

Bone health in cancer patients: ESMO Clinical Practice Guidelines[†]

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There are three distinct areas of cancer management that make bone health in cancer patients of increasing clinical importance. First, bone metastases are common in many solid tumours, notably those arising from the breast, prostate and lung, as well as multiple myeloma, and may cause major morbidity including fractures, severe pain, nerve compression and hypercalcaemia. Through optimum multidisciplinary management of patients with bone metastases, including the use of bone-targeted treatments such as potent bisphosphonates or denosumab, it has been possible to transform the course of advanced cancer for many patients resulting in a major reduction in skeletal complications, reduced bone pain and improved quality of life. Secondly, many of the treatments we use to treat cancer patients have effects on reproductive hormones, which are critical for the maintenance of normal bone remodelling. This endocrine disturbance results in accelerated bone loss and an increased risk of osteoporosis and fractures that can have a significant negative impact on the lives of the rapidly expanding number of long-term cancer survivors. Finally, the bone marrow micro-environment is also intimately involved in the metastatic processes required for cancer dissemination, and there are emerging data showing that, at least in some clinical situations, the use of bone-targeted treatments can reduce metastasis to bone and has potential impact on patient survival.

introduction

Cancer and the treatments applied can have profound effects on bone health. Clinicians treating cancer patients need to be aware of both the multidisciplinary treatments available to reduce skeletal morbidity from metastatic disease and the strategies required to minimise cancer treatment-induced damage to the normal skeleton. These guidelines provide a framework for maintaining bone health in patients with cancer.

normal bone physiology and turnover

Healthy bone is in a constant state of remodelling, an essential process to preserve structural integrity and minimise the risk of fragility fractures. Bone-derived osteoblasts and osteoclasts work together through the influence of cytokines and other humoral factors to couple formation and resorption. In normal health, the relationship between osteoblastic bone formation and osteoclastic bone resorption is finely balanced. However, bone diseases including malignancy disturb this balance and result in a loss of the normal structural integrity of the skeleton [1].

pathophysiology of bone metastases

The process of cancer metastasis includes tumour cell seeding, tumour dormancy and subsequent metastatic growth. The primary tumour releases cells that pass through the extracellular matrix, penetrate the basement membrane of angiolymphatic vessels and are then transported to distant organs via the circulatory system. Circulating breast and prostate cancer cells have a particular affinity for bone. Most disseminated tumour cells die, but the bone marrow micro-environment may act as a reservoir for malignant cells. More specifically, the haematopoietic stem cell niche appears to be the site for dormant tumour cells that only result in relapse many years after the diagnosis (Figure 1) [2].

Once within the bone micro-environment, tumour cells have the capacity to produce a wide range of cytokines and growth factors including parathyroid hormone-related peptide, prostaglandins and interleukins that may increase the production of receptor activator of nuclear factor kappaB ligand (RANKL) by cells of the osteoblastic lineage. This will lead to activation of osteoclasts and disturbance of the balance of new bone formation and bone resorption. As the bone matrix is broken down, a rich supply of bone-derived factors is released that may lead to increased growth and proliferation of the tumour cell population. These multiple interactions between metastatic tumour cells and the bone micro-environment may contribute to the development of metastases both within and, potentially, also outside bone.

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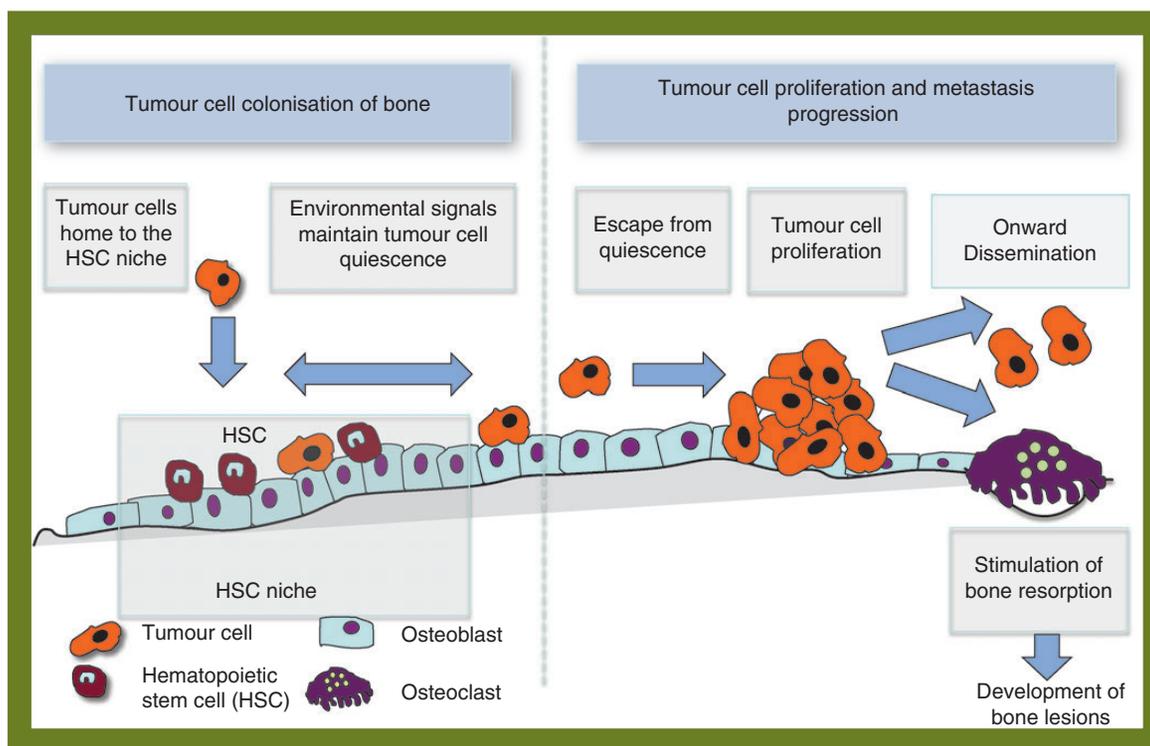


Figure 1. The development of bone metastases can be considered in several stages: colonisation, quiescence, progression either locally leading to overt metastasis in bone or dissemination to another site. Reprinted from [3], with permission from Elsevier.

The overall effect is the creation of a self-sustaining vicious cycle with multidirectional interactions between cancer cells, osteoclasts, osteoblasts and the bone micro-environment [4].

incidence, epidemiology and clinical consequences

bone metastases

Metastatic bone disease is most commonly seen with specific cancer types, notably those arising from the breast, prostate, lung and kidney, as well as multiple myeloma (MM). The most common sites of bone metastases are throughout the axial skeleton. Bone metastases affect many patients with advanced disease, and, whether lytic or blastic in appearance, often lead to skeletal complications typically referred to as skeletal-related events (SREs). This term (SRE) usually refers to five major objective complications of tumour bone disease: pathological fracture, the need for radiotherapy to bone, the need for surgery to bone, spinal cord compression and hypercalcaemia, although the latter is often of para-neoplastic origin, especially in the absence of bone metastases. The need for radiotherapy and pathological fractures are the most common skeletal events, reflecting the burden of bone pain and structural damage caused by metastatic involvement. These complications are associated with life-altering morbidity and can reduce overall survival (OS). In a population-based cohort study of nearly 36 000 newly diagnosed breast cancer patients followed for up to 9 years, the median survival for breast cancer patients with bone metastases was 16 months, but was only 7 months for patients with bone metastases and a subsequent SRE [5]. Typically, skeletal events are associated with

loss of mobility and social functioning, a decrease in quality of life (QoL) and a substantial increase in medical costs [6].

Across all tumour types, patients with breast cancer have the highest incidence of skeletal complications. In the absence of bone-targeted treatments, the mean skeletal morbidity rate, i.e. the mean number of SREs per year, in breast cancer patients with bone metastases varied between 2.2 and 4.0 [7].

In prostate cancer, histo-morphometric studies have shown the characteristic association of osteoblastic response to the presence of metastatic prostate cancer cells, but there is a wide spectrum of bone responses often seen within an individual patient [8]. Bone resorption rates, as determined by measurement of collagen breakdown products, are also high in prostate cancer patients [9], and SREs, notably pain requiring radiotherapy, fractures and spinal cord compression, are frequent.

In patients with lung cancer and bone metastases, the median survival time is only 6–12 months. However, bone metastases present with an SRE in around one-quarter of patients, while 40% will experience an SRE during follow-up [10]. In renal clear-cell carcinoma, the presence of bone metastasis is the independent variable most significantly associated with poor survival [11].

Bone pain, most often in the back due to vertebral fractures, is a presenting feature in three quarters of patients with MM. Extensive lytic lesions are frequent and, typically, they do not heal despite successful antineoplastic treatment. Diffuse osteoporosis can also be a presenting feature in myeloma [12].

cancer treatment-induced fractures

The rate of bone loss increases with age in both women and men, and is associated with a rapid increase in fracture rate

in both sexes above the age of 70 years [13, 14]. The lifetime risk of a fracture of the hip, spine or distal forearm from age 50 years onwards is almost 40% in white women and 13% in white men [14].

Risk factors for osteoporosis-related fractures have been validated in large prospective as well as population-based studies in postmenopausal women but not specifically defined for either women with a history of breast cancer or men with prostate cancer (Table 1) [15–18].

diagnosis and monitoring

diagnosis of bone metastases

Metastatic involvement of the skeleton typically affects multiple sites and causes pain and bony tenderness. The diagnosis is often straightforward but occasionally can be difficult to make, and confusion with benign pathology is particularly a problem for elderly patients, in whom degenerative disease and osteoporosis are common.

Plain radiographs are an insensitive test for metastasis, as for a destructive lesion in trabecular bone to be recognised, it must be >1 cm in diameter with loss of ~50% of the bone mineral content. The radionuclide bone scan provides information on osteoblastic activity and skeletal vascularity, with preferential uptake of tracer at sites of active bone formation that reflects the metabolic reaction of bone to the disease process, whether neoplastic, traumatic or inflammatory. When bone metastases develop, there is usually sufficient increase in blood flow and reactive new bone formation to produce a focal increase in tracer uptake, often before bone destruction can be seen on X-ray. With the exception of patients with MM, the bone scan is more sensitive than plain radiographs for the detection of skeletal pathology, although the specificity is low.

A computed tomography (CT) scan produces images with excellent soft tissue and contrast resolution. Bony destruction and sclerotic deposits are usually clearly shown and any soft tissue extension of bone metastases is easily visualised. CT can also help with the diagnosis of spinal metastases and is particularly useful to localise lesions for biopsy.

Magnetic resonance imaging (MRI) has the advantage of providing multi-planar images that permit imaging of the entire spine in the sagittal plane. Detection of bone metastases by MRI

depends on differences in MR signal intensity between tumour tissue and the normal bone marrow. Metastatic tumour is therefore visualised directly, in contrast to the indirect changes observed by X-ray or radionuclide bone scanning. Like CT, MRI is useful for evaluating patients with positive bone scans and normal radiographs and for elucidating the cause of a vertebral compression fracture. MRI is excellent for demonstrating bone marrow infiltration and is more sensitive than a bone scan for the early detection of spinal metastases. It is the preferred imaging method in the case of spinal cord compression and subsequent planning of palliative radiation therapy.

Scanning with ¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET) provides the opportunity to visualise functional aspects. However, its role in the routine identification of bone metastases is unclear.

screening for osteoporosis

Osteoporosis is defined as a systemic skeletal disease in both men and women characterised by low bone mass and micro-architectural deterioration of bone tissue that results in a high risk of fracture. Bone loss results from age, lifestyle, disease and treatment-related influences on normal bone turnover at sites of the skeleton characterised by higher proportions of trabecular bone (e.g. the spine and the proximal and distal ends of long bones). Bone loss leads to thinning and perforation of the trabecular plates, and the subsequent loss of normal architecture results in a disproportionate loss of strength for the amount of bone lost.

Oestrogen deficiency is the major cause of accelerated bone loss leading to an increased incidence of fractures [19]. Consequently, oestrogen deprivation in women with breast cancer and in men receiving androgen deprivation therapy (ADT) will accelerate bone turnover leading to a decrease in bone mineral density (BMD) and a 40%–50% increase in fracture incidence [19, 20]. In at-risk patients, an assessment of clinical risk factors and measurement of BMD by dual X-ray absorptiometry (DXA) is required (Table 2).

assessment of response

The current imaging methods used to assess response to treatments are qualitative and include plain radiographs, CT scans

Table 1. Risk factors that increase fracture risk^a in postmenopausal women with breast cancer [18]

Aromatase inhibitor (AI) treatment
BMD T-score of <−2.5
Increasing age (>65 years)
Oral corticosteroid use for more than 6 months
Low body mass index (BMI) (<20 kg/m ²)
Family history of hip fracture
Personal history of fragility fracture after age 50
Smoking

^aIn males with prostate cancer, androgen deprivation therapy increases risk and the other factors are probably also valid.

Table 2. Prevention of bone loss in patients with treatments known to increase the risk of fractures (e.g. ovarian suppression/ablation, aromatase inhibitors, androgen-depletion therapy and long-term corticosteroids) [18, 19]

Baseline fracture risk factor assessment
BMD measurement
Lifestyle changes
Take more weight-bearing exercise
Stop smoking
Reduce alcohol consumption
Dietary measures and supplements
Adequate calcium (1000 mg/day) intake
Supplementary vitamin D (to total intake of 1000–2000 units/day)
In selected cases: bone-directed anti-resorptive therapy to manage low BMD or rapid bone loss

and, in particular situations, MRI and PET assessment of metabolic uptake. However, the role of these latter technologies in routine practice has not been precisely defined. Bone is the only site of metastatic disease that has separate criteria for evaluation of response to treatment, based on bone repair and destruction rather than on changes in tumour volume [21]. Assessing the response of bone metastases to therapy is difficult; the events in the healing process are slow to evolve and quite subtle, with sclerosis of lytic lesions only beginning to appear 3–6 months after the start of therapy and taking more than a year to mature.

A complete review of bone radiographs since the start of treatment is necessary to evaluate a treatment response. It is generally accepted that sclerosis of lytic metastases with no radiological evidence of new lesions constitutes tumour regression (a partial response). Confounding factors include the appearance of sclerosis in an area that was previously normal. This could represent progression of a new metastasis but could also indicate a response, reflecting healing within a lesion that was present at the start but was not destructive enough to be visible radiographically.

The use of bone scanning for assessment of response to therapy has always been contentious, and is certainly unreliable when lytic metastases predominate. After successful therapy for metastatic disease, the healing processes of new bone formation cause an initial increase in tracer uptake (akin to callus formation), and scans carried out during this phase are likely to show increased intensity and number of hot spots. After treatment for 6 months, the bone scan appearances might improve, as the increased production of immature new bone ceases and isotope uptake gradually falls. This ‘deterioration’ followed by subsequent ‘improvement’ in the bone scan appearances after successful therapy has been termed the flare response [22].

biomarkers

Biochemical markers of bone turnover provide insight into ongoing rates of skeletal metabolism and tumour–bone interactions in patients with malignant bone disease. This interplay between tumour and bone dysregulates these otherwise balanced and spatially coupled activities, resulting in increased rates of osteolysis and osteogenesis and release of high levels of distinct biochemical markers that are amenable to non-invasive measurement in blood or urine [23]. Therefore, biochemical markers of bone metabolism, such as the cross-linked collagen peptides that are breakdown products from osteolysis, e.g. the amino [N]- and carboxy [C]-terminal cross-linked telopeptides of type I collagen, or NTX and CTX) and the terminal peptides that are cleaved from procollagen before its integration into new bone matrix (e.g. procollagen type I N-terminal and C-terminal peptides, or PINP and PICP), can provide meaningful insight into the ongoing effects of tumour growth on bone turnover. Serum levels of CTX and urinary concentration of NTX reflect ongoing rates of osteolysis, whereas bone-specific alkaline phosphatase (bone ALP) and PINP levels in serum reflect ongoing rates of osteogenesis [23]. In addition, some markers of bone metabolism may be associated with both osteolysis and osteogenesis (e.g. osteocalcin).

Biochemical markers of bone metabolism reflect ongoing rates of bone resorption and formation in the body as a whole. Therefore, bone marker assessments do not provide information

specific to individual lesion sites. Moreover, changes in bone marker levels are not disease specific, but are associated with alterations in skeletal metabolism independent of the underlying cause [24]. Emerging evidence suggests that bone markers may help identify patients at high risk for bone metastasis or bone lesion progression, thereby allowing improved follow-up [23, 24]. Results from ongoing clinical trials evaluating such potential applications of bone markers are awaited to identify the true value of bone markers in clinical practice.

treatment

multidisciplinary management of bone metastases

In general, the treatment of bone metastases is aimed at palliating symptoms, with cure only rarely a realistic aim (e.g. in lymphoma). Treatments vary depending on the underlying disease. External beam radiotherapy, endocrine treatments, chemotherapy, targeted therapies and radioisotopes are all important. In addition, orthopaedic intervention may be necessary for the structural complications of bone destruction or nerve compression. Complementing these treatments is the role of bone-targeted agents.

Optimal management requires a multidisciplinary team that includes not only medical and radiation oncologists, orthopaedic surgeons, (interventional) radiologists and nuclear medicine physicians, but also palliative medicine specialists and a symptom control team with some expertise in bone complications from cancer. Treatment decisions depend on whether the bone disease is localised or widespread, the presence or absence of extra-skeletal metastases and the nature of the underlying malignancy. Radiotherapy is relevant throughout the clinical course of the disease. Resistance to systemic treatments can be expected to develop, necessitating periodic changes of therapy in an effort to regain control of the disease.

palliative radiotherapy

Local external beam irradiation is highly effective for bone pain. Overall, response rates of around 85% are reported, with complete relief of pain achieved in one-half of patients. Pain relief usually occurs rapidly, with more than 50% of responders showing benefit within 1–2 weeks. If improvement in pain has not occurred by 6 weeks or more after treatment, it is unlikely to be achieved [25]. Several trials have shown no difference in outcome between fractionated radiotherapy treatment and use of a single fraction. The accumulated evidence now strongly favours single-fraction radiotherapy as the treatment of choice for most patients with painful bone metastases [26].

Targeted radiotherapy with therapeutic radioisotopes has theoretical advantages over external beam radiotherapy in that the radiation dose may be delivered more specifically to the tumour and normal tissues partially spared unnecessary irradiation. Follicular carcinoma of the thyroid commonly metastasises to bone and the treatment of bone metastases with ¹³¹iodine is well established. In prostate and breast cancers with blastic metastases, useful palliation of bone pain has been demonstrated with ⁸⁹strontium and ¹⁵³samarium [27]. Most recently, the bone-seeking, α -particle-emitting radiopharmaceutical ²²³radium chloride has been developed. The high-energy α -particles provide a high dose of radiotherapy to cells within 1 μ m of the bone

surface with minimal systemic effects. In castrate-resistant prostate cancer (CRPC) patients, a randomised phase III trial evaluating the addition of radium chloride to best supportive care in advanced CRPC showed a 3.6 month significant improvement in OS in addition to beneficial effects on QoL and the incidence of skeletal morbidity [28].

bone-targeted agents

The bisphosphonates are analogues of pyrophosphate, with carbon replacing the central oxygen. The side chains from the central carbon provide the different bisphosphonates with their affinity for hydroxyapatite and their relative potencies. Bisphosphonates decrease bone resorption and increase mineralisation by specifically inhibiting osteoclast activity. Bisphosphonates concentrate in the skeleton, primarily at active remodelling sites. They are embedded in bone, released in the acidic environment of the resorption lacunae under active osteoclasts and are taken up by them. They will then interrupt the 'vicious cycle' of tumour-mediated osteolysis by inhibiting the activity of bone-resorbing osteoclasts and inducing their apoptosis [29].

There are two classes of bisphosphonates, non-nitrogen-containing and nitrogen-containing, with somewhat different effects on osteoclasts. Etidronate, clodronate and tiludronate are non-nitrogen-containing bisphosphonates, and the nitrogen-containing bisphosphonates (more potent osteoclast inhibitors and the most often used nowadays) include pamidronate, alendronate, ibandronate, risedronate and zoledronic acid (Table 3).

Bisphosphonates have a direct apoptotic effect on osteoclasts, inhibit their differentiation and maturation and thereby act as

potent inhibitors of bone resorption [29]. In preclinical models, the nitrogen-containing bisphosphonates have also been shown to influence macrophages, gamma delta T cells and osteoblasts. In addition to their effects on host cells, bisphosphonates may also have anti-tumour and/or anti-angiogenic effects, but this is a controversial area. Investigations are ongoing to better define the clinically relevant anti-tumour effects of bisphosphonates in patients with cancer [57].

Although radiotherapy is the treatment of choice for localised bone pain, many patients have widespread pain that is difficult to localise, while others experience recurrence of bone pain after radiotherapy. The bisphosphonates provide an additional treatment approach for the relief of bone pain that is useful across the range of tumour types [58].

Denosumab is a fully human, monoclonal, synthetic antibody that binds to RANKL with high affinity, preventing its interaction with RANK in a way that is similar to the natural endogenous inhibitor osteoprotegerin [59]. Moreover, as a circulating antibody, denosumab is expected to reach all sites within bone, whereas the strong affinity of bisphosphonates for hydroxyapatite and sites of active bone turnover may limit their even distribution throughout the skeleton.

In early clinical development, a single s.c. dose of denosumab was shown to cause rapid suppression of bone turnover in MM and breast cancer patients [60] and encouraged the clinical development of this targeted treatment (Table 3). Denosumab also provided substantially greater percentage reductions in tartrate-resistant acid phosphatase, a surrogate marker of osteoclast number, compared with i.v. bisphosphonate therapy. This indicated that functioning osteoclasts are still present in patients

Table 3. Summary of anti-resorptive agent efficacy and regulatory approval in cancer patients

Indications	Regulatory approval
Prevention of skeletal-related events	
Zoledronic acid 4 mg i.v. every 3–4 weeks [30–35]	All solid tumours and multiple myeloma ^{a,b}
Denosumab 120 mg s.c. every 4 weeks [36–38]	All solid tumours ^{a,b}
Pamidronate 90 mg i.v. every 3–4 weeks [30, 31, 39]	Breast cancer and multiple myeloma ^{a,b}
Clodronate 1600 mg p.o. daily [40, 41]	Osteolytic lesions ^a
Ibandronate 50 mg p.o. daily [42,43]	Breast cancer ^a
Ibandronate 6 mg i.v. monthly [44]	Breast cancer ^a
Prevention of breast cancer metastases	
Zoledronic acid 4 mg i.v. 6 monthly [45, 46]	None
Zoledronic acid 4 mg i.v. monthly × 6 then 3–6 monthly [47]	None
Clodronate 1600 mg daily [48,49]	None
Prevention of prostate cancer metastases	
Denosumab 120 mg s.c. monthly [50]	None
Prevention of treatment induced bone loss	
Denosumab 60 mg s.c. 6 monthly [51, 52]	Prostate cancer and breast cancer ^{a,b}
Zoledronic acid 4 mg i.v. 6 monthly [46]	None
Alendronate 70 mg p.o. weekly [53]	None
Risedronate 35 mg p.o. weekly [54]	None
Ibandronate 150 mg p.o. monthly [55]	None
Pamidronate 90 mg i.v. every 3 months [56]	None

^aEuropean approval.

^bUnited States.

i.v., intravenous; s.c., subcutaneous, p.o., per os (by mouth).

showing an inadequate biochemical response to bisphosphonate therapy, and that switching to denosumab may help suppress their activity. This finding suggests that denosumab may prove to be especially effective in patients who respond poorly to bisphosphonate therapy [61].

prevention of skeletal morbidity in metastatic bone disease

In the last two decades, the bisphosphonates and denosumab have become established as a valuable additional approach to the range of current treatments. Multiple, randomised, controlled trials have clearly demonstrated that they are effective in reducing skeletal morbidity from metastatic cancer [62]. Assessment of treatment effects has often used the first-event analyses, such as the proportion of patients with at least one SRE or time to the first event. These are objective but conservative end points that do not take into account all subsequent events. From a clinical perspective, an aggregate score of symptomatic SREs is more relevant. Multiple-event analyses have been increasingly used, as they are able to model all events and the time between events, allowing the calculation of a hazard ratio (HR) that indicates the relative risk of events between two different treatments [63].

breast cancer. Randomised placebo-controlled trials of pamidronate infusions for up to 2 years in addition to chemo- or hormonal therapy in breast cancer patients with at least one lytic bone metastasis demonstrated that bisphosphonates can reduce skeletal morbidity rate by more than one-third, increase the median time to the occurrence of the first SRE by almost 50% and reduce the proportion of patients having any SRE [30, 31].

Subsequently, more convenient and effective aminobisphosphonates have emerged including zoledronic acid and both i.v. and oral ibandronate [42, 44]. A randomised, double-blind, multicentre trial compared the efficacy of zoledronic acid and pamidronate in 1648 patients with breast cancer or MM. The proportion of patients with at least one SRE (the primary efficacy end point) was similar in all treatment groups and the pre-established criterion for noninferiority of zoledronic acid to pamidronate was met [32]. A multiple-event analysis in the breast cancer subgroup, however, showed that zoledronic acid (4 mg) reduced the risk of developing a skeletal complication by an additional 20% compared with that achieved by pamidronate ($P < 0.05$) [33]. The short infusion time also offers a more convenient therapy. Oral ibandronate has recently been compared with i.v. zoledronic acid in a large randomised trial in 1404 patients. Oral ibandronate was deemed inferior to zoledronic acid in reducing the overall risk of skeletal events [rate ratio for SREs 1.148, 95% confidence interval (CI) 0.967–1.362], although similar to zoledronic acid in delaying time to the first event [43].

Denosumab has been evaluated in three identical, double-blind, phase III registration studies that included a total of 5723 bisphosphonate-naïve patients with bone metastases [36–38]. The patients were randomly assigned to receive 4 weekly s.c. injections of denosumab (120 mg) or i.v. zoledronic acid (4 mg), with supplements of calcium and vitamin D. The primary end point was the time to first SRE. In the 2046 patients with bone

metastases secondary to breast cancer, denosumab was statistically superior to zoledronic acid in delaying the first SRE (HR 0.82, 95% CI 0.71–0.95; $P = 0.01$). The median time to a first SRE was 26.4 months for zoledronic acid-treated patients, whereas the median time to first SRE was not reached during the study in those treated with denosumab [36]. Denosumab was also superior to zoledronic acid in preventing subsequent SREs and reduced the overall risk by 23% (HR 0.77, 95% CI 0.66–0.89; $P = 0.001$) [36]. In patients who had no/mild pain at baseline, a 4-month delay in progression to moderate/severe pain was observed with denosumab compared with zoledronic acid, while fewer patients who received denosumab reported a clinically meaningful worsening of pain severity [64]. An additional 10% of patients had a clinically meaningful improvement in health-related QoL with denosumab relative to zoledronic acid, regardless of baseline pain levels [65].

It is recommended to start zoledronic acid or denosumab in all patients with metastatic breast cancer and bone metastases, whether they are symptomatic or not [34].

prostate cancer. Zoledronic acid is the only bisphosphonate to demonstrate a significant reduction in skeletal complications from bone metastases in patients with advanced prostate cancer. In a placebo-controlled study of 643 patients with CRPC, zoledronic acid was significantly more effective than placebo across all primary and secondary end points including fewer SRE(s) (33% versus 44% with placebo; $P = 0.021$), and a 4-month prolongation in time to first skeletal complication ($P = 0.011$) [35]. Using the Andersen–Gill multiple-event analysis, zoledronic acid reduced the overall risk of skeletal complications by 36%, and reduced bone pain at all time points.

In a placebo-controlled double-blind study comparing denosumab to zoledronic acid for the prevention of skeletal morbidity in men with bone metastases from CRPC, superiority in terms of time to first SRE and cumulative mean number of SREs with denosumab was achieved. The time to first SRE was extended from 17.1 to 20.7 months (HR 0.82, 95% CI 0.71–0.95; $P = 0.008$ for superiority) [37]. Second and subsequent SREs were also delayed, resulting in an 18% reduction in cumulative SREs.

It is recommended to start zoledronic acid or denosumab in all patients with CRPC and bone metastases, whether they are symptomatic or not [34].

other solid tumours. Data on the use of bone-targeted agents in lung cancer and other solid tumours are more limited than for breast and prostate cancers and MM. However, in a placebo-controlled trial of zoledronic acid in 773 patients with skeletal metastases from cancers other than breast and prostate, treatment with zoledronic acid significantly reduced the number of SREs (38% versus 47%) and prolonged the time to first event (230 versus 163 days) [66].

Denosumab has also been studied in this population of patients with metastatic bone disease. A phase III trial compared denosumab and zoledronic acid in 1776 patients with bone metastases from a solid tumour or MM other than breast or prostate cancer [40% non-small-cell lung cancer (NSCLC), 10% MM, 9% renal cell carcinoma, 6% small-cell lung cancer (SCLC), 35% other tumour types]. Denosumab extended the time to first SRE from

16.3 to 20.6 months and achieved the primary end point of confirming non-inferiority of denosumab for the study as a whole [38]; additionally, an *ad hoc* analysis of the solid tumour patients (excluding MM) did confirm superiority of denosumab over zoledronic acid (HR 0.81, 95% CI 0.68–0.96; $P=0.017$) [67]. Furthermore, an exploratory analysis of the 811 patients with lung cancer (including 702 with NSCLC and 109 with SCLC), showed that treatment with denosumab was associated with a small but statistically significant improvement in OS (median 8.9 versus 7.7 months, HR 0.80, 95% CI 0.67–0.95) [68].

Zoledronic acid or denosumab are thus recommended in selected patients with advanced lung cancer, renal cancer and other solid tumours with bone metastases [34]. Patients should be selected if they have a life expectancy of more than 3 months and are considered at high risk of SREs.

multiple myeloma. The Cochrane Myeloma Review Group concluded that both pamidronate and clodronate reduce the incidence of hypercalcaemia, the pain index and the number of vertebral fractures in myeloma patients [69]. The typical dose of pamidronate is 90 mg every 3–4 weeks, but a recent study of patients with newly diagnosed MM suggested that pamidronate 30 mg monthly achieved comparable time to first SRE and SRE-free survival time, compared with pamidronate 90 mg monthly [70]. Patients received pamidronate for at least 3 years in this trial; over this time frame, there was a trend toward lower risks of osteonecrosis of the jaw (ONJ) and nephrotoxicity in the low-dose group. Zoledronic acid has been shown to have a comparable efficacy to pamidronate in a randomised phase III trial including myeloma patients [32, 33].

The superiority of zoledronic acid over clodronate was demonstrated in the Medical Research Council Myeloma IX trial conducted in 1960 patients with newly diagnosed MM. A significantly smaller proportion of patients receiving zoledronic acid developed SREs before progression (27.0% versus 35.3% for clodronate; $P<0.001$) [71]. Zoledronic acid reduced the risk of SREs by 26% relative to clodronate (HR 0.74; $P<0.001$). Reduction in the risk of any SRE was shown in zoledronic acid-treated patients with and without bone lesions at baseline compared with clodronate-treated patients. Most importantly, this study demonstrated that, in comparison to clodronate, the addition of zoledronic acid to standard first-line anti-myeloma therapy reduced the risk of death by 16% ($P=0.012$) and prolonged median OS by 5.5 months (50 versus 44.5 months) and median progression-free survival by 2 months (19.5 versus 17.5 months) [72].

Denosumab has been studied in only a limited number of myeloma patients contained within a much larger phase III trial including patients with the range of tumours other than breast or prostate associated with bone metastases [38]. In an *ad hoc* analysis of OS in this subgroup of patients with myeloma, there was an unfavourable trend for possible worse survival with denosumab [73]. As a result, denosumab does not have regulatory approval for the treatment of MM and further studies are ongoing.

practical recommendations

The choice of the bone-targeting agent to be administered remains open. The recent guidelines from the American Society of Clinical Oncology (ASCO) state that there is insufficient

evidence to recommend one bone-modifying agent (zoledronic acid, pamidronate, denosumab) over another in the management of metastatic bone disease in breast cancer [74]. However, while the greater efficacy of zoledronic acid compared with pamidronate in breast cancer could only be shown by *post hoc* multiple event analyses [33], this is not the case for the comparisons between zoledronic acid and denosumab, in which the greater efficacy of the latter was demonstrated in various classical pre-specified end points.

There is a lack of consensus regarding the optimal duration of treatment. It is now recommended to start bisphosphonates or denosumab as soon as bone metastases are definitively diagnosed in order to delay the first SRE and reduce subsequent complications from metastatic bone disease. ASCO guidelines recommend that, once initiated, *i.v.* bisphosphonates should be continued until there is a substantial decline in the patient's general performance status [74]; however, criteria are lacking to determine whether and for how long an individual patient benefits from bone-targeted therapy. Stopping zoledronic acid therapy after several years, at least temporarily, or reducing the frequency of the infusions (e.g. an infusion every 3 months) are often considered in patients whose bone disease is not 'aggressive' and is well controlled by the antineoplastic treatment. However, ongoing treatment is recommended for patients with progression of underlying bone metastases, a recent SRE and/or elevated bone resorption markers.

There are no prospective data on the validity of intermittent treatments, and data on reduction in the frequency of zoledronic acid infusions are limited. The ZOOM trial randomly assigned 425 patients, after completion of 12–15 months of monthly treatment with zoledronic acid, in a 1:1 ratio to either continue treatment every 4 weeks or extend to 12-week treatment intervals for at least 1 year [75]. The skeletal morbidity rate was 0.26 (95% CI 0.15–0.37) in the 12-week group versus 0.22 (95% CI 0.14–0.29) in the 4-week group, suggesting that the 12-week schedule was similar in efficacy to the 4-week schedule, at least during the first year after monthly treatment. However, non-inferiority could not be established within this relatively small study. Furthermore, higher bone turnover levels were seen with the 12-weekly schedule [75]. In the BISMARCK trial, a bone marker-directed schedule of zoledronic acid was compared with standard 3- to 4-weekly treatment in 289 patients. Multivariate analysis for all SREs showed an HR for marker-directed versus standard treatment of 1.41 (90% CI 0.98–2.02; $P=0.12$) and non-inferiority could not be established. NTX levels were significantly higher at all time points with the marker-directed schedule [76].

The pharmacokinetics of denosumab argues against intermittent treatments. Unlike bisphosphonates, denosumab is not stored in bone and interrupting its administration is probably not without risks, at least if the bone disease is not well controlled by the antineoplastic treatment. Based on current knowledge of its pharmacodynamics and systemic distribution, denosumab for metastatic bone disease appears to require continuous monthly therapy [77].

ASCO guidelines recommend starting bisphosphonates in myeloma patients with lytic disease on plain X-rays or imaging studies, or with spine compression fracture(s) from osteopaenia [78]. The panel considered it to be 'reasonable' to start

bisphosphonates in patients with osteopaenia based on plain radiographs or BMD measurement, but did not recommend them in patients with solitary plasmacytoma or smouldering or indolent myeloma [78]. More recent guidelines recommend more widespread use of bisphosphonates. The European Myeloma Network (EMN) also firmly recommends starting bisphosphonates upon detection of severe osteopaenia/osteoporosis [79]. According to the recent recommendations of the International Myeloma Foundation's International Myeloma Working Group (IMWG), bisphosphonates should similarly be initiated in patients with MM, with or without detectable osteolytic bone lesions on conventional radiography [80].

The three expert myeloma groups recommend only i.v. pamidronate or zoledronic acid, and consider that both drugs are equally effective in terms of reducing SREs. The EMN guidelines advise that bisphosphonates should be given for 2 years and continued only if there is evidence of active myeloma bone disease [79]. Along the same line, ASCO recommends treating physicians to consider discontinuing bisphosphonates in patients with responsive or stable disease after 2 years of therapy [78]. Bisphosphonates should then be resumed upon relapse with new-onset SREs. Recent recommendations from the IMWG are in agreement [80]. A consensus from the Mayo Clinic advises decreasing the frequency of the infusions to every 3 months if bisphosphonates are continued after 2 years but there are no prospective trials data to support this guideline [81].

safety aspects

Both bisphosphonates and denosumab are generally well-tolerated treatments. However, zoledronic acid is associated with more episodes of acute phase response and renal dysfunction than denosumab, while hypocalcaemia is more frequent and more likely to be symptomatic with denosumab [82]. It is important that physicians strongly advise patients to take calcium and vitamin D supplements and regularly monitor serum calcium levels, especially in denosumab-treated patients.

The most important adverse event associated with prolonged administration of potent inhibitors of bone resorption is ONJ. The definition, diagnosis and follow-up of ONJ have been reviewed by an American Society for Bone and Mineral Research task force and various experts [83, 84]. ONJ is more common when i.v. bisphosphonates or denosumab are administered on a monthly basis for control of metastases, and is much less frequent with less intensive use of bisphosphonates or denosumab for preservation of bone mass, for example oral bisphosphonates or use of 6-monthly basis parenteral treatment [84].

In the pre-specified, integrated analysis of the three phase III denosumab trials, the incidence of ONJ did not differ significantly between the denosumab and zoledronic acid-treated groups [45]. Of 5372 patients, 89 (1.6%) were determined to have ONJ; 37 of these (1.3%) had received zoledronic acid and 52 (1.8%) had received denosumab ($P=0.13$) [45]. However, the risk of ONJ increases with time and reaches 5% when denosumab is continued beyond 3 years. The clinical characteristics of ONJ cases were similar between treatment groups. ONJ management was mostly conservative, and healing occurred in more

than one-third of patients. Evidence is insufficient to conclude that discontinuing zoledronic acid or denosumab therapy will facilitate the resolution of ONJ. Most of the patients with confirmed ONJ had a history of tooth extraction (62%), poor oral hygiene and/or use of a dental appliance [45]. Before zoledronic acid or denosumab therapy is initiated, patients should undergo an oral examination and appropriate preventive dentistry, and be advised on maintaining good oral hygiene. Patients should avoid invasive dental procedures (extractions and implants) during therapy if possible.

The side-effects of bisphosphonates in myeloma patients are similar, although particular attention should be paid to the potential renal toxicity of bisphosphonates and renal monitoring. The product label advocates stepwise dose reductions when baseline creatinine clearance is 30–60 ml/min, and zoledronic acid is not recommended in patients with severe renal deterioration or those taking nephrotoxic medications. The frequency of ONJ in MM patients may be higher than in those with solid tumours.

role of bone-targeted treatments to prevent metastasis

Improvements in both disease-free survival (DFS) and OS in women with early breast cancer have been demonstrated in several large randomised adjuvant trials of either oral clodronate or i.v. zoledronic acid. The evidence for a beneficial impact on disease outcomes is particularly strong in patients with low levels of reproductive hormones, including premenopausal women receiving ovarian suppression therapy and those who have passed through menopause at the time of diagnosis.

Results from the Austrian Breast and Colorectal Cancer Study Group trial-12 (ABCSG-12) trial showed that zoledronic acid treatment every 6 months for 3 years significantly improved DFS in premenopausal women with endocrine-sensitive early-stage breast cancer treated with ovarian suppression therapy (goserelin) and tamoxifen or anastrozole [85]. Updated results from this trial at a median of 84 months follow-up showed that the improvement in DFS with adjuvant zoledronic acid treatment was maintained (HR 0.71, 95% CI 0.55–0.92; $P=0.011$) and that OS was improved [86].

Improvements in DFS and OS were also reported in the cohort of patients with established menopause (>5 years since last menstrual period) treated in the AZURE trial [47]. In this study, 3360 patients with stage II or III breast cancer (unselected by menopausal status or oestrogen receptor expression) were randomly assigned to receive standard adjuvant systemic therapy with or without zoledronic acid every 3–4 weeks for six doses, then every 3–6 months thereafter, for a total of 5 years. Although no benefits in DFS were seen in the population as a whole, pre-specified subgroup analyses after a median follow-up of 59 months showed a significant improvement in DFS with zoledronic acid in the 1041 patients with established menopause. Five-year invasive DFS was 71% in the control arm and 78% in those treated with zoledronic acid (adjusted HR 0.75, 95% CI 0.59–0.96; $P=0.02$).

A study-level meta-analysis of postmenopausal women treated with adjuvant bisphosphonates showed an 18%

improvement in DFS (HR 0.82, 95% CI 0.74–0.92; $P \leq 0.001$), with reductions in relapse rates not only in bone but also at extra-skeletal and locoregional sites [87]. The Early Breast Cancer Trials Collaborative Group is conducting a formal individual patient meta-analysis in more than 22 000 women involved in randomised trials of adjuvant bisphosphonates for early breast cancer; preliminary results indicate a consistent benefit in postmenopausal women with a 34% reduction in risk of bone recurrence ($P = 0.00001$) and a 17% reduction in risk of breast cancer death ($P = 0.004$) [88]. However, there were no effects on breast cancer recurrence or mortality in women who were still menstruating. If these results are maintained when the peer-reviewed publication appears, the use of adjuvant bisphosphonates is likely to become part of routine clinical practice but should be restricted to postmenopausal women.

Prostate cancer spreads predominantly to bone and provides an ideal clinical setting for the evaluation of bone-targeted treatments. In men with CRPC but no evidence of overt metastases (rising prostate-specific antigen), denosumab significantly increased bone metastasis-free survival by a median of 4.2 months over placebo (HR 0.85; $P = 0.028$), and delayed time to symptomatic first bone metastases, but had no impact on OS [50].

treatment algorithm for the prevention of bone loss

Several guidelines recommend that women with breast cancer receiving an aromatase inhibitor (AI) or ovarian suppression [89, 90] and men with prostate cancer undergoing ADT [91] should have their bone health monitored for fracture risk (Figure 2). BMD measurement should not be the sole criterion for determining fracture risk but an overall fracture risk assessment used that combines risk factors provides the most accurate evaluation [92]. The World Health Organisation Fracture Risk Assessment tool (FRAX) algorithm is valid for postmenopausal women and calculates the 10-year fracture risk with or without BMD measurement and includes several fracture-related risk factors, although anticancer treatments are not included as a specific risk factor [92].

To identify and manage secondary causes of osteoporosis, a comprehensive laboratory assessment is required and should include serum levels of calcium, phosphate, 25-hydroxyvitamin D, parathyroid hormone, haemoglobin, C-reactive protein, ALP, thyroid-stimulating hormone, creatinine clearance and protein electrophoresis (serum and/or urine) [18]. The consensus from expert panels recommended treatment with anti-resorptives in patients receiving AI therapy with a T -score < -2.0 or having

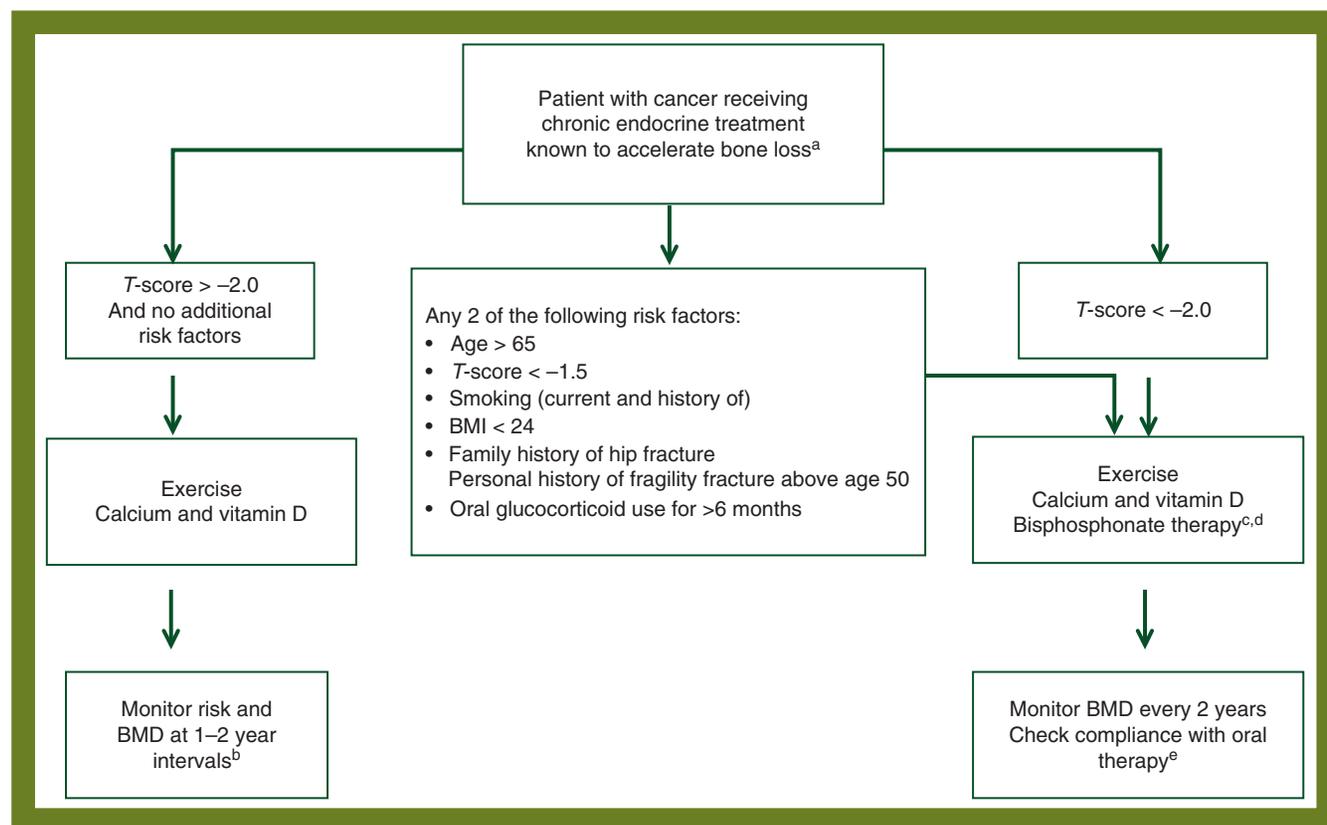


Figure 2. Recommended algorithm for managing bone health during cancer treatment. Adapted from Hadji et al. [18], with permission from Elsevier.

^aIncludes aromatase inhibitors and ovarian suppression therapy/oophorectomy for breast cancer and androgen deprivation therapy for prostate cancer. ^bIf patients experience an annual decrease in BMD of $\geq 10\%$ (or $\geq 4\%$ – 5% in patients who were osteopaenic at baseline) using the same DXA machine, secondary causes of bone loss such as vitamin D deficiency should be evaluated and antiresorptive therapy initiated. Use lowest T -score from spine and hip. ^cSix monthly i.v. zoledronic acid, weekly oral alendronate or risedronate or monthly oral ibandronate acceptable. ^dDenosumab may be a potential treatment option in some patients. ^eAlthough osteonecrosis of the jaw is a very rare event with bone protection doses of antiresorptives, regular dental care and attention to oral health is advisable. BMD, bone mineral density; BMI, body mass index.

Table 4. Summary of key points and levels of evidence for prevention and treatment recommendations**Incidence and clinical features**

- Bone metastases are especially prevalent in advanced breast and prostate cancers.
- Metastatic bone disease is a major cause of morbidity in cancer.
- Complications include pain, impaired mobility, pathological fracture, spinal cord compression, hypercalcaemia and suppression of bone marrow function.
- Cancer treatments may induce accelerated bone loss and increased fracture risk.

Pathophysiology

- Tumour cells home to the haematopoietic stem cell niches in bone, and may remain dormant for prolonged periods of time before progression to overt metastases.
- The cellular interactions within the bone marrow micro-environment are thought to be of great importance in tumour dormancy and metastasis.
- Osteolytic damage is mediated largely by stimulation of osteoclasts via tumour-derived cytokines.

Diagnosis

- Differential diagnosis includes osteoporosis, degenerative disease and Paget's disease of bone.
- The isotope bone scan is a sensitive test to detect the presence of skeletal pathology but gives little information about its nature.
- Structural information on skeletal damage from metastatic bone disease is best obtained by computerised tomography and magnetic resonance imaging.
- Positron emission tomography (PET) provides functional information that may aid in diagnosis.
- Dual-energy X-ray absorptiometry (DEXA) scans should be carried out in patients at risk for cancer treatment-induced accelerated bone loss.

Evaluation of the patient

- An assessment of patients' symptoms and activity status is essential.
- Skeletal radiography assesses response to treatment, but the information is delayed and the method insensitive.
- Isotopic bone scanning is not useful in monitoring response to treatment.
- Biochemical markers of bone metabolism may provide information on prognosis and response to bone-specific treatments but are not recommended for routine clinical use.

Treatment**Prevention of metastasis**

- Bisphosphonates reduce the frequency of bone metastases and improve survival in postmenopausal women (natural or induced) with breast cancer (I, A).
- Bisphosphonates do not improve disease outcomes in premenopausal women (I, A).
- Denosumab delays bone metastases in castrate-resistant prostate cancer (I, B).

Prevention of treatment-induced bone loss

- Bisphosphonates and denosumab prevent bone loss associated with use of ovarian suppression or aromatase inhibitors in early breast cancer and androgen deprivation therapy in prostate cancer (I, B).

Bone metastases

- Multidisciplinary management integrating expertise in systemic treatments, radiation therapy, orthopaedic surgery, radiology and supportive care including palliative medicine is required for effective treatment of metastatic bone disease (V, B).
- Radiotherapy is the treatment of choice for palliation of localised bone pain (II, B).
- Single fractions are as effective as fractionated radiotherapy for relief of pain (I, A).
- The bisphosphonates and denosumab are inhibitors of osteoclast activity that have become important agents for the treatment of metastatic bone disease, because they delay complications, relieve symptoms and improve quality of life (I, A).
- Zoledronic acid is the most effective bisphosphonate for prevention of morbidity from metastatic bone disease (I, B).
- Denosumab is more effective than zoledronic acid for prevention of skeletal morbidity from solid tumours (I, B).
- Bone-targeted therapy should be commenced at diagnosis of metastatic bone disease (III).
- Bone-targeted therapy for metastatic bone disease should continue indefinitely and throughout the course of the disease (III).

two or more clinical risk factors for fracture [89, 90]. However, the guidelines and algorithms base their recommendations on different cut-off points for *T*-score and age, while risk factors other than *T*-score are not used uniformly.

In premenopausal women, treatments may induce premature menopause or be specifically designed to suppress ovarian function and reduce circulating oestrogen levels. In addition to bone loss associated with low oestrogen levels, cytotoxic chemotherapy may also have a direct negative effect on bone metabolism. As a result, cancer treatment-induced bone loss poses a significant threat to bone health in premenopausal women with breast cancer. Current fracture risk assessment tools are based on data

from healthy postmenopausal women and do not adequately address the risks associated with treatments in younger premenopausal women. Guidance from expert groups for premenopausal women with breast cancer has been published and recommends that all premenopausal women be informed about the potential risk of bone loss before beginning anticancer therapy with use of anti-resorptives if the BMD *T*-score is < -2 [90, 93].

All patients receiving treatments that are known to adversely affect bone health should be advised to consume a calcium-enriched diet, exercise moderately (resistance and weight-bearing exercise) [94] and take 1000–2000 IU vitamin D every day (Table 2) [95].

The data from randomised clinical trials in >5000 patients show that bisphosphonates (both i.v. and oral) and denosumab administered at doses and schedules that approximate to those used for the treatment of postmenopausal osteoporosis can prevent bone loss in women with breast cancer [18]. Although these trials were not designed for a fracture-prevention end point, data from the osteoporosis setting have demonstrated a correlation between BMD improvements and fracture prevention. Therefore, data from the larger studies in this group may be considered as evidence for preserving skeletal health during therapy.

prevention of bone loss in prostate cancer

ADT leads to accelerated bone loss and an increase in fracture rate, as evidenced by large retrospective epidemiological studies [96, 97]. Alendronate, risedronate, pamidronate and zoledronic acid have all been shown to prevent loss in BMD in patients with locally advanced prostate cancer [98]. Of these treatments, 6–12 monthly zoledronic acid and 6-monthly denosumab are considered the most convenient and reliable treatments [51, 99]; however, only denosumab has a specific license for treatment-induced bone loss associated with ADT. In a placebo-controlled trial of denosumab in 1468 men receiving ADT for non-metastatic prostate cancer, 36 months of denosumab treatment was associated with a 62% relative reduction in new vertebral fractures (1.5% with denosumab versus 3.9% with placebo) [51]. BMD increased from baseline at all sites in the denosumab group but declined in the placebo group, leading to BMD differences of 6.7% at the lumbar spine and 4.8% at the total hip after 36 months.

special considerations in the elderly

Although anti-resorptive therapies are especially important for elderly patients with cancer, they are typically underutilised in this population [100]. Older age is associated with increased

risk for invasive malignancies, such as breast and prostate cancer, with a higher risk of bone metastasis. Underuse of anti-resorptive therapies may be more detrimental in elderly patients compared with younger patients because of multiple fracture risk factors, including physiological decreases in BMD and increases in vertebral fracture rate with increasing age [101]. Special considerations should be made for elderly patients who may have renal impairment from hypertension or diabetes and are likely to be taking more concomitant medications due to comorbid conditions. Careful monitoring of such comorbidities is essential to ensure the safety and comfort of elderly patients, especially during chemotherapy [102].

In addition to preventing SREs in the oncology setting, anti-resorptive therapies are indicated for fracture risk reduction in elderly patients with osteoporosis [103]. Although oral bisphosphonates such as risedronate and alendronate have demonstrated efficacy in the postmenopausal osteoporosis setting, their dosing schedule and strict dosing regimen can lead to poor patient compliance [104]. Alternatively, i.v. bisphosphonates can be considered; a single annual infusion of zoledronic acid has proven effective for the treatment of postmenopausal osteoporosis [105]. Thus far, no dose adjustments based on age have been suggested for denosumab, and this would be necessary only if safety issues (e.g. severe hypocalcaemia) developed.

personalised medicine

Results from ongoing clinical trials evaluating the potential application of bone markers to individualise care are awaited to identify the true value of bone markers in clinical practice [106].

note

A summary of recommendations is provided in Table 4. Levels of evidence and grades of recommendation have been applied using the system shown in Table 5. Statements without grading

Table 5. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System^a)

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

^aBy permission of the Infectious Diseases Society of America [107].

were considered justified standard clinical practice by the experts and the ESMO faculty.

conflict of interest

RC has received consulting and speaker fees from Amgen, Bayer, Celgene and Novartis and given expert testimony on behalf of Novartis. JJB has received consulting and speaker fees from Amgen and Novartis. MA has received consulting and speaker fees from Amgen, Bayer, Celgene, Roche and Novartis. PH has received consulting and speaker fees from Amgen, Pfizer, Astra Zeneca, Roche and Novartis and given expert testimony on behalf of Novartis. JH has reported no potential conflicts of interest.

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