Patients admitted with actual or imminent pathological fractures should be reviewed by that clinician during the next working day and a management plan formulated. Complex cases or those requiring endoprosthetic or custom surgery are likely to be discussed with the regional orthopaedic oncology centre, in a manner similar to the recognized procedure for complex pelvic fractures.

The lead clinician should take part in a regular clinical conference with the oncologist to review cases where prophylactic intervention may be indicated. Parallel clinics might be useful, although they may not be a practical proposition in many hospitals.

We consider it essential that purchasers should require evidence that an appropriate strategy for the management of these patients is in place when placing contracts for metastatic cancer services.

### *Radiotherapy*

Radiotherapy is effective for relieving local pain from bony metastases with responses occurring in 70–80% of patients. Radiotherapy will not, however, help mechanical pain (management of this is discussed in other sections). If pain is occurring at several sites, then the emphasis of treatment will shift to effective systemic therapy, such as endocrine therapy, chemotherapy or intravenous bisphosphonates. Nevertheless, it may be appropriate to give local radiotherapy to the most painful sites.

**Evidence level: Grade C Level IV**

Hemibody radiotherapy can be effective but may compromise subsequent chemotherapy and is therefore usually used when systemic therapy options have been exhausted.

As discussed in the section on orthopaedic management, the likelihood of imminent fracture should always be assessed prior to radiotherapy. If there is a risk of fracture, management should be discussed at the multi-disciplinary meeting which includes an orthopaedic opinion (see Table 9).

The dose prescription should be according to ICRU 50.[18]

*Local radiotherapy* Radiotherapy to a single site of moderate to severe pain due to metastatic bone disease is frequently given as a single fraction of 8–10 Gy using megavoltage radiotherapy. A single direct field or parallel opposed fields can be used. However, if the fields are large or there is bowel within the radiation portals, fractionation may be increased to 20 Gy in five fractions. It may be appropriate to use orthovoltage radiotherapy (300 kV), especially for rib metastases.

**Evidence level: Grade A Level 1B**

*Widefield radiotherapy* This is occasionally appropriate. Treatment is on megavoltage radiotherapy using parallel opposed fields and it would be reasonable to use a dose of 8 Gy single fraction or up to 20 Gy in five fractions. Anti-emetics of the $5HT_3$ class should usually be given with single fraction widefield treatment.

*Radioisotope treatment* Radioisotope therapy is an alternative to external beam radiotherapy. Isotopes such as samarium[19] and strontium have been shown to be clinically useful in metastatic breast cancer (at the time of writing, strontium is not licensed for metastatic breast cancer in the UK, but has a licence in the USA and Sweden).

*Solitary metastases* As previously discussed, patients who have an apparently solitary metastasis must have confirmation of the diagnosis of metastasis (e.g. histology, tumour markers, MRI; see pages 8–9). In this situation, especially if there has been a long disease-free interval, some clinicians may wish to give high dose palliation (e.g. 40–50 Gy in 15–20 fractions); otherwise, fractionation will be as before under local radiotherapy.

*Post-stabilization* Radiotherapy is normally given following surgical stabilization as soon as the wound is healed. Radiotherapy should be fractionated giving 20 Gy in five fractions with megavoltage radiotherapy.[20]

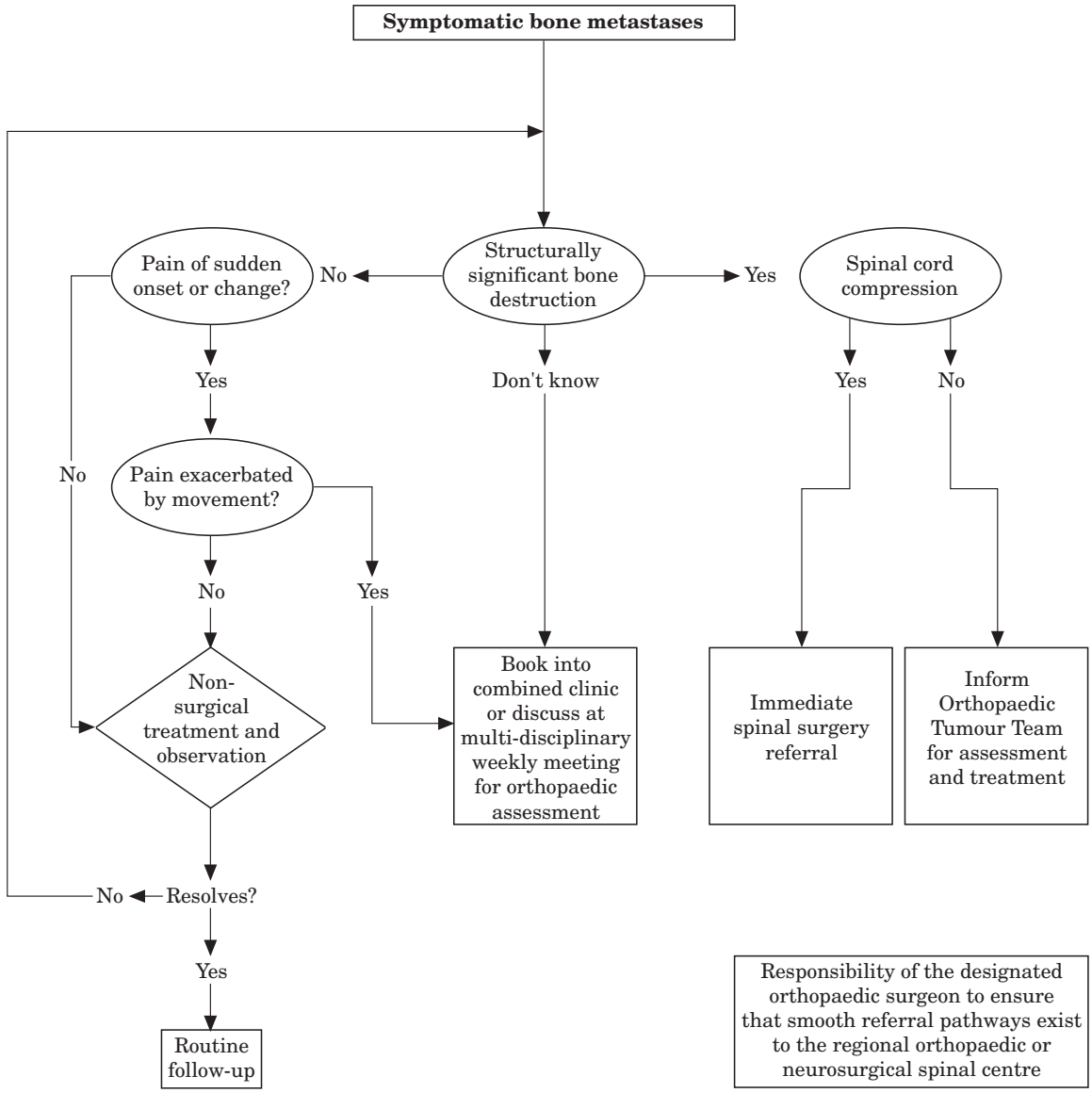



**Fig. 3.** An algorithm for the orthopaedic assessment of symptomatic bone metastases.

**Table 9.** Avoid the occurrence of a pathological fracture

| Quality objectives | Action |
|---|---|
| To avoid fractures occurring during or immediately after radiotherapy | If there is a risk of fracture, inter-disciplinary assessment including orthopaedic opinion to be undertaken within 48 h, and certainly prior to radiotherapy |

Patients may get immediate pain relief following the first fraction of radiotherapy, but it is more usual for there to be an improvement in pain 2 weeks after radiotherapy and improvement may take up to 6 weeks. Patients should be assessed 4 weeks after completion of radiotherapy and, if there has been no improvement in pain control, a surgical referral should be considered in case the symptoms are due to mechanical pain and the possibility of referred pain reviewed.

Management of spinal cord compression is considered below.

### *Management of spinal cord compression (SCC)*

Spinal cord compression is an oncological emergency. It is important that a route for rapid intervention for patients with SCC is clearly established and well publicised (see Table 10). The most important aspect is early recognition. There is great potential for professional education to ensure that all those likely to encounter the problem can recognize the prodromal symptoms and signs (see Table 11).

Treatment options are surgery or radiotherapy. On diagnosis of SCC, patients should be given high-dose steroids, and proceed to surgery or radiotherapy within 12 h. Steroid treatment must be accompanied by anti-ulcer medication. Steroids are usually recommended for a short period, to be re-assessed and stopped or tailed off as

**Table 10.** Standards for the management of spinal cord compression

| Quality objectives | Outcome measures | Action |
|---|---|---|
| Immediate diagnosis, assessment and treatment of patients with SCC | MRI should be performed immediately if available on site, followed by assessment by the spinal surgeon within 2–4 h. If MRI is not on site, the immediate first step should be the surgical assessment. In the case of rapid onset SCC, the aim should be to commence surgery, if indicated, within a total time of 12 h.<br>If radiotherapy is to be given as sole treatment, the aim should be to give this within 12 h. | The Breast Cancer Unit to establish an agreed protocol/route of intervention for the management of patients with SCC. This should be well-publicised to all those likely to be involved. |
| To ensure SCC is not missed | All cases of SCC to be audited | Breast-care team to provide educational opportunities to explore the at-risk group and the symptoms/signs to SCC, for hospital colleagues and GPs |

**Table 11.** Symptoms of spinal cord compression

| Prodromal symptoms and signs of SCC (may precede compression by several weeks) |
|---|
| Pain |
| Site-specific pain (e.g. thoracic) |
| Girdle pain (circumferential band around body) |
| Night pain |
| Progressive weakness |
| Altered sensation |
| Ataxia |
| Change in urinary frequency |
| Onset of deformity/gibbus |

appropriate after surgical decompression or completion of radiotherapy.

*Surgery* Studies that compared outcomes between radiotherapy and laminectomy have been cited as demonstrating that spinal surgery has little role to play in the management of SCC.[21–23] However, it should be stressed that laminectomy alone, in patients with spinal cord compression from vertebral metastases, violates all three principles of surgical management. In general, spinal decompression must be followed by spinal stabilization. With modern imaging and surgical instrumentation, it is possible to decompress and stabilize the vertebral column, either anteriorly or posteriorly, to an extent which was not generally possible during the periods reviewed by these largely retrospective and unrandomized studies. There is a consensus that surgical decompression and stabilization, combined with post-operative radiotherapy, offers an improved quality of life for many of these patients.

**Evidence level: Grade C Level IV**

Management decisions should be based on clinical assessment and good quality imaging. The recommendations which follow are based on the best available evidence and the authors' judgement of what is likely to become best practice. This does not, at the current time, include controlled randomized trials. Specific surgical techniques are not identified, as it is believed such recommendations would rapidly become outdated. Rigorous audit of results is recommended.

Patients with SCC need urgent MRI (or CT myelogram if MRI is contraindicated) followed by multi-disciplinary assessment which includes the opinions of an oncologist/radiotherapist and an orthopaedic surgeon or neurosurgeon with expertise in the management of spinal disease (see Table 10). If the on-call spinal surgeon is not available at District level, the multi-disciplinary team must establish and detail arrangements for immediate transfer of images. The decision on treatment will depend on many factors, including the site and number of levels, whether the compression is partial or complete, fixability, duration, performance status and predicted survival. In the case of rapid onset SCC, when surgery is indicated, the aim should be to commence surgery within 12 h (speed of onset bears an important relation to response).

**Evidence level: Grade B Level III**

Where surgical intervention is undertaken, the use of MRI-compatible fixators is recommended, as this greatly facilitates future assessment.

*Radiotherapy* Radiotherapy should be given if surgical decompression is not appropriate, or following surgery. It is unusual to use a single fraction of radiotherapy for SCC. If the spinal cord has not been surgically decompressed, and it is soon after the onset of symptoms, then it is recommended that the patient should be on high-dose dexamethasone as previously mentioned.

Radiotherapy should be given as outlined below, with the dose prescription in accordance with the ICRU 50.[18]

*Cervical/thoracic spine* A direct posterior field is used, giving 20 Gy in five fractions. Sometimes, when irradiating the cervical spine, paired lateral portals can be employed, which largely avoids irradiation of the mouth, oropharynx and other soft tissues.

*Lumbar spine* Usually a single posterior field is employed. However, it is not always appreciated that the terminal part of the cord and cauda equina are at considerable depth (unless the patient is very thin—separation less than 21 cm). It may be more appropriate to treat with parallel opposed fields to ensure a reasonable percentage depth dose is achieved.

## Systemic therapies

*Endocrine and chemotherapy*

All patients with metastatic breast cancer should be considered for some form of systemic therapy.

**Evidence level: Grade C Level IV**

The appropriate treatment will be determined by:

(1) the patient's overall condition (performance status (PS));
(2) the sites and extent of metastatic disease;
(3) oestrogen receptor status;
(4) previous adjuvant therapy (if any).

The principles of treating bony metastatic disease are the same as for any other metastatic site, except:

(1) metastases limited to or mainly in bone are relatively likely to be hormone-sensitive;
(2) bisphosphonates may be useful systemic agents (see Bisphosphonates section below).

Both hormone therapy and chemotherapy can produce useful control of symptoms in patients with bony metastases. Hormone therapy is less toxic than chemotherapy and hence is usually the first line of therapy. Oestrogen receptor (ER) status is an accurate predictor of response, with a positive ER status in the primary tumour associated with response in about 60% of patients, and a negative ER status with response in <10%.[24] Patients who also have advanced visceral metastases (e.g. lymphangitis carcinomatosa or liver involvement and deteriorating liver function tests) often fail to respond to hormone therapy and delay in starting chemotherapy may be deleterious. For these patients chemotherapy should be first-line treatment. In patients with advanced bony metastases, the bone marrow reserve may be poor and hence these patients need particularly close haematological monitoring while on chemotherapy.

On failure of hormone therapy, patients should be considered for either further endocrine therapy (if they have had a clinically useful response to first-line therapy) or chemotherapy. A clinically useful response is defined as either an objective response or static disease for at least 6 months. Careful assessment of response is essential (see page 17) and a change of systemic therapy should be considered at the first indication of symptomatic progression.

Guidelines for the consideration of systemic therapy are shown in Fig. 4. (note that bisphosphonates are considered separately below).

We recommend that the Breast Cancer Unit should agree a protocol based on these guidelines.

Notes on Fig. 4.

(1) If there is extensive life-threatening/visceral disease at diagnosis and PS 0–2, consider giving chemotherapy, according to local protocols, as first treatment.

**Evidence Level: Grade C Level IV**

(2) ER status has been considered as negative/positive only, but in fact there is a wide range of possible values, depending on the methodology chosen for assessment (biochemical or immunohisto/cytochemical). ER status is essentially used as a surrogate to predict the likelihood of the disease responding to endocrine therapy, and therefore the absolute level of ER as well as other predictive factors such as disease-free interval, menopausal status and progesterone receptor (PgR) expression should also be considered before deciding whether endocrine treatment is appropriate.

**Evidence level: Grade B Level IIA, III**

(3) When considering second-line endocrine therapy, evidence should be sought for endocrine-sensitivity of the disease such as proven response to prior endocrine therapy (e.g. for advanced disease or neoadjuvant), or a long disease-free interval after adjuvant hormonal treatment.

Second-line endocrine therapy = aromatase inhibitor or megestrol acetate (or tamoxifen if not previously given).

**Evidence level: Grade A Level IB, IIB**

(4) On failure of second-line endocrine therapy, consider third-line endocrine therapy (if tumour was sensitive to prior hormonal agents) or chemotherapy (mindful of age, performance status, and level of symptoms).

**Evidence level: Grade C Level IV**

*Bisphosphonates*

*Acute treatment of hypercalcaemia*

**Evidence Level: Grade A Level IB**

Hypercalcaemia is associated with poor prognosis and limited survival.[25,26] There is good evidence for the benefit of bisphosphonates administered at high doses by intravenous infusion.[27–30] These agents should be regarded as first-line therapies in patients with hypercalcaemia persisting despite adequate rehydration, and typical management is shown in Table 12.

*Acute treatment of severe bone pain*

**Evidence level: Grade A Level IB**

There is also evidence that high-dose intravenous bisphosphonates are of benefit in patients with severe bone pain which is unresponsive to hierarchical use of analgesics

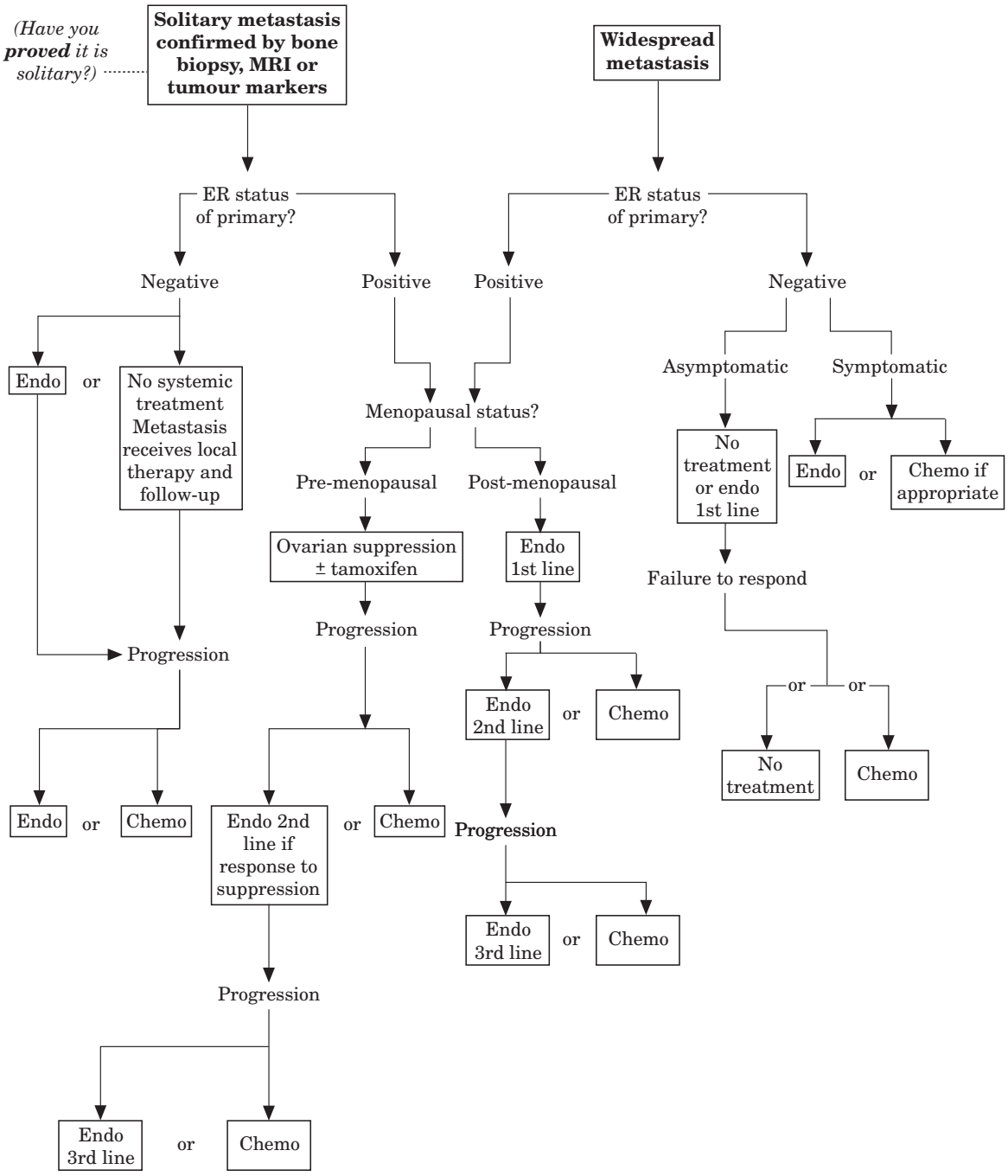



**Fig. 4.** Guidelines for systemic anti-cancer therapy. Chemo, chemotherapy; Endo, endocrine therapy.

**Table 12.** Acute management of hypercalcaemia in breast cancer

| |
|---|
| Adequate rehydration with normal saline (3–4 litres/day) |
| Avoid loop diuretics unless fluid overload occurs |
| Single intravenous infusion of bisphosphonate<br>Clodronate<br>or<br>Pamidronate<br>(doses and administration according to data sheets) |
| Repeat intravenous infusions of clodronate (2-weekly) or pamidronate (4-weekly), or oral clodronate, may be given to prevent/treat recurrent hypercalcaemia |

and is too widespread for local radiotherapy.[31–34] Though the mechanism(s) remain unclear, the effect does bear some relationship to their anti-resorptive effects as judged by the response in biochemical markers of bone resorption.[35] Higher doses or more frequently repeated infusions appear to be required than for the treatment of hypercalcaemia[31,32] but responses, if obtained, can be of useful duration. Suggested protocols for treatment are shown in Table 13.

*Long-term use to decrease skeletal morbidity in the presence of skeletal metastases* Several placebo-controlled randomized studies in women with skeletal metastases and breast cancer have shown significant reductions (25–50%) in skeletal

**Table 13.** Acute management of severe bone pain in breast cancer

| |
|---|
| Ensure patient is adequately hydrated |
| Single intravenous infusion of bisphosphonate<br>Clodronate<br>or<br>Pamidronate<br>(Doses and administration according to data sheets) |
| Treatment should be discontinued if there is a failure to respond after 2–3 infusions |
| Repeat intravenous infusions of clodronate (2-weekly) or pamidronate (4-weekly) can be given depending on the duration of response (oral clodronate can be given as continuing therapy once severe pain is controlled) |

morbidity (pathological fractures, bone pain requiring skeletal radiotherapy and hypercalcaemia).[36–38] Treatment is relatively expensive and targeting of treatment to subgroups who might benefit most seems the rational approach based on current knowledge. Limited cost-effectiveness analysis in the USA suggests that their use in patients with symptomatic bone metastases which have shown minimal or no benefit from systemic therapies may reduce the costs of treating skeletal complications.[39]

**Evidence level: Grade A Level IB**

The duration of therapy is unclear. Published studies have either had set durations[36] or continued treatment until death.[38] It is clear that osteolysis which fails to respond to systemic therapies will continue for the rest of the course of the disease with a high incidence of pathological events. Unlike tumour responsiveness, there is little convincing evidence that osteoclastic bone resorption becomes resistant to the use of bisphosphonates at adequate dosage until the terminal stages of disease. The persistence of bone disease suggests that, where possible, treatment with bisphosphonates should be continued indefinitely.

Patients with osteolytic disease are at increased risk of further pathological skeletal events and treatment with bisphosphonates reduces and delays this risk[36–38] but does not abolish the risk completely. The role of biochemical markers of bone turnover in monitoring response to treatment, although promising, requires further investigation.[40]

In view of the financial and logistic implications of long-term bisphosphonate treatment, it is clear that some selection of patients for treatment is necessary. A suggested schema to prioritize bisphosphonate use is shown in Appendix 3.

*Future use of bisphosphonates in breast cancer*

Though the largest body of evidence for the use of bisphosphonates is in patients with skeletal metastases, there is increasing interest in their use in other clinical settings in patients with breast cancer. These situations are:

- to prevent bone loss associated with the use of endocrine therapy or chemotherapy, partly mediated by their effects on gonadal function; and/or
- to reduce the incidence of skeletal metastases in women with breast cancer.

*Prevention of bone loss* Women with breast cancer may be at increased risk of osteoporosis due to premature ovarian failure and/or treatment effects on bone metabolism. Several recent studies have shown that long-term treatment with bisphosphonates can decrease bone turnover in pre- and post-menopausal women with consequent improvements in bone mineral density.[41,42] It is likely that the use of bisphosphonates will increase in this setting given the continuing uncertainty over the use of HRT in such women.[43,44]

**Evidence level: Grade A Level IB**

*Prevention of bone metastases* It is clear that multiple steps are involved in the metastasis of breast cancer tumour cells to distant sites with the ability of tumour cells to interact with marrow stromal cells or extracellular matrix playing a crucial role. There is increasing interest in the ability of bisphosphonates to interrupt many of these interactions and animal studies have demonstrated a reduction in skeletal burden of disease using concomitant administration of bisphosphonates.[45] Some recent data suggest that bisphosphonates may influence the development of bone metastases[46,47] but these results require confirmation by further randomized trials before preventative bisphosphonate therapy can be considered to be clinically appropriate.

**Evidence level: Grade A Level IB**

## Assessment of response in bone metastases

*Subjective*

Any treatment is palliative and hence a careful clinical assessment of symptoms is crucial. This will be based on an assessment of level of pain, analgesic requirements (worsening pain indicates a poor response) and mobility.

**Evidence level: Grade C Level IV**

*Objective*

In addition to clinical assessment, response to therapy should be measured objectively (Fig. 5). This is so that effective therapy can be continued, to help direct therapy at relapse (if a response to hormonal therapy is confirmed, second-line hormone therapy could be used on failure), and equally importantly so that ineffective and possibly toxic therapy can be stopped. The possible methods of assessment are as follows.

*Skeletal scintigraphy* While useful in the diagnosis of bony metastases (see pages 6–8), it is of little use in the assessment of response. Response to therapy may be associated with

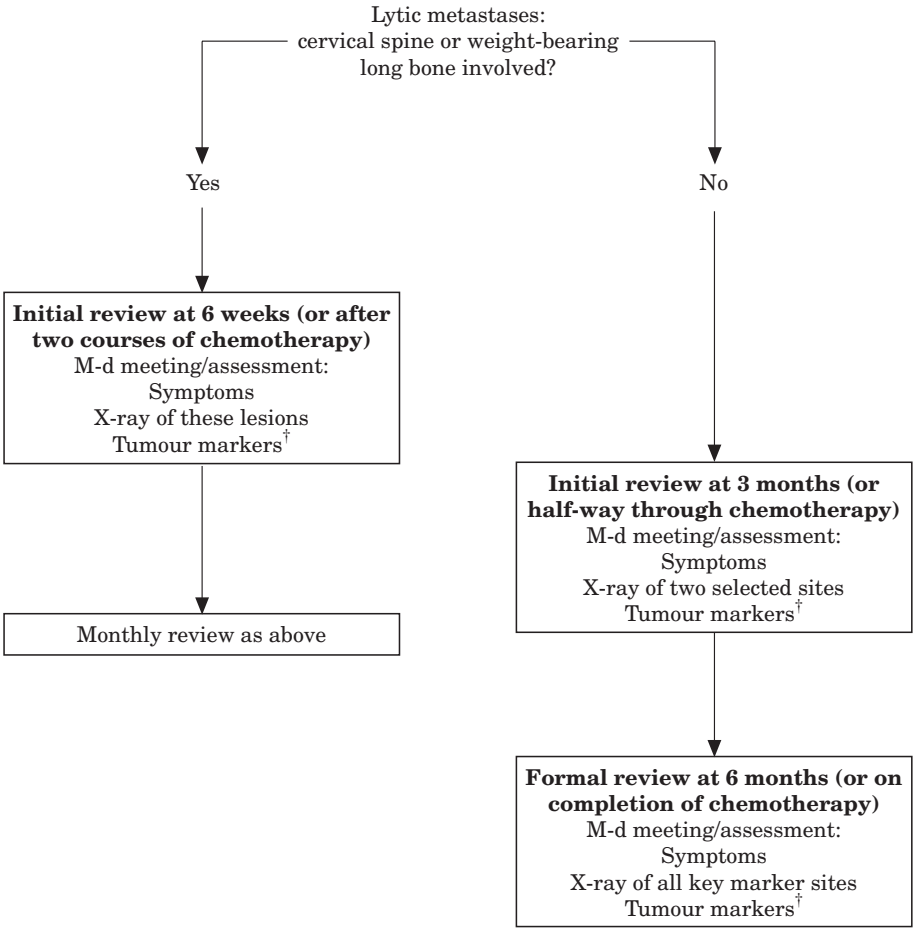



**Fig. 5.** Objective assessment of response to systemic therapy in lytic bone metastases. M-d, multi-disciplinary; †depending on local protocols. Systemic therapy: radiotherapy, endocrine therapy, biphosphonates, chemotherapy (assumes that the need for surgical intervention has been excluded).

a 'flare'—increased uptake of the scanning agent by the metastases and even by previously undetected 'hot spots'—during the first 6 months of treatment. This response is indistinguishable from that of progressive disease.[48]

*Plain radiography* Lytic metastases can be seen to 'heal' (sclerose) on plain radiographs.[49] It is therefore recommended that a few (e.g. 4–5) key lesions be identified and radiographed. Some of these (e.g. two selected ones, or those at high risk of fracture such as cervical spine or weight-bearing bones) should be re-assessed at 3 months. All of these lesions should be re-assessed at 6 months. Obviously, if some areas have received palliative radiotherapy, then they cannot be used to assess response to systemic therapy. Response in sclerotic metastases cannot be assessed by plain radiographs.

**Evidence level: Grade B Level III**

*MRI* There is very little published work on the role of MRI in the assessment of response in bone metastases. However, recent work suggests that MRI can be predictive in distinguishing progressive from non-progressive disease.[50] Further studies are ongoing, and we may be able to make a more definitive statement in future editions of these guidelines.

*Serum tumour markers* Tumour markers (such as CA15-3, CEA, etc.) can be of use in assessing response to therapy, especially in the absence of readily measurable disease.[51]

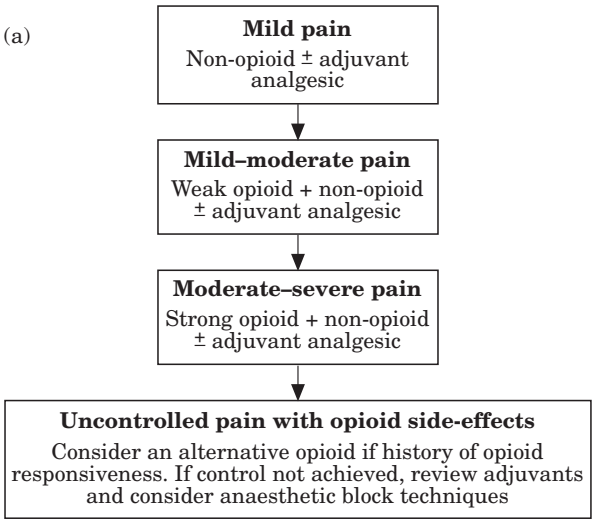
Some retrospective and subsequent prospective studies have shown that changes in tumour markers (CA15-3, CEA and ESR), using each patient as their own control, correlate very closely with response to both hormone and chemotherapy as measured by UICC criteria.[52–54] In particular, biochemical response at 3 months correlates with UICC response at 6 months, i.e. biochemical markers can give a lead time in predicting both therapeutic response and failure.

**Evidence level: Grade B Level IIA**

For patients whose disease is not assessable by UICC criteria, because of sclerotic metastases or because index lesions have been irradiated, tumour markers provide the only validated method of objectively assessing response.[49,51] Markers are measured at 3 and 6 months.

A guide to the scoring of response using markers is shown in Appendix 2.

(a)




| Drug | Dosage | Indications | Side-effects |
|---|---|---|---|
| NSAIDS<br>e.g. naproxen | 250–500 mg po/pr bd | Bone metastases<br>Soft tissue infiltration | Gastric irritation, fluid retention, headache, vertigo. Caution in renal impairment |
| diclofenac | 50 mg po tds<br>100 mg pr daily | Liver pain | |
| Steroids<br>e.g. dexamethasone | 8–16 mg/day | Raised intracranial pressure<br>Nerve compression<br>Soft tissue infiltration<br>Liver pain | Gastric irritation if with NSAID, fluid retention, confusion, cushingoid appearance |
| Amitriptyline | 25 mg nocte (starting dose) | Nerve pain—in area of altered sensation<br>Also useful in lancinating pain | Sedation, dizziness, dry mouth, constipation, urinary retention |
| Carbamazepine | 200 mg nocte (starting dose) | Nerve pain—lancinating | Vertigo, constipation, rash |

Other adjuvant drugs, e.g. ketamine and lamotrigine, for central sensitization pain, should not be used without specialist advice.

**Fig. 6.** Pain ladder (a) and adjuvant analgesics (b).

Multi-centre randomized trials, further evaluating the role of tumour markers, are currently in preparation, and these trials merit support.

### Palliative care—principles of bone pain management

The advice of a palliative care physician will often be required. Patients who have metastatic disease particularly involving bone are likely to have symptoms relating to bone pain, poor mobility, anaemia and may require psychological support.

The principles of bone pain management can be summarized as:

(1) identify the cause;
(2) reverse the reversible. Remember that movement-related pain needs mechanical treatment, i.e. orthopaedic referral;
(3) pharmacological control of pain will be a necessary adjunct to tumouricidal therapy or as the sole treatment;
(4) remember that non-physical factors will lower the pain threshold and must be addressed;
(5) remember chronic pain syndromes related to cancer treatments, e.g. post-mastectomy neuropathic pain syndrome and radiation fibrosis of brachial plexus.

#### *Pharmacological management of pain*

The recommendation is to adopt a standard approach using the World Health Organisation (WHO) analgesic guidelines, choosing the strength of analgesia according to the severity of the pain and using the appropriate adjuvant according to the type of pain. The pain ladder, and a list of adjuvant analgesics and their indications, are shown in Fig. 6.[55–61]

For severe pain, analgesia should be titrated with an immediate-release morphine preparation. It is important

to remember that inadequate explanations about opioids, inadequate prevention/management of adverse effects, and an inappropriate rate of titration of opioids will all result in an imbalance between wanted and unwanted effects, i.e. the balance will be shifted from analgesia to adverse effects. Opioid responsiveness is a continuum; no pain is inherently unresponsive to opioids, although some pains are less responsive. Some pains may respond to a switch of opioids to gain a better balance between wanted and unwanted effects.[58]

If pain remains uncontrolled anaesthetic block techniques may be useful.

Non-pharmacological approaches such as explanations, relaxation techniques and more formal cognitive approaches can all help to raise the pain threshold.

*Anaesthetic techniques*

In a minority of patients the chosen local and/or systemic therapy and adequate use of analgesics fails to provide adequate pain relief, and anaesthetic techniques should be considered.

(1) Spinal (epidural or intrathecal) opioids—indicated for opioid-responsive pain in those patients who have intolerable adverse effects at the dose needed for adequate analgesia (when the drug is taken by systemic routes).
(2) Local anaesthetic via a spinal catheter may be particularly useful in managing movement-related incident pain.
(3) Indwelling catheters with a subcutaneous reservoir are appropriate for patients responding to spinal analgesia and who have a medium- to long-term prognosis.
(4) Neurolytic techniques have the following preconditions:
    (i) failure of primary pain management;
    (ii) accurate diagnosis of the cause of pain;
    (iii) a condition that responds to neurodestructive techniques;
    (iv) a risk-benefit ratio acceptable to patient, relatives and clinicians;
    (v) availability of facilities and skills.

Where appropriate, local anaesthetic block should be performed before destructive techniques.

## Clerical and data support

This document reveals the large number of different specialists who may be involved in the care of women with breast cancer and bone metastases. Co-ordination of management requires adequate secretarial and clerical support. In particular, there may be a future need for a separate record of decisions made at the multi-disciplinary meetings.

The management of metastatic bone disease is currently difficult to audit. These guidelines have been constructed in order to try and improve the management of metastatic bone disease. This means that the management needs to be audited and therefore there must be adequate provision for audit support.

## Regular review of guidelines

These guidelines are based on evidence and information which is up-to-date at the time of writing (November 1998). We are aware that much relevant work is in progress or being planned. It is our intention to review the guidelines and publish a revised document in 2 years' time.

## Acknowledgements

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The guidelines have been decided solely by the multi-disciplinary group of specialists shown on the title page in consultation with other interested clinicians, with no input or influence from the sponsors. As such, they do not necessarily represent the views of the sponsors.

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## Appendix 1

*US Agency for Health Care Policy and Research*[5]

**Table A1.** Definitions of types of evidence and grading of recommendations

| Level | Type of evidence |
|---|---|
| Ia | Evidence obtained from meta-analysis of randomized controlled trials |
| Ib | Evidence obtained from at least one randomized controlled trial |
| IIa | Evidence obtained from at least one well-designed controlled study without randomization |
| IIb | Evidence obtained from at least one other type of well-designed quasi-experimental study |
| III | Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies |
| IV | Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities |
| **Grade** | **Recommendations** |
| A (evidence levels Ia, Ib) | Required—at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendations |
| B (evidence levels IIa, IIb, III) | Required—availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation |
| C (evidence level IV) | Required—evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality |

## Appendix 2

*Monitoring therapy with tumour markers*

These recommendations are based on the protocols used in the Nottingham Breast Unit, which are themselves based on the results of local studies.

*Usefulness of markers* Therapy can be monitored using tumour markers (CA15-3, CEA, ESR). Each patient serves as their own control. In one series, at the time of diagnosis of metastatic disease, 83% of patients had elevation of one or more of the markers and a further 13% showed an increase in one or more markers when they developed progressive disease.[40] Only 4% of patients showed no change in markers.

*A scoring system* The scoring system[52] is based on a cut-off level for each individual marker, defined as the mean +2 SD of a normal control population of women—this cut-off becomes the upper limit of normal. Changes in markers are measured with respect to each patient's pretreatment baseline level. Biochemical progression is thus either change from normal levels to abnormal, or a significant (>10%) increase in the levels of already abnormal levels. Biochemical response is the reverse. This is summarized in Table A2.

**Table A2.** Change in tumour marker status and biochemical response criteria

| Baseline marker level (pretreatment) | Subsequent marker level | Biochemical status |
|---|---|---|
| <Upper limit normal | >Upper limit normal | Progression |
| >Upper limit normal | >10% increase in level | Progression |
| >Upper limit normal | <Upper limit normal | Response |
| <Upper limit normal | >10% decrease in level | Response |
| >Upper limit normal | <10% increase or decrease in response | Stable |

These changes are formally scored for each marker as shown in Table A3 and a summated score produced (potential range of scores is −5 to +6). A final score of >0 indicates disease progression and any score ≤0 indicates non-progression (i.e. disease responding or stable).

**Table A3.** Scores for changes in marker concentration

| Marker | Upper limit of normal | Non-elevated marker | Decrease (−>10%) | Stable (±10%) | Increase (+>10%) |
|---|---|---|---|---|---|
| CEA | 6 μ/l | 0 | −2 | +1 | +2 |
| CA 15-3 | 22 kU/ml | 0 | −2 | +1 | +2 |
| ESR | 20 mm/h | 0 | −1 | +1 | +2 |

## Appendix 3

*Suggested prioritization of long-term bisphosphonate treatment for metastatic disease from breast cancer*

These are *local* guidelines developed at the Yorkshire Cancer Research Campaign (YCRC) Department of Clinical Oncology, Sheffield, and adopted for use by local oncologists. They are offered for consideration as the Working Party were unable to identify National Guidelines.

The score for an individual patient is calculated according to Table A4 and, according to the total score, the relative priority for recommending repeated/long-term bisphosphonates can be judged.

*Total score and interpretation*

>11 Highest priority for long-term bisphosphonate treatment.

7–11 Moderate priority for long-term bisphosphonate treatment.

<7 Low priority for long-term bisphosphonate treatment.

**Table A4.** YRC scoring system for deciding on long-term bisphosphonate use in an individual patient

| | Score |
|---|---|
| Disease extent | |
| Bone (marrow) only | 3 |
| Bone and soft tissue | 2 |
| Bone and visceral disease | 1 |
| Bone morbidity | |
| Previous skeletal event ± bone pain | 3 |
| Bone pain | 2 |
| Asymptomatic | 1 |
| Eastern Co-operative Oncology Group (ECOG) performance status[62] | |
| 1,2 | 3 |
| 0,3 | 2 |
| 4 | 1 |
| Underlying treatment | |
| Requiring chemotherapy/endocrine resistant | 2 |
| Potentially endocrine sensitive | 1 |
| Good prognostic factors | |
| Disease-free interval >3 years | 1 |
| Pre-menopausal | 1 |
| Ductal grade 1 or 2 or lobular histology | 1 |
| Bone metastases at initial presentation | 1 |