

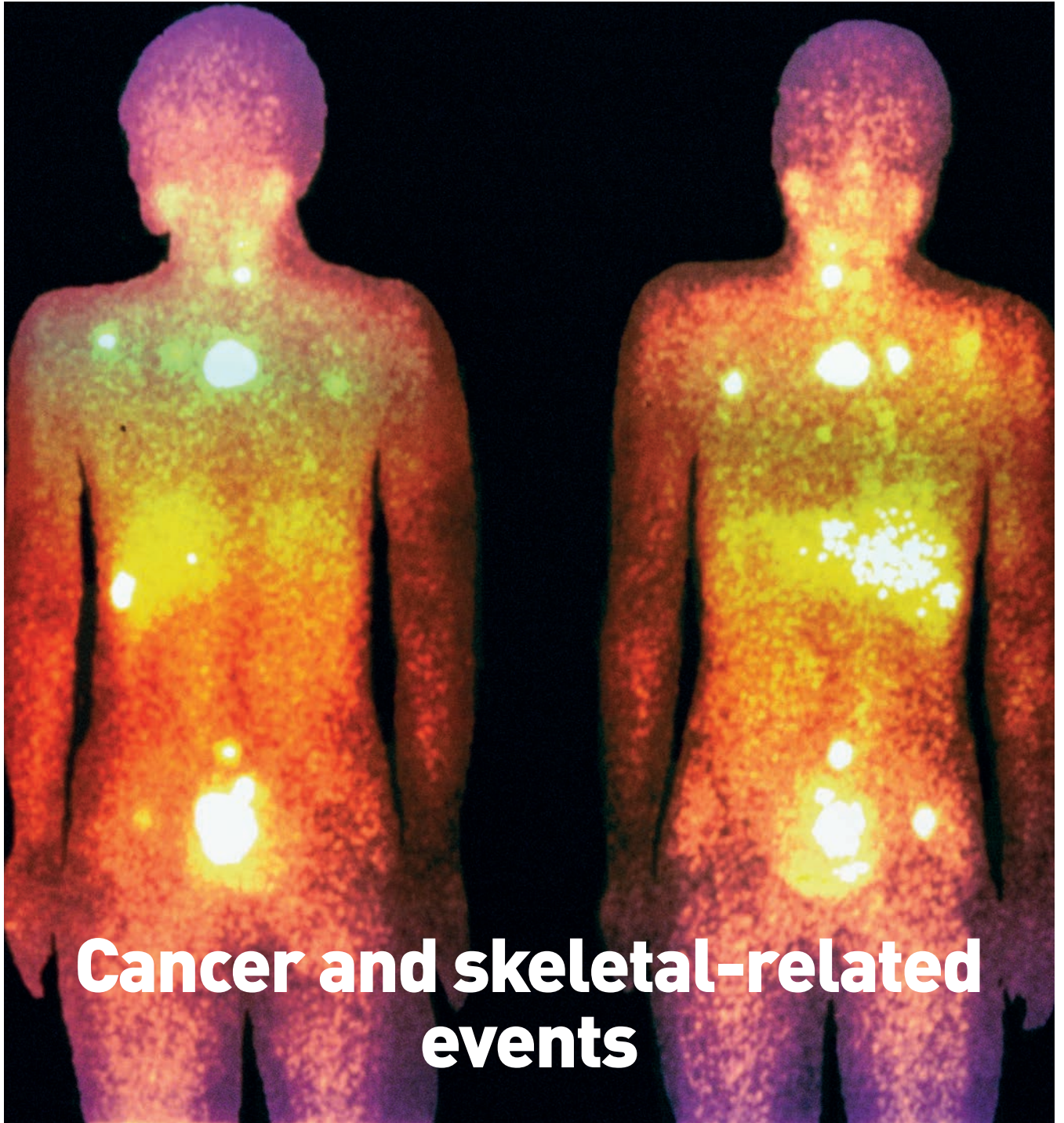
# HOSPITAL PHARMACY EUROPE

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# HANDBOOK

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## Cancer and skeletal-related events

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# Foreword

Bone metastases are a common complication of cancer. Metastatic bone disease can result in severe pain, fractures, hypercalcaemia, the need for radiotherapy treatment and, in some cases, spinal cord compression.

Drawing on the extensive experience of distinguished clinicians across Europe, this educational handbook from *Hospital Pharmacy Europe* comprehensively reviews metastatic bone disease and details how these skeletal-related events impact not only patients' quality of life and activities of daily living but also those of families and carers.

Metastatic bone disease is classified as osteoblastic or osteolytic based on radiological appearance, although both forms can occur simultaneously in many cases. In essence, bone metastases disrupt normal bone physiology, resulting in remodelling.

The apparent collusion of bone cells with tumour cells to facilitate the process is somewhat surprising, and to set the scene, Professor Carsten Bokemeyer reviews the complex pathophysiology involved and the ensuing burdens placed on healthcare services.

The impact of bone metastases encompasses financial costs to health services and individuals; they affect the quality of life, impose an emotional burden and have mental health implications, including grief, depression, body image concerns, fear of recurrence, survivor guilt, workplace concerns, anxiety and relationship issues. Caregivers are also affected: they, too, are prone to significant psychological stress and may suffer from depression and anxiety as a result of looking after someone with cancer.

The rich arterial supply of the bone makes it a common site of metastatic spread. The skeleton is the third most common site of disease after the lung and liver. Bone is a particularly prevalent site of metastases in certain tumour types, the most prominent being prostate and breast cancer. Professor Peyman Hadji reviews the osteophilic nature of these cancers and how they affect changes in bone mineral density and emphasises how optimal management of skeletal health is an increasingly important part of cancer care. He also considers how certain treatments may be implicated in the loss of bone integrity and their adverse effects on the skeleton.

Many bone metastases can be asymptomatic. However, historically, it has been estimated that 50% of patients with bone metastases will develop a complication without bone-directed treatment. This, coupled with the cost of metastatic bone disease, both in monetary terms and in health and quality of life, is a key driver in the search for new and improved methods of prevention and treatment of metastases.

To this end, Professor Mario Di Palma discusses how a deeper knowledge of the mechanisms underlying metastases



onset has led to the development of effective therapeutic agents, such as anti-resorptive drugs. Although these medications are usually well tolerated, adverse events can arise with their use, and these challenges are also discussed.

Finally, Professor Cyrille Confavreux highlights crucial concepts surrounding the holistic management and supportive care of patients with bone metastases. He discusses how holistic management requires a precise, personalised goal for each patient and the significant challenges clinicians face, which must be addressed to ensure effective treatment. Care optimisation also depends on clinicians thoroughly appreciating the complementary benefits of the various management strategies and their limitations.

Some cases may be more straightforward to manage than others. However, complex cases will benefit from the involvement of medical oncologists, rheumatologists, osteoarticular radiologists, orthopaedic/spine surgeons, radiation oncologists, nuclear medicine physicians and palliative care/pain specialists. Therefore, a multidisciplinary approach to management is essential to ensure the proper integration of local and systemic therapies.

We hope you find this handbook interesting, informative, and a valuable resource for supplementing your knowledge on critical issues related to the complexities of osteoporosis and bone fragility in metastatic malignant disease.

Thank you for reading!

# Pathophysiology of bone metastases: clinical implications and burden

Metastatic bone disease disrupts bone physiology, resulting in pain, fractures, hypercalcaemia, the need for radiotherapy treatment, and, in some cases, spinal cord compression – these are termed skeletal-related events. Here, we review the pathophysiology of bone metastases and consider the impact and burden on patients, their caregivers, the health service, and society

**Carsten Bokemeyer MD**

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Metastatic bone disease is classified as osteoblastic or osteolytic – based on its radiological appearance, although in many cases both forms can actually occur simultaneously.<sup>1</sup> The classification is made according to the characteristic radiographic appearances of the lesions based on the predominance of lysis or sclerosis in the bone.<sup>2</sup> How likely cancer cells are to be malignant depends on their ability to metastasise, thus to pass over the basement membrane and extracellular matrix surrounding the primary cancer, invade surrounding tissues, and enter the lymphatic system and the bloodstream as well as on their potential to seed within other organs and proliferate there successfully.<sup>1</sup>

## Spotlight on pathophysiology

In essence, bone metastases disrupt normal bone physiology, resulting in remodelling. In osteolytic bone metastasis, typically seen, e.g., in breast cancer, the differentiation and function of osteoclasts is stimulated, and osteoblast function is reduced. In contrast, osteoblastic metastases, typically occurring in prostate cancer, involve increased osteoblast function and differentiation, while osteoclast activity is reduced. The result is a net gain of bone tissue.<sup>3</sup>

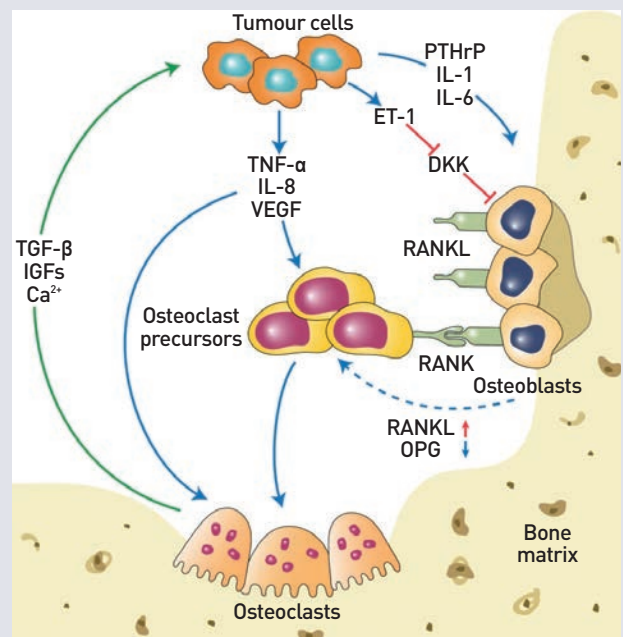
Cancer cells reach the site of the metastasis via blood circulation and can move out of the blood vessels and into the extracellular space around the bone. The process is facilitated in the bone marrow because the sinusoidal blood vessels there are fenestrated and lack capillaries that usually serve as a supporting structure. This particular architecture makes extravasation of tumour cells through the vessel walls more likely. Once penetrating through the vessel wall, the tumour cells can form a stable cell mass by mechanical adhesion using the cytokine CXCL 12, also known as a stromal-derived factor 1.<sup>3</sup>

Osteocytes – the most common bone cells – attract tumour cells to the bone by excreting CXCL 12. They have several other effects on tumour cells; for example, they downregulate Snail, a factor involved in the epithelial-to-mesenchymal transition, encouraging epithelial traits and tumour cell colonisation of the bone.<sup>3</sup>

Some osteocytes inhibit osteoblast activity by secreting dickkopf 1 (DKK1) and sclerostin, factors involved in bone turnover regulation, which favours bone degradation in metastatic bone disease, and direct contact between osteocytes and tumour cells establish Notch signalling, which induces osteocyte apoptosis and enhances tumour cell proliferation.<sup>3</sup>

**FIGURE 1**

## The development of osteoclastic and osteoblastic bone metastases



**Ca<sup>2+</sup>**, calcium; **DKK1**, dickkopf 1; **ET-1**, endothelin-1; **IGFs**, insulin-like growth factors; **ILs**, interleukins; **PTHrP**, parathyroid-hormone-related peptide; **RANKL**, receptor activator of nuclear factor- $\kappa$ B ligand; **TGF- $\beta$** , transforming growth factor-beta; **TNF- $\alpha$** , tumour necrosis factor-alpha; **VEGF**, vascular endothelial-like growth factor

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Prostate cancer preferentially metastasises to bone. As well as an ongoing osteolytic component, there are also typically osteoblastic lesions associated with prostate cancer metastases, which lead to an increase in bone formation. However, despite the osteoblastic appearance, this erratic bone formation process results in a weak structure prone to pathological fractures.<sup>4</sup>

Figure 1 shows some cytokines and receptors activated in the formation of osteoclastic and osteoblastic bone metastases.

### Example of invasion, colonisation and proliferation in prostate cancer bone metastasis

A number of steps are involved in the process leading to metastases, including the invasion, colonisation, and proliferation of prostate cancer cells in the bone microenvironment.<sup>4</sup> Prostate cancer cells interact with all bone components, including osteoblasts, osteoclasts, osteocytes, and bone matrix, through paracrine, autocrine, and inhibitory mechanisms. They secrete osteoclast-activating factors, such as RANKL (receptor activator of nuclear factor- $\kappa$ B ligand), that activate bone resorption.

Osteolysis releases prostate cancer growth-promoting factors from the bone matrix, including transforming growth factor-beta (TGF- $\beta$ ), insulin-like growth factor-1 (IGF-1), matrix metalloproteinases (MMPs), fibroblast growth factors (FGFs), bone morphogenetic proteins (BMPs), and platelet-derived growth factors (PDGFs) thus providing advantages for cancer cell proliferation. A variety of other cancer-derived and bone cell-derived secretory factors contribute to the osteolytic phase of prostate cancer bone metastases. Prostatic acid phosphatase (PAP) secreted by prostate cancer cells in bone indirectly inhibits osteoclasts by decreasing RANKL while increasing osteoprotegerin in the bone niche.<sup>4</sup>

Prostate cancer cells also interact with all bone components during the osteoblastic phase. Prostate cancer-derived soluble factors such as endothelin-1 (ET-1), TGF- $\beta$ , u-plasminogen activator (uPA), IGF-1, FGFs and BMPs have been shown to induce the dysfunctional osteoblastic phenotype. High levels of osteoprotegerin are associated with end-stage osteoblastic bone metastases. PAP secreted by prostate cancer cells in bone has autocrine and paracrine effects that together result in higher osteoprotegerin/RANKL in the bone niche, leading to osteoblastic lesions.<sup>4</sup>

### Common sites for bone metastases

Bone is a frequent site of metastases in many tumour types, the most prominent being prostate and breast cancer. It is overall the third most frequent site for metastases to occur after lung and liver in cancer patients.<sup>2,5</sup> Among haematological malignancies bone is most frequently affected in multiple myeloma patients.

Sites in the skeleton where metastases most commonly occur include:<sup>5</sup>

- Spine
- Pelvis
- Ribs
- Skull
- Upper arm
- Femur.

The relative incidence of bone metastasis by type of tumour in patients with advanced metastatic disease is 65–75% breast cancer; 65–75% prostate, 60% thyroid; 30–40% lung, 40% bladder; 20–25% renal cell carcinoma; and 14–45% melanoma.<sup>5</sup> Furthermore, the incidence of detected bone metastases may also depend on the method of detection, being lower for conventional X-ray compared with PET-CT, bone scintigraphy or specific MRT techniques.

### What are the complications?

Skeletal-related events (SREs) are a result of the five major complications of bone cancer: pathological fracture, spinal cord compression, hypercalcaemia, radiation bone to relieve pain or reduce structural damage, and surgery to repair a fracture.<sup>2</sup>

Bone pain is experienced by 60–84% of patients who have bone metastases. Initially, the pain may be dull and continuous, but it becomes more severe as the cancer progresses.<sup>6</sup>

The presence of bone metastases has been linked with the development of cachexia, a potentially fatal syndrome that results from an accumulation of symptoms, including extreme weight loss, anorexia, muscle wasting, and fatigue.<sup>6</sup>

Hypercalcaemia is the most common metabolic complication of malignancy. It occurs in approximately 20% of all cancer patients.<sup>7</sup> Hypercalcaemia may occur with or even without the presence of bone metastases. Still, in all cases the increased calcium blood levels result from release from bone structures. The main mechanisms leading to hypercalcaemia are either excessive paracrine secretion of parathyroid-related protein from the tumour – without the necessary presence of bone metastases or, by contrast, bone metastases releasing osteoclast-activating factors. Additionally, the production of calcitriol (1,25-dihydroxy vitamin D), which increases both bone resorption and intestinal calcium absorption, may contribute to hypercalcaemia.<sup>5</sup>

If left untreated, hypercalcaemia causes symptoms such as nausea, constipation, fatigue, polydipsia and polyuria.<sup>5</sup>

Finally, as bone metastases tend to affect red blood cell production sites in the bone marrow, anaemia may also be a feature of patients with metastatic bone disease.<sup>8</sup>

### Risk of SREs

The incidence of SREs in patients with bone metastases is highest among people with breast cancer and multiple myeloma. The proportion of people with bone metastases who experience SREs varies by cancer type and the same holds true whether the event is a fracture, hypercalcaemia, spinal cord compression or the need for surgery or radiotherapy (see Table 1).<sup>2</sup>

Hospital data for Spain between 2000 and 2006 show that the incidence rates for patients developing a skeletal-related event following a diagnosis of metastatic bone disease were 211 per 1000 (95% CI 183–242) for breast cancer, 260 per 1000 (95% CI 236–285) for lung cancer (males 260 per 1000 [95% CI 234–288]; females 258 per 1000 [95% CI 198–332]), and 150 per 1000 (95% CI 131–171) for prostate cancer.<sup>9</sup> Thus overall about 15–25% of patients with bone metastases will experience at least one SRE.

### Economic burden of SREs/metastases

A study of cancer patients in Belgium whose data were retrieved from the IMS hospital disease database from 2005–2007 found the average cost per single SRE type for all solid tumour types was €5,015 for a vertebral fracture; €7,087 for a non-vertebral fracture; €15,267 for spinal cord compression; €12,885 for surgery to bone, and €2,653 for radiation to bone. The costs were extrapolated to 2010 using the progression in hospitalisation costs since 2001.<sup>10</sup>

A study involving health insurance claims data in Germany collected between the beginning of 2010 and June 2018 found that just under half (45.20%) of 9,832 patients with advanced cancer who had not been treated with bone-targeting drugs had had at least one bone metastasis from solid tumours.<sup>11</sup> When 2434 pairs of patients – those with a SRE and those without – were compared, it was found that there were significant differences in the average number of hospitalisation days per patient-year (35.80 compared with 30.80) and associated inpatient-care costs (€14,199.27 compared with €10,787.31). The average cost per patient-year was €23,689.54 for patients with SREs compared to €20,403.27 for those without.<sup>11</sup> Of course, it must be kept in mind that the occurrence of SREs may also be a sign of a more advanced cancer stage.

Data from the US suggest that the annual cost of care attributed to skeletal metastases was around US\$18,272 for →

TABLE 1

Percentage of patients experiencing SREs with different cancer types<sup>2</sup>

|                    | Skeletal-related event | Fracture | Need for radiotherapy | Hypercalcaemia | Spinal cord compression | Need for surgery |
|--------------------|------------------------|----------|-----------------------|----------------|-------------------------|------------------|
| <b>Cancer type</b> |                        |          |                       |                |                         |                  |
| Breast*            |                        | 49%      | 33%                   | 12%            | 4%                      | 10%              |
| Prostate           |                        | 25%      | 33%                   | –              | 8%                      | –                |
| Multiple myeloma   |                        | 37%      | 34%                   | 9%             | –                       | –                |

\* Before the introduction of bone-targeted treatments, at 1-year follow-up

each patient, according to a paper published in 2015.<sup>12</sup> It is estimated that bone metastases account for up to 20% of the total cost of oncological care, being driven by the costs for the treatment of SREs. For example, a study from Spain published in 2014 put the mean price of one skeletal-related event in people with metastatic bone disease at US\$2,684 to US\$8,923.<sup>12</sup> In another paper from Spain published in 2010, the cost of hospital admission was found to rise from an average of US\$2,775 for a first admission for breast, prostate or lung cancer to US\$4,112 for a first admission with metastatic bone disease and finally for US\$4,382 for a first admission with a skeletal-related event.<sup>12</sup> So overall, there is no question that bone metastases are a factor in increasing the cost of care for cancer patients.

#### Functional and social impact on patients

The median survival after being diagnosed with bone metastases is approximately one year for patients with lung cancer and up to three to five years for people with breast cancer, prostate cancer or multiple myeloma.<sup>2</sup>

Pain is frequently the first symptom patients with metastatic bone disease experience, and the greater the pain, the higher the level of functional impairment and lower health-related quality of life scores when measured, e.g. by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core (EORTC QLQ-C30). Patients with severe pain had a 21-point reduction in Global Health Status (GHS) score/QOL (using the EORTC QLQ-C30, where the total possible score is 100) compared with those who had no bone pain or only mild or moderate bone pain ( $p < 0.05$ ) and an 18-point reduction in their physical functioning score compared with those with mild or no bone pain ( $p < 0.05$ ).<sup>13</sup> Cancer pain also impacts general activities, mood, walking ability, work and overall enjoyment of life.<sup>14</sup> Pain experienced by those with metastatic bone cancer is caused by inflammation and bone remodelling, which results in nociceptive pain or by damage to or dysfunction of the nervous system, leading to neuropathic pain due to tumour invasion. Patients often experience both types of pain.<sup>13</sup>

As well as an impact on quality of life, cancer survivors may also go through significant financial hardship.<sup>15</sup>

A systematic review of 45 US studies published between 1990 and 2015 found that the mean annual indirect cost to patients ranged from \$380 in a sample of prostate cancer survivors (year of dollars not stated) to \$8,236 in breast cancer survivors (at 2,000 US\$ prices). Indirect costs/productivity loss as the loss of income included missed or lost days from work because of illness (i.e., absenteeism, short- and long-term

disability, days spent in bed), patient time costs and limitations in the ability to do activities related to work and outside of work.<sup>16</sup> The reviewers also found that 12–62% of survivors reported being in debt as a result of their treatment, 48% said they experienced financial distress, and 4–45% of survivors did not take their recommended prescription medicines because of the cost.<sup>16</sup> Indeed, these data were generated in the US health care system; however, there are also data from European cancer survivors indicating a financial burden of disease, even so with a somewhat lower magnitude compared to US data. However, data on the specific effect of bone metastases on the financial impact of a cancer diagnosis, treatment and follow-up has not been separately analysed.

Finally, people with cancer can be significantly affected by emotional and mental problems, including grief, depression, body image concerns, fear of recurrence, spiritual guidance, survivor guilt, workplace concerns, anxiety and relationships.<sup>12,15</sup>

#### Family/caregiver impact

Caregiver burden varies according to a range of factors, including the type and stage of cancer as well as the long-term prognosis of the patient they are looking after. Many caregivers who are working will have to give up some time in employment to care for a patient with cancer, which carries with it a loss of earnings. Caregivers are also prone to significant psychological stress and may suffer from depression and anxiety as a result of looking after someone with cancer.<sup>12,17,18</sup>

Caring for someone with spinal metastases, for example, can be physically exhausting and may lead to caregivers neglecting their health, being unable to manage work-life burdens and social burdens adequately, and even falling short in their parental roles and relationships. Lack of sleep can also contribute to these problems.<sup>19</sup>

A descriptive cross-sectional study of 121 patients with prostate cancer and at least one bone metastasis and their caregivers was conducted to evaluate caregiver burden and quality of life using the ZCBI Caregiver Burden Interview (ZCBI) and Short Form 36 (SF-36). The number of bone metastases affected all questionnaire results ( $p < 0.001$  –  $p = 0.013$ ). SF-36 and ZCBI questionnaire results were worse in cases with complications resulting from bone metastases ( $p < 0.001$  –  $p = 0.044$ ).<sup>20</sup>

#### Hospital and healthcare burden

Patients with bone metastases are likely to need significant levels of health care relating to the management of SREs. Therefore, their treatment and care are likely to be associated

with substantial levels of healthcare resource needs. This becomes true in particular since the overall prognosis of patients with advanced cancers has significantly improved over the last years with several new treatment options including personalised therapies and immunotherapy thus transforming metastatic disease in a more chronic health condition. The longer survival times increase, the more SREs become likely and more relevant.

In a cohort study, people diagnosed for the first time with lung cancer and bone metastases from 2003 to 2009 were identified in the Danish Cancer Registry and the Danish National Registry of Patients and followed until the end of 2010 to determine who had SREs, i.e. spinal cord compression; pathological or osteoporotic fracture; surgery to bone, or conventional external radiation therapy.<sup>21</sup>

In the cohort of 28,443 patients with lung cancer, 1,668 had bone metastases. Of those with bone metastases, 1,146 had at least one SRE.

Of the patients with SREs (n=852), over 75% had more than one SRE. The number of hospital bed-days was high following an SRE (28.2 per 100 person-days) compared with the period before the event (10.7 per 100 person-days);

For patients with one SRE, inpatient bed days numbered 3,448 before and 3,538 after the SRE. For those with more than one SRE, there were 8,308 inpatient days before compared with 17,914 after the events. Similarly, outpatient clinic visits were higher for people with more than one SRE before the event (3,961) compared with 7,205 after the events; for those with one SRE, the values were 1,467 visits before and 1,075 after the event, respectively.<sup>19</sup>

Hospital data for Spain between 2000 and 2006 show that the length of stay in hospital for the first admission among people with bone metastases was 12–18 days for people with SREs and 9–11 days for patients with cancer and metastatic bone disease.<sup>9</sup>

Costs increase if the patient presents a bone metastasis or a skeletal-related event on first admission. The average cost of the first (index) admission for those with breast cancer was €2,374, with the average cost of the first admission with metastatic bone disease increasing to €3,515 and €3,757 for the first admission with an SRE. In contrast, for prostate cancer patients, the average costs were €3,194, €3,180 and €3,585, respectively. In comparison, the index admission cost for lung cancer patients was higher than subsequent admissions for metastatic bone disease or SREs (€4,994, €4,227, €4,298, respectively).<sup>9</sup>

## Key learning points

- Metastatic bone disease is classified as osteoblastic or osteolytic disease, although bone metastases in most cancer types usually lie somewhere between these two ends of the spectrum. The classification is made according to the characteristic radiographic appearances of the lesions based on the predominance of lysis or sclerosis in the bone.
- Bone metastases disrupt normal bone physiology, resulting in remodelling.
- Bone is a frequent site of metastases in many tumours, in particular in prostate and breast cancer. It is overall the third most frequent site for metastases to occur after lung and liver.
- SREs include the five major complications of bone cancer: pathological fracture, spinal cord compression, hypercalcaemia; radiation bone to relieve pain or reduce structural damage, and surgery to repair a fracture.
- Bone pain is experienced by 60%–84% of patients with bone metastases. Initially, the pain may be dull and continuous, but it becomes more severe as the cancer progresses.
- Pain is frequently the first symptom patients with metastatic bone disease experience, and the greater the pain, the higher the level of functional impairment and lower health-related quality of life scores will be.
- Data from Spain published in 2014 found the mean cost of one skeletal-related event in people with metastatic bone disease to be US\$2,684 to US\$8,923.

## Conclusion

Bone metastases are found in several types of cancer, with a high predominance in breast and prostate cancer and multiple myeloma. Bone involvement in malignancies can result in health and well-being consequences for patients and may also impact their caregivers and health services and, as such, society as a whole.

The pathophysiology of bone metastases development is complex and the apparent collusion of bone cells with tumour cells to facilitate the process is somewhat surprising.

The cost of metastatic bone disease, both in monetary terms and in health and quality of life, strongly encourages the search for new and improved methods of prevention and treatment of metastases.

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# Osteophilic cancers: an introduction

Osteoporosis can lead to an increased risk of fracture with resultant loss of quality of life and higher dependence on health care resources so optimal management of skeletal health is an increasingly important part of cancer care. In this article, we consider some of the cancers that affect changes in bone mineral density and how treatments may also be implicated in the loss of bone integrity and negative effects on the skeleton

## Peyman Hadji MD PhD

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Osteoporosis is associated with several cancers, in particular hormone-dependent cancers such as those of the breast and prostate.<sup>1</sup> Bone loss associated with cancer can be caused by the cancer cells themselves – that is, the pathological process, particularly metastases – and/or treatment itself and other factors.<sup>2</sup>

### Which cancers are associated with an increased risk of bone events?

Table 1 summarises the main osteophilic cancers and the incidences of bone metastases.<sup>2-4</sup>

Cancers such as of the central nervous system (CNS), cervix and gastrointestinal are also associated with osteoporosis but to a lesser degree.<sup>5</sup>

### Complications of bone metastases

Complications that can occur with bone metastases include pathological fracture, spinal cord compression, severe pain, impaired mobility, bone marrow aplasia, and, possibly, hypercalcaemia.<sup>6</sup> Typically, these events result in loss of social functioning, reduced quality of life, greater dependence on health care resources and lower survival.<sup>7</sup>

### Incidence

Buzasi et al observed an increased risk of bone fracture in 15 of 20 cancers compared with the risk in people without cancer.<sup>8</sup>

In this population-based matched cohort study, using electronic health records from the UK Clinical Practice Research Datalink linked to hospital data, 578,160 adults with cancer diagnosed in 1998–2020 were matched to 3,226,404 individuals who did not have cancer. The adjusted hazard ratios (HRs) were found to be highest for individuals with multiple myeloma (1.94, 95% CI 1.77–2.13) and prostate cancer (1.43, 95% CI 1.39–1.47).<sup>8</sup>

HRs in the range 1.20–1.50 were seen for stomach, liver, pancreas, lung, breast, kidney and CNS cancers; more minor associations (HR <1.20) were found for malignant melanoma, non-Hodgkin lymphoma, leukaemia, and oesophageal, colorectal and cervical cancers.<sup>8</sup>

### Age, sex and other risk factors

While metastases are a significant cause of bone loss leading to osteoporosis, age is a general risk factor, and older patients

TABLE 1

## Main osteophilic cancers and the incidences of bone metastases

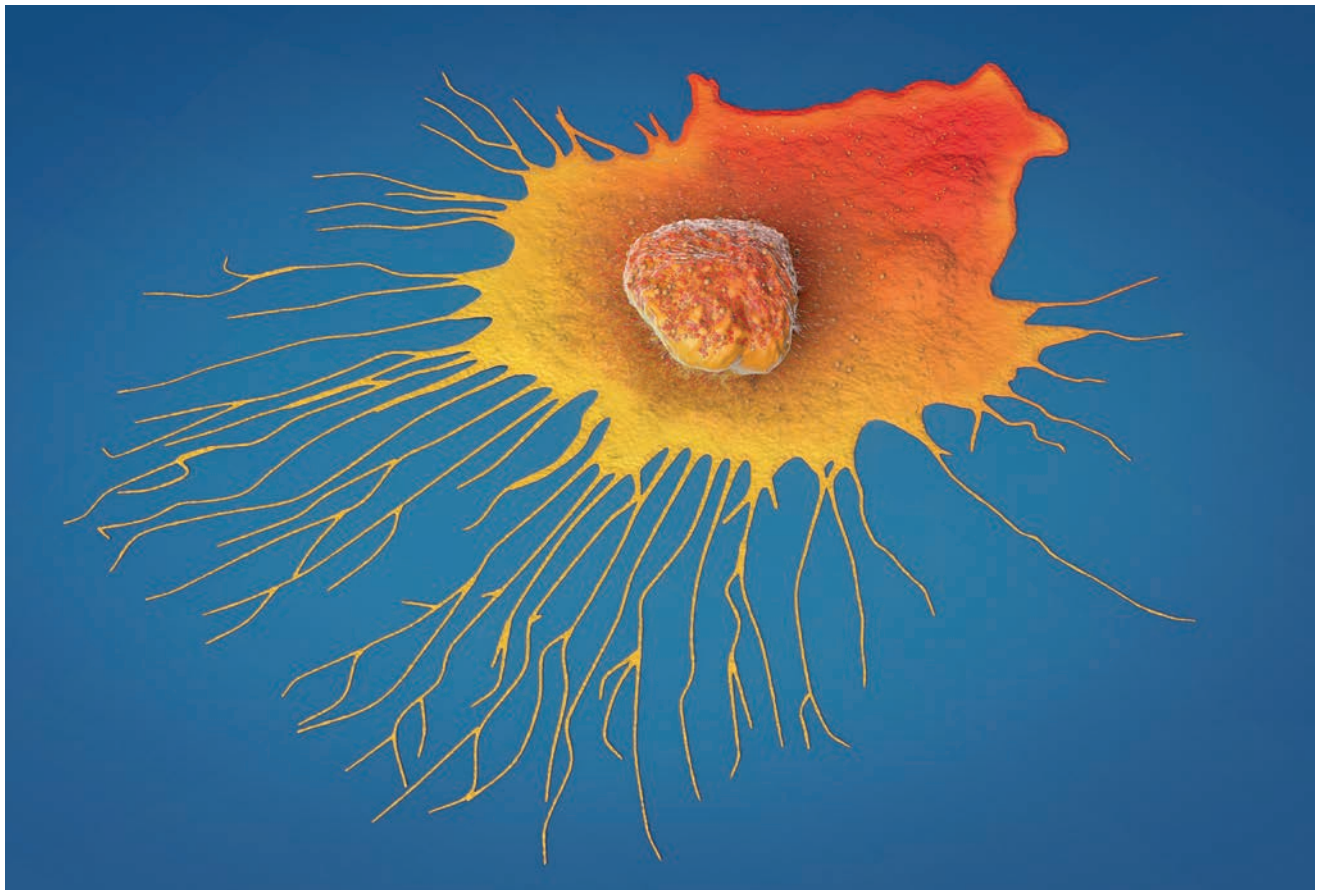
| Cancer type      | Incidence of bone events   |
|------------------|--|
| Breast           | Breast cancer and its treatments, particularly aromatase inhibitors, can significantly increase the risk of osteoporosis, especially in postmenopausal women (65%–75% incidence)   |
| Prostate         | Patients with prostate cancer, especially those undergoing androgen deprivation therapy, are at high risk for osteoporosis and increased bone turnover.<br>A total of 25–40% of patients with prostate cancer have a diagnosis of osteoporosis |
| Multiple myeloma | Multiple myeloma originates in the bone marrow and has a significant association with bone destruction, with 80%–90% of patients developing bone issues  |
| Lung             | 30%–40% of patients with metastatic lung cancer develop bone metastases  |
| Bladder          | Approximately 40% of patients  |
| Kidney           | 20%–25% of patients  |
| Thyroid          | Approximately 60% of patients  |
| Melanoma         | 14%–45% of patients  |

may well have existing osteoporosis before a diagnosis of cancer. Central to this bone loss is the decline in sex steroid (primarily oestrogen and testosterone) levels in both sexes with ageing.

The lifetime risk of a fracture of the hip, spine or distal forearm after the age of 50 years is 40% for Caucasian women and 13% for Caucasian men.<sup>7</sup>

Older cancer survivors may be at increased risk of frailty-related bone fractures, such as fractures of the pelvis, wrist and vertebrae, compared with those who have never had a cancer diagnosis.

An analysis of Medicare claims data from 92,431 people diagnosed with cancer in the Cancer Prevention Study II



(CPS-II) Nutrition Cohort (CPS-II NC) in the US found a higher risk of total frailty-related fractures compared with people never diagnosed with cancer.

The cohort included 51,820 (56.1%) women and 40,611 (43.9%) men; 90,458 (97.9%) were White, 1037 (1.1%) were Black, and 936 (1.0%) were classified as all other races and ethnicities (including Asian and Pacific Islanders, Indigenous Americans, an 'other race' category, and Hispanic and Latino ethnicity of all races).<sup>9</sup>

The mean age of the cohort was 69.4 (SD 6.0) years. Cancer survivors were more likely to be males (8,054 [56.9%] versus 6,105 [43.1%] female;  $p < 0.001$ ) and former smokers (7,732 [54.6%] versus 5,618 [39.7%] who never smoked and 809 [5.7%] current smokers;  $p < 0.001$ ).<sup>9</sup>

There was a 57% higher risk of fracture, particularly pelvic and vertebral fractures, within the first year from diagnosis (HR, 1.57; 95% CI, 1.38–1.79) compared with people in the study who had never been diagnosed with cancer. The authors concluded that higher rates of osteoporosis were the reason for a higher risk of bone fracture among cancer survivors. Other factors such as low muscle mass, poor balance and unexpected changes in gait also played a part, they commented.<sup>9</sup>

In prostate cancer, increased expression of transforming growth factor-beta (TGF- $\beta$ ) and parathyroid hormone-related protein may contribute to osteoporosis. *In vitro*, the growth and survival of prostate tumour cells increases.<sup>4</sup>

Research also points to another mechanism that may be implicated in bone loss among people with cancer; that is, inflammation. Cancer is one of many conditions known to promote inflammation in the body, which results in prolonged raised levels of pro-inflammatory cytokines, including interleukins and tumour necrosis factor-alpha. These

substances are known to affect and upregulate osteoclast activity.<sup>10</sup>

#### Pharmacotherapy and osteoporosis

Hormonal therapies associated with osteoporosis in cancer patients include:<sup>4</sup>

- Aromatase inhibitors (breast cancer)
  - Steroidal (exemestane)
  - Non-steroidal (anastrozole, letrozole)
- Gonadotrophin-releasing hormone (GnRH) agonists (breast cancer: goserelin, triptorelin)
- Selective oestrogen receptor modulators (breast cancer)
- Androgen deprivation therapy (prostate cancer)
- Luteinising hormone-releasing hormone (LHRH) analogues (goserelin, buserelin, leuprorelin, triptorelin)
- LHRH antagonists (goserelin)
- Antiandrogens (enzalutamide, bicalutamide, flutamide, nilutamide)
- Glucocorticoids (multiple myeloma, prostate cancer, palliation)

An audit of 236 men showed that, at the start of androgen deprivation therapy, 11% had osteoporosis, and 40% had osteopenia.<sup>11</sup>

Lifestyle changes during treatment, such as lower calcium and vitamin D intake and less exercise, may also contribute to lower bone mineral density.

Osteoporosis induced by glucocorticoids, which are used either therapeutically or palliatively in a range of cancers, is the most common type of secondary osteoporosis. The risk increases with higher dosage and greater length of treatment.<sup>12</sup>

Breast cancer patients may develop osteoporosis as a result of oestrogen deprivation induced by hormone therapy, in particular, aromatase inhibitors.<sup>4</sup>

Bone resorption and loss are reduced by oestrogen binding to alpha and beta receptors, which are expressed in osteoblasts and osteoclasts.<sup>4</sup> A loss of 6–8% of bone is possible in the first year of treatment with hormone therapy such as non-steroidal aromatase inhibitors. The effect is especially seen in the trabecular bone.

The risk is most significant among premenopausal women with chemotherapy-induced menopause treated with GnRH agonists and lowest for women treated only with aromatase inhibitors, particularly those aged under 70 years.<sup>4</sup>

Women treated with aromatase inhibitors can experience significant bone resorption with a two- to threefold increase in bone loss compared with that seen in postmenopausal women due to physiological causes.<sup>13</sup>

Approximately one in ten women will have a fracture as a result of five years of treatment with aromatase inhibitors, according to data from randomised controlled trials. However, data from other studies that may reflect real-world use of aromatase inhibitors suggest that around one in five women with breast cancer may have a fracture after five years of treatment with an aromatase inhibitor.<sup>13</sup>

GnRH and LHRH analogues used to suppress ovarian function in patients with cancer can cause bone loss during amenorrhoea. Bone loss recovers after treatment stops, particularly in those in whom menstruation starts again.

In a substudy of Austrian Breast and Colorectal Cancer Study Group trial-12 (ABCSCG-12), 404 patients who received endocrine therapy alone or endocrine therapy with zoledronic acid found that after three years of treatment, bone mineral density had decreased by 11.3% at the lumbar spine and by 7.3% at the trochanter. Two years after treatment, bone mineral density in those receiving endocrine therapy without zoledronic acid recovered but did not reach baseline levels.<sup>14</sup>

Bone loss associated with androgen deprivation therapy affects trabecular and cortical bone.<sup>15</sup> In men, oestrogen is produced by the aromatisation of androgen, which regulates the RANKL signalling pathway.<sup>16</sup> Lower testosterone and oestrogen levels resulting from androgen deprivation therapy interfere with the regulation of bone remodelling and lead to higher bone turnover and bone loss.<sup>17</sup>

As many as 80% of patients treated with androgen deprivation therapy for prostate cancer may have osteoporosis after ten years of treatment, affecting the radius and spine in particular. Bone mineral density can fall by 5–10% in the first year of treatment.<sup>4</sup>

Indeed, men with prostate cancer being treated with androgen deprivation therapy are four-times more likely to

## Key learning points

- A number of cancers are associated with a higher risk of osteoporosis compared with people who have never been diagnosed with cancer.
- Pharmacotherapy for cancer can be associated with bone mineral density loss and the development of osteoporosis.
- Cancer therapies that reduce the levels of oestrogen or testosterone, such as aromatase inhibitors and androgen deprivation therapy, are associated with a reduction in bone mineral density.
- Osteoporosis is associated with a higher risk of fracture, which leads to reduced quality of life and greater use of healthcare resources.
- Bone loss can recover after cessation of some cancer therapies. Still, it may not reach pre-treatment levels without active treatment of the impact of cancer pharmacotherapy on the bone mineral density itself.

develop significant bone deficiency. Among men who were still alive five years after a diagnosis of prostate cancer and who had been treated with androgen deprivation therapy, 19.4% had a fracture. Among those who did not receive androgen deprivation therapy, 12% had a fracture.<sup>15</sup>

There may be a link between thyroid-stimulating hormone suppression in people with thyroid cancer and fractures resulting from osteoporosis. However, the idea is somewhat controversial in the eyes of some researchers. High thyroid hormone levels can result in bone remodelling, loss of bone, reduced bone mineral density, and increased risk of osteoporotic fractures.<sup>18</sup>

## Conclusion

Nearly all patients with cancer are at increased risk for bone loss and fractures due to a combination of factors, including the underlying malignancy, an often-advanced age, and therapeutic regimens that directly or indirectly affect bone cells.

The consequence of these effects is an increase in individuals' fracture risks. Fractures are associated with lower quality of life and greater use of health care resources and will be discussed fully elsewhere in this handbook.

Screening for bone mineral density, as well as treatment and prevention of osteoporosis, should therefore form part of the overall management of people with cancer.

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# Management of osteoporosis and bone metastases: a focus on prostate and breast cancer

Management of osteoporosis and bone metastases plays a significant part in the treatment of people with cancer, not least because fractures associated with the disease and skeletal-related events can lead to loss of mobility and social functioning and reduce patients' quality of life

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Metastatic cancer and certain treatments used to manage it can have a significant impact on bone health as both can damage the skeleton, resulting in pathologies such as osteoporosis.<sup>1</sup> Therefore, pharmacotherapy is now integral to managing and preventing bone metastases.

ESMO clinical practice guidelines on bone health in cancer advise that clinicians 'need to be aware of the multidisciplinary treatments available to reduce skeletal morbidity from metastatic disease and minimise cancer treatment-induced damage to the normal skeleton' when managing patients with cancer.<sup>2</sup>

Bone metastases usually affect the axial skeleton and often cause skeletal complications – skeletal-related events (SRE) – including pathological fracture, spinal cord compression and hypercalcaemia. These complications may require radiotherapy or surgery to bone if pharmacological treatments are unsuccessful. Patients can experience reduced mobility and social functioning, their quality of life may be affected, and they may have shorter lives.<sup>2</sup>

## Cancer treatment and bone health

In premenopausal women with early breast cancer, head-to-head randomised controlled trials indicate an annual bone mineral density loss of up to 11% associated with treatment with aromatase inhibitors/ovarian function suppression due to profound oestrogen production suppression. In postmenopausal women, treatment with aromatase inhibitors has been associated with an increase in bone turnover and loss as well as increased fracture risk compared with tamoxifen.<sup>3</sup>

Osteoporosis is a significant issue for all patients with prostate cancer undergoing androgen deprivation therapy.<sup>4</sup> A study of the records of 50,613 men with prostate cancer from the database of the Surveillance, Epidemiology, and End Results program and Medicare, from 1992 to 1997, found that among men still alive five years after diagnosis, fractures were seen in 19.4% of those who had been treated with androgen-deprivation therapy compared with 12.6% of those who had not received androgen-deprivation therapy.<sup>5</sup>

## Management and prevention strategies

Bone-targeting agents such as bisphosphonates and denosumab prevent the resorption of bone and can help lower the risk of SRE and treat hypercalcaemia associated with malignancy.<sup>2</sup>

Anti-resorptive therapy is usually combined with treatment

of the cancer itself.<sup>2,6,7</sup> Treatment with bone-targeting agents should be individualised and guided by skeletal event-related risk and the overall status of tumour control.

Once the benefits and risks of treatment have been explained to patients, ESMO guidelines recommend that, in most cases, treatment with a bone-targeting agent should start as soon as bone metastases have been diagnosed, irrespective of whether or not the patient has symptoms. Of note anti-resorptive therapies are not indicated in castration-sensitive prostate cancer. Generally, a treatment duration of over two years is possible but the benefit–risk imbalance must be evaluated case by case.<sup>2</sup>

Denosumab should be given every four weeks. After monthly treatment for three to six months, zoledronate can be given every 12 weeks.<sup>2</sup> A longer dosing interval for zoledronate was examined in a randomised, open-label clinical multicentre trial involving 1822 patients with metastatic breast cancer, metastatic prostate cancer, or multiple myeloma who had at least one site of bone involvement. The study found that treatment with zoledronic acid administered intravenously every four weeks (n=911) or every 12 weeks (n=911) for two years showed no significant difference in the increase in risk of SRE.<sup>8</sup>

## Efficacy of bone-targeting agents

Denosumab has been found to be superior to zoledronic acid in preventing skeletal-related events in a number of settings. In a multicentre randomised controlled study, men with castration-resistant prostate cancer with no previous exposure to intravenous bisphosphonate received either 120 mg subcutaneous denosumab plus intravenous placebo (n=950) or 4 mg intravenous zoledronic acid plus subcutaneous placebo (n=951), every four weeks. Participants were recruited from 342 centres across 39 countries. The median duration of treatment with denosumab was 12.2 months, and 11.2 months for zoledronic acid. The median time to the first skeletal-related event during the study was 20.7 months (95% CI 18.8–24.9) with denosumab versus 17.1 months (15.0–19.4) with zoledronic acid (hazard ratio (HR) 0.82, 95% CI 0.71–0.95; p=0.0002).<sup>6</sup>

An analysis of six randomised controlled trials involving 7722 patients demonstrated that denosumab had a significant effect on delaying the time to first SRE (HR 0.92, 95% CI 0.86–0.98, p = 0.01) compared with intravenous bisphosphonates. Denosumab also reduced the time to subsequent SRE (relative risk (RR) 0.92, 95% CI 0.86–0.99, p=0.03) and the use of radiation therapy to bone metastases (RR 0.81, 95% CI 0.71–0.92, p=0.02).<sup>9</sup>

Severe hypocalcaemia was more frequent with





denosumab (RR 1.99, 95% CI 1.11–3.54,  $p=0.02$ ), but renal impairment was less frequent (RR 0.75, 95% CI 0.61–0.91,  $p=0.003$ ).<sup>9</sup>

A Cochrane review of randomised controlled trials comparing different bisphosphonates and RANKL-inhibitors with each other or against no further treatment or placebo involving men with prostate cancer and bone metastases found that the risk of SRE was 393 per 1000 (RR 0.84; 95% CI 0.72–0.97) with zoledronic acid treatment and 337 per 1000 (RR 0.72; 95% CI 0.54–0.96) with denosumab treatment. The analysis was based on 12 studies, including 5240 participants, with a follow-up period of 5–60 months. The assumed risk with no treatment or placebo was 468 per 1000.<sup>10</sup>

A meta-analysis of three randomised trials of the effect of denosumab on bone health in 5,140 patients with prostate cancer being treated with androgen-deprivation therapy or with breast cancer receiving adjuvant endocrine treatment showed a reduction in the risk of bone mineral density loss up to 36 months at the lumbar spine (RR 0.13, 95% CI 0.10–0.16), total hip (RR 0.18, 95% CI 0.16–0.22), femoral neck (RR 0.30, 95% CI 0.27–0.35) and distal third radius (RR 0.34, 95% CI 0.25–0.47).<sup>11</sup>

At 24 months, there was a bone mineral density increase with denosumab at the lumbar spine (mean difference (MD) 7.50; 95% CI 5.66–9.34), total hip (MD 5.07, 95% CI 3.91–6.22), femoral neck (MD 4.10, 95% CI 3.17–5.03) and distal third radius (MD 5.85, 95% CI 4.18–7.52). Similarly, at 36 months, bone mineral density increased at the lumbar spine (MD 8.82, 95% CI 6.26–9.45), total hip (MD 6.45, 95% CI 4.80–8.10), femoral neck (MD 5.23, 95% CI 3.84–6.62) and distal third radius (MD 6.90, 95% CI 4.35–9.45). There were also fewer new vertebral and femoral fractures at 24 and 36 months with denosumab treatment compared with placebo.<sup>11</sup>

Despite evidence of efficacy, some would argue that the use of antiresorptive therapy in patients with bone metastases is unacceptably low. Agarwal et al analysed data for 1,492,301 patients with a new diagnosis of bone metastases captured in the Mariner dataset of the PearlDiver database between January 2010 and October 2021 and found that only 7.7% of patients were prescribed these treatments. During the same

period, the incidence of pathologic fracture within two years of a new diagnosis was 7.3%.<sup>12</sup>

It should be noted that in the case of castration-sensitive bone metastatic prostate cancer, there is no indication for bone-targeting agents for SRE except on an individual case basis.<sup>13</sup>

#### **Metastatic breast cancer and osteoporosis**

Women with breast cancer need management for bone health in early and advanced disease. Management in early disease mainly includes the prevention of bone loss and bone metastases and the use of adjuvant bone-modifying drugs. In patients with advanced breast cancer, the key goals are to prevent and treat SRE and enhance the quality of life.<sup>14</sup>

Two studies examined the effects of bone-targeting agents on fractures in women with breast cancer: the Austrian Breast Cancer Study Group (ABCSCG) trial 18, a double-blind, placebo-controlled trial of denosumab/placebo in 3,425 postmenopausal women receiving an aromatase inhibitor<sup>15</sup> and an update of the randomised, open-label AZURE trial with 84 months of follow-up.<sup>16</sup> The ABCSCG 18 trial, one of the few in women with breast cancer with a primary endpoint of reduction in fractures found a hazard rate for the reduction in fractures of 0.50 (95% CI 0.39–0.65)<sup>15</sup> while the AZURE trial found five-year fracture rate of 3.8% (95% CI 2.9–4.7%) for patients receiving zoledronic acid and 5.9% (95% CI 4.8–7.1%) for the control group.<sup>16</sup>

Another randomised controlled study found denosumab was superior to zoledronic acid in delaying time to first SRE during the study (HR 0.82, 95% CI, 0.71–0.95;  $p=0.01$  superiority) and time to first and subsequent (multiple) SRE during the study (RR 0.77, 95% CI, 0.66–0.89;  $p=0.001$ ). For the study, patients with breast cancer with bone metastases were randomly assigned to receive either subcutaneous denosumab 120 mg and intravenous placebo ( $n=1,026$ ) or intravenous zoledronic acid 4 mg adjusted for creatinine clearance and subcutaneous placebo ( $n=1,020$ ) every four weeks.<sup>17</sup>

#### **Real-world evidence**

In a real-world study looking at the use of bone-targeting agents in patients with metastatic prostate cancer, 358

physicians practising across Europe (79 in Spain, 76 in Germany, 76 in Italy, 69 in France, 42 in the UK and 16 in Belgium) provided data for 3667 patients with prostate cancer (including 1971 with bone metastases and 551 with metastases at sites other than bone).<sup>18</sup>

A bone-targeting agent was given to almost three-quarters (74%; n=1454) of patients with bone metastases, 53% (n=1048) of whom received treatment within three months of diagnosis.<sup>18</sup>

Seventy-eight per cent (n=1191) of patients with bone metastases treated by oncologists received a bone-targeted drug compared with 60% (n=263) treated by urologists. Over half (56%; n=861) of patients managed by oncologists were started on the treatment within three months of bone metastases diagnosis compared with 43% (n=187) of those treated by a urologist. The main reasons for not treating patients with a bone-targeting agent were recent bone metastases diagnosis and perceived low risk of bone complications.<sup>18</sup>

### Side-effects and tolerability

In general, bone-targeting agents are well tolerated. When administered intravenously, the main side effects for bisphosphonates, such as chills, fever, bone pain, fatigue, arthralgia, myalgia, stiffness, and arthritis, occur during the acute phase. They generally resolve spontaneously and can be managed with antipyretics.<sup>19</sup> In some patients, changes in calcium, magnesium and phosphorus serum levels are observed. The drugs can also impact renal function, which should be monitored during treatment. The effect depends on dosage and infusion rate.

Treatment with bone-targeting agents, particularly those containing nitrogen, can lead to jaw osteonecrosis because the drugs affect osteoclast-mediated bone resorption and osteoclast formation.<sup>1</sup> Before therapy is initiated, an oral examination and preventive dentistry are recommended, and good oral hygiene should be maintained throughout. In case of re-occurrence of the osteonecrosis, the patient must be seen by a specialised dental professional.

Bone-targeting agents may cause hypocalcaemia, and calcium levels must be monitored, especially during early treatment. Vitamin D levels should be monitored before treatment commences, and any deficiencies should be corrected with supplementation (vitamin D and oral calcium supplementation are mandatory in denosumab treatment,

## Key learning points

- Maintaining bone health in patients with cancer, in particular those with metastatic disease, is an integral part of management.
- The effectiveness of bone-targeting agents has been demonstrated in clinical trials.
- ESMO guidelines recommend the use of denosumab and zoledronic acid.
- Treatment with a bone-targeting drug should start as soon as bone metastases have been diagnosed, irrespective of whether or not a patient has symptoms.
- Treatment with bone-targeting agents should be individualised and guided by skeletal event-related risk and the overall status of tumour control.
- Patients need to be made aware of and educated about potential side effects of bone-targeting agents.

even when their blood levels are normal; regular monitoring of calcaemia is also mandatory).<sup>2</sup>

Studies have shown an increase in bone turnover and a decrease in bone mineral density after denosumab therapy is discontinued – a rebound osteolysis.<sup>20</sup> Bisphosphonate therapy should be considered to prevent or reduce the rebound and risk of skeletal fractures.<sup>2</sup>

### Conclusion

Maintaining bone health in patients with cancer, in particular those with metastatic disease, is a challenge for clinicians who need to be aware of the treatments available and how to employ them best to protect their patients.<sup>2</sup>

We have seen that denosumab and bisphosphonates have proven efficacy in preventing the resorption of bone and can help lower the risk of SRE and treat hypercalcaemia associated with malignancy.<sup>2</sup> While these drugs can help people with breast cancer and castration-resistant metastatic prostate cancer, there is no indication for bone-targeting agents for SRE in patients with castration-sensitive bone metastatic prostate except on an individual case basis.<sup>13</sup>

It is essential to inform patients about the potential side effects of bone-targeting agents and the monitoring required and how calcium and vitamin D supplementation is important and may in some cases be mandatory.

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# Holistic management of bone metastases and supportive care

Treatment of metastatic bone disease has evolved over the last 50 years, but a lack of awareness and recognition of symptoms can delay referral to specialist teams. This article highlights crucial concepts surrounding the holistic management of patients with bone metastases and emphasises the need for a multidisciplinary approach

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Bone metastases are localisations of tumour cells in bone at a distance from the primary tumour that more or less faithfully reproduce the characteristics of the primary tumour. Not all cancers have the same propensity to metastasise to bone; some tumours are more osteophilic than others (see earlier article in this handbook). One explanation for this is the phenomenon of chemotaxis, which refers to the attraction that bone can exert on specific tumour cells to release chemokines. This sets the tumour cell in motion and moves it up the chemokine concentration gradient and is particularly true for bone metastases with CCL2–CXCR4 and RANK–RANKL pairs.<sup>1,2</sup> Once at the bone site, some tumour cells adapt better than others to the new microenvironment.

This osteophilic nature is reflected in the epidemiology of bone metastases. The most recent survey conducted in France, using a representative sample of the general population, showed that between 2009 and 2018, the number of new patients with bone metastases was 175,000–180,000, all histologies combined. The most osteophilic cancers were breast and prostate, followed by lung, digestive and urological cancers. There was also a three- to four-fold increase in symptomatic bone metastases.<sup>3</sup>

However, these figures are considered underestimates because they do not consider pauci-symptomatic bone metastases. These figures raise three critical issues for the management of bone metastases:

- 1 The number of patients affected is considerable and transdisciplinary
- 2 The identification of bone metastases at-risk of complications among asymptomatic localisations is a significant challenge
- 3 The epidemiology of bone metastases and bone events is evolving with advances in oncology, improving overall survival and enabling the possibility of local treatment of bone lesions.

## Complications of bone metastases

Many bone metastases are asymptomatic. However, historically, it has been estimated that 50% of patients with bone metastases will develop a complication without bone-directed treatment.<sup>4</sup> Complications include severe bone pain, life-threatening hypercalcaemia and pathologic fractures. Fractures can significantly impact a patient's autonomy and mobility, and can lead to decubitus and extensive treatment such as orthopaedic or spinal surgery, radiotherapy or interventional radiology.<sup>5</sup> In addition, bone complications are

associated with interruptions in treatment, high costs, and reduced survival and quality of life.<sup>6–10</sup>

The occurrence of bone complications varies from patient to patient. They may occur during the treatment of a patient with known metastatic cancer. For example, the study by Hortobagyi et al reported that 60% of breast cancer patients with bone metastases experienced a pathologic fracture within a median of 15 months after the identification of bone metastases.<sup>11</sup> Conversely, it is not uncommon to observe patients whose cancer diagnosis is made at the time of the first complication of bone metastases.<sup>12</sup> In a cohort of 859 breast cancer patients, Plunkett et al reported 19% hypercalcaemia and 35% pathological fractures, including 20% vertebral and 12% long bone fractures.<sup>13</sup>

## Current challenges in the treatment of bone metastases

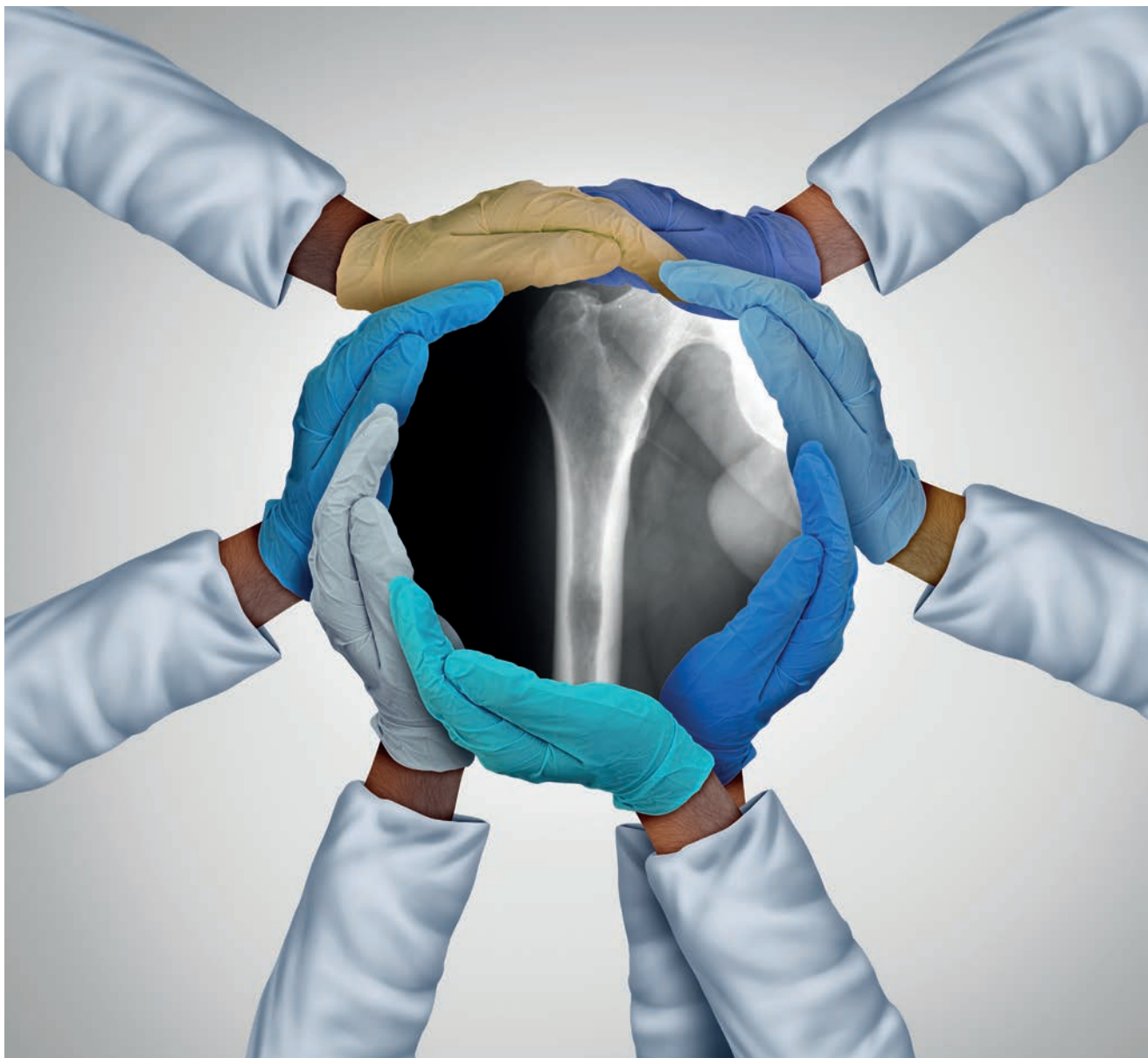
In recent years, significant advances in cancer treatment have been made, with hormone therapies, targeted small molecules, monoclonal antibodies, and immune checkpoint inhibitors added to conventional chemotherapy protocols (see the article on medical management in this handbook). These therapeutic advances are helping to change the prognosis for many cancer patients. Many patients now benefit from prolonged remissions, even in metastatic disease. This must be taken into account in the management of bone metastases. As such, the clinician currently faces seven significant challenges, which are detailed below.

### Which of the patient's multiple bone metastases are symptomatic or at risk for complications?

This requires mapping the bone lesions as comprehensively as possible and isolating only those that require treatment. While distal metastases are rare, humeral and femoral lesions are common. For this reason, imaging with a PET scan or bone scintigraphy is recommended, as it allows evaluation up to the elbows and below the knees.

### At what stage is the disease?

It is one thing to be confronted with initial bone metastases synchronous with the discovery of cancer and quite another to be faced with late-stage disease. The clinician must assess the patient's expected survival, the possibility of prolonged remission, and the potential response of the bone metastasis to oncologic treatment. These factors affect the choice of local treatment, depending on the severity of the proposed therapy, potential toxicity, length of rehabilitation required, and the patient's life expectancy. We must also consider the mechanical forces placed on the pathological bone. For example, nailing, resection prosthesis, interventional



radiology, or simple offloading may be possible for certain lesions.

#### **What is the patient's terrain?**

For each patient, the clinician will consider: 1) the difference between the patient's age and physiological age; 2) the presence of comorbidities, especially cardiovascular, dental, renal, cognitive or locomotor; 3) previous local treatment in the location under consideration; and 4) the patient's willingness to adhere to the therapeutic regimen.

#### **What is the proposed treatment strategy?**

Establishing close and harmonious communication with the patient's referring oncologist is vital. This will help ensure that any treatment is compatible with bone management. Indeed, some combinations are particularly prone to complications, such as bone-targeting agents and anti-angiogenic agents, which carry a high risk of osteonecrosis of the jaw. Others are incompatible and require an interruption of treatment. For example, cytotoxic chemotherapy is not compatible with orthopaedic surgery, or there is a need for a therapeutic window for gemcitabine during radiotherapy. Conversely,

certain combinations, such as epidermal growth factor receptor inhibitors and denosumab, may be synergistic. This stage also provides an opportunity to discuss the urgency of oncologic and musculoskeletal treatment with the oncologist. The timings of the two treatments and how to prioritise them may influence the choice of techniques used.

#### **What local techniques are routinely available at my centre?**

It is not uncommon for several approaches to be proposed for the same patient and the same bone lesion. Each approach has advantages and disadvantages. When deciding, it is important to ensure the technique is safe for the patient. This varies significantly from centre to centre.

#### **What is the patient's pain level?**

Regardless of the pain level assessed by the patient and physician using the visual analogue scale, it is essential to understand the painful location, and whether the pain is related to bone metastases (differential diagnosis) and which particular lesion. This is especially true for multiple vertebral lesions. It is also helpful to characterise the presence of mechanical pain on weight-bearing, which is an important →

**TABLE 1**
**Simplified comparison of advantages and disadvantages of the main local treatments for bone metastases**

| Local treatment type     | Site  | Procedure duration                   | Effect on spine epiduritis | Effect on gait                                    | Immediate biomechanical effect              | Longevity    | Long-term bone reconstruction |
|--------------------------|---|--------------------------------------|----------------------------|---|---|--------------|-------------------------------|
| Radiotherapy             | All   | Multifractionated<br>Single fraction | +++<br>+++                 | Delayed, incremental (15 days after last session) | 0<br>0                                      | ++++<br>++   | +++<br>+                      |
| Cementoplasty            | Vertebrae, pelvis                             | One shot                             | 0                          | Immediate   | Compression forces                          | +++          | 0                             |
| Contention and unloading | Vertebrae, long bones                         | One shot                             | 0                          | Partial (efficient for loading pain and movement) | Temporary                                   | Constraining | 0                             |
| Screw + cementoplasty    | Pelvis, proximal hip                          | One shot                             | 0                          | Immediate   | Compression forces and mild on shear stress | Intermediate | 0                             |
| Nail surgery             | Long bones (diaphysis, metaphysis)            | One shot, poorly invasive            | 0                          | Immediate   | +++   | Intermediate | 0                             |
| Osteosynthesis surgery   | Long bones (diaphysis, metaphysis, vertebrae) | One shot, invasive, healing required | +++ (for vertebrae)        | Immediate   | +++   | Intermediate | 0                             |
| Arthroplasty surgery     | Joints  | One shot, invasive, healing required | 0                          | Immediate   | +++   | Long term    | NA                            |

criterion for surgical decisions. It is also beneficial to determine if the pain is neuropathic. At the same time, the clinician needs to understand the patient's psychological state, which has a significant impact on the experience of pain.

**What is the fracture risk of the lesion?**

The specific assessment of the strength of a metastatic bone lesion is complex. It comes on top of the patient's basic bone strength, which is the result of their entire history, such as genetic makeup, peak bone mass, hormonal status (e.g., menopause/post-menopausal), physical activity habits, smoking/alcohol intake, certain drugs (proton pump inhibitors, antidepressants) and chronic diseases (inflammatory rheumatism, diabetes, renal function). Few scores are available to assess the resistance of bone metastasis.

Today, with the refinement of tumour molecular profiling, only the Mirels score for long bones<sup>14</sup> and the SINS score<sup>15</sup> for vertebrae remain, as they do not include tumour characteristics and focus solely on biomechanical aspects. However, the Mirels score has a low sensitivity and specificity of approximately 0.5.<sup>16</sup>

The SINS score is a vertebral mechanical score that assesses lesion stability to aid in deciding whether or not a neurosurgical intervention should be undertaken. The mechanical strength of a load-bearing bone containing

a metastatic lesion is scored for bone metastases.<sup>17</sup> There is also the longitudinal evolution of the mechanical strength and fracture risk of bone metastasis as a function of response to oncological treatment, and systemic and local bone treatments.

New techniques are being developed to improve the assessment of the mechanical strength of bone metastases based on finite element analysis of patients' CT images.<sup>18</sup> Prototypes, such as the MEKANOS tool<sup>19</sup>, are also under development. The ultimate goal is to obtain a personalised prediction of the mechanical resistance of bone metastases to help tailor patient management.

**Tools available for the treatment of bone metastases**

Treatments are either systemic or local.

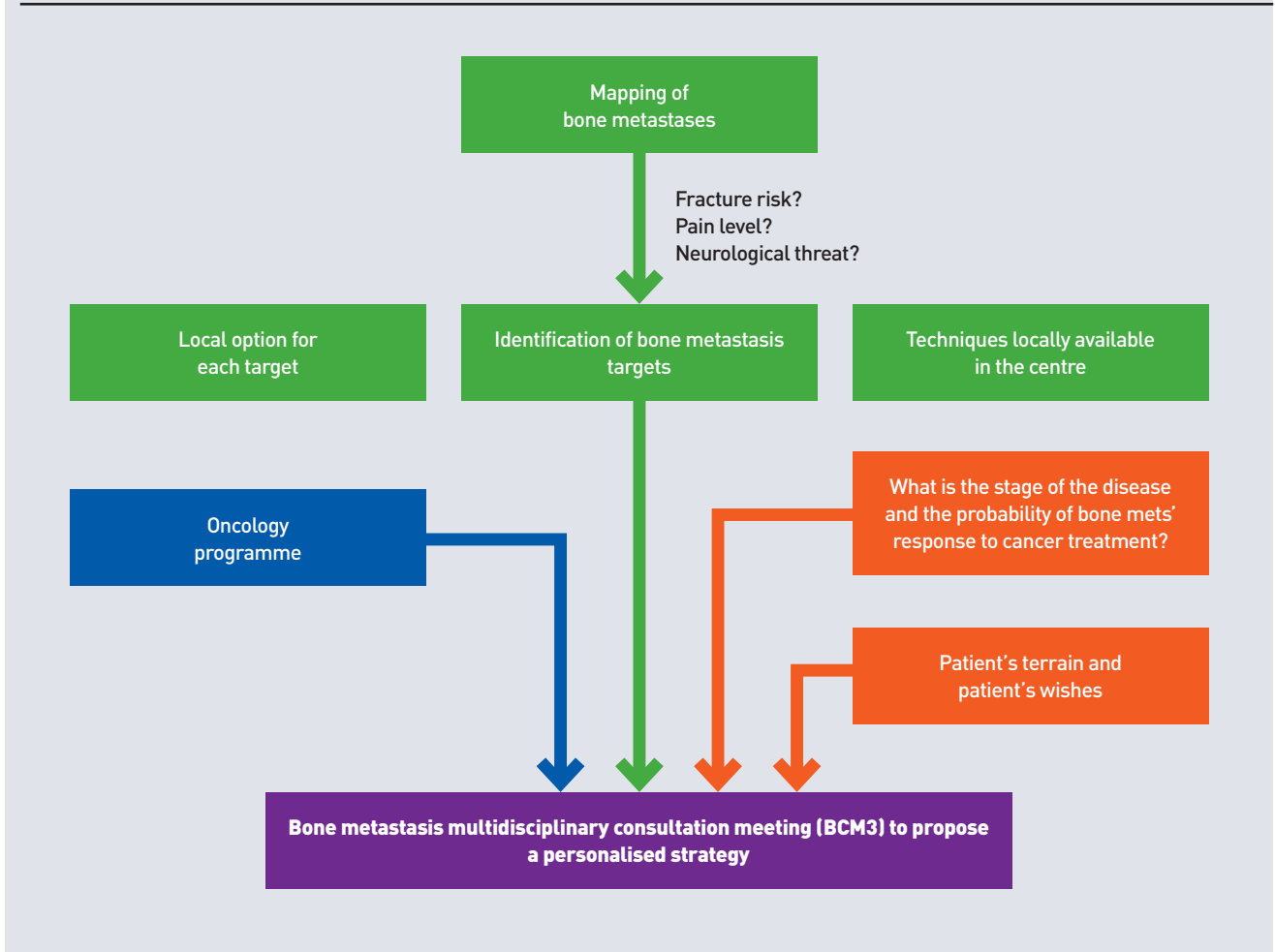
**Systemic treatment**

The first systemic treatment for bone metastases is oncological therapy as long as the tumour is still responding. This is usually combined with systemic antiresorptive treatment to stop the vicious cycle of bone metastasis by blocking bone resorption. The goal of antiresorptive therapy is to reduce the incidence of bone events.<sup>9,20-23</sup>

There are two types of anti-resorptive: bisphosphonates (zoledronic acid) and denosumab, a receptor activator of

**FIGURE 1**

**Holistic integration of the key issues to define a personalised management programme integrating bone metastases and oncological pathways**



nuclear factor kappa-B ligand (RANKL) inhibitor. The international ESMO guidelines state that for breast cancer, treatment should be started as soon as bone metastases are detected. In prostate cancer, antiresorptive therapy is indicated at the onset of hormone resistance. For all other bone tumours, it is recommended that treatment be started as soon as bone metastases are clinically significant and patients have an estimated overall survival of more than three months.<sup>24</sup> Anti-resorptive agents are combined with correcting any vitamin D deficiency, followed by calcium supplementation.

**Local treatments**

There are several local treatments for bone metastases, each having advantages and disadvantages (see Table 1). Treatments can sometimes be used in combination. Techniques include immobilisation by brace and unloading, radiation therapy, surgery, and interventional radiology with cementation and/or screws.

The most commonly used radiotherapy is fractionated conformal radiotherapy (3D or IMRT), typically 30 Gy in ten fractions. Single-fraction radiotherapy has the same analgesic effect but is more toxic, and recurrence is more likely. Radiotherapy is considered a palliative treatment for pain, for vertebral metastases with spinal cord compression, and as an adjuvant postoperative treatment (spine or extremities). It can

also be used to prevent the morbidity of bone metastases, especially fractures and vertebral epiduritis. Radiation therapy has a re-ossification effect on non-fractured lytic bone in 65%–85% of cases. In the treatment of oligo-metastases, ablative radiotherapy is usually delivered by stereotaxy.

Interventional radiology allows local percutaneous treatments. The most common indications are pain caused by well-identified lytic lesions treated by cementoplasty. Cementoplasty involves the placement of a polymethylmethacrylate polymer, which sets into the intraosseous tumour zone within a few minutes. The cement is injected percutaneously through a needle under fluoroscopic and/or scannographic control. The analgesic effect is rapid for mechanical (mainly compression) pain, especially in the spine, pelvis and acetabulum. It has no impact on epiduritis. Cement does not have good mechanical properties with respect to shear forces. Diagnostic biopsy may be performed during the procedure. Cementoplasty has no local anti-tumour effect.

Other techniques exist; in particular, the combination of screw fixation with cementoplasty to achieve a better biomechanical effect. Interventional radiology can also provide local anti-tumour control (or tumour reduction) by thermal effects, using radiofrequency ablation (hot) or cryoablation (cold).<sup>25</sup>

Surgery can be performed on the extremities or the



spine. It can be either preventive, when the risk of fracture is too high, or curative, when a fracture has occurred at a pathological lesion causing disabling pain and/or spinal cord compression. Radiation therapy to the entire bone and construct is generally recommended postoperatively. The type of surgery (screw-plate or nail osteosynthesis, arthroplasty or reconstructive surgery) depends on the location of the lesion, the patient's general condition and prognosis. In the case of hypervascularised bone metastases (e.g., renal cancer), surgery is usually preceded by preoperative embolisation to limit the risk of bleeding.<sup>26–28</sup>

### Holistic management of bone metastases

Holistic management of bone metastases requires defining a precise, personalised goal for the patient based on the seven challenges mentioned above. In some cases of oligometastases, curative resection or ablative radiation may also be indicated (see Figure 1).

Simple situations require simple, quick responses. For complex cases, seeking advice from a bone metastasis multidisciplinary consultation meeting (BCM3) is helpful. The BCM3 brings together rheumatologists, osteo-articular radiologists, orthopaedic/spine surgeons, radiation oncologists and nuclear medicine physicians. Medical oncologists, organ-specific oncologists (especially pulmonologists, senologists, and urologists), pathologists, and palliative care/pain specialists often attend the meeting to present their patients. The BCM3 is complementary to the oncology multidisciplinary consultation meeting. BCM3 decisions must be made with the oncologists to optimise the coordination of bone-related care and overall treatment. Discussions allow for establishing a personalised management programme integrating bone metastases and oncological pathways.<sup>17</sup> The programme should include a reassessment of bone metastases from the outset.

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## Key learning points

- Because of significant advances in cancer therapies, many patients now benefit from prolonged remissions, even in metastatic disease. This must be taken into account in the management of bone metastases.
- Treatments for bone metastases are either systemic or local. Systemic antiresorptive therapy should be commenced as soon as bone metastases are detected in breast cancer; and treatment is indicated at the onset of hormone resistance in prostate cancer.
- Surgery can be either preventive when the risk of fracture is too high, or curative when a fracture has occurred at a pathological lesion, causing disabling pain and/or spinal cord compression. Radiation therapy to the entire bone and construct is generally recommended postoperatively.
- Holistic management of bone metastases requires defining a precise, personalised goal for the patient based on seven challenges.
- Multidisciplinary management strategies are key in optimising patient care and outcomes.

### Conclusion

Bone metastases are a common complication of cancer. Skeletal-related events from malignant bone disease cause considerable morbidity and severely impact patients' quality of life. Holistic management of bone metastases requires a precise, personalised goal for the patient based on the seven challenges. The optimisation of care also depends on clinicians thoroughly appreciating the complementary benefits of the various management strategies and their limitations and the multidisciplinary team plays a crucial role.

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# Conclusion

Cancer is a major risk for both generalised and local bone loss, with bone loss substantially higher in cancer patients than in the general population, independent of cancer type and other risk factors.

Approximately 65%–75% of patients with advanced prostate or breast cancer have bone metastases, which can lead to devastating consequences. Skeletal-related events, such as pathological fracture, spinal cord compression, hypercalcaemia, radiation to the bone to relieve pain or reduce structural damage, and surgery to repair a fracture are common. Delaying these events and delivering appropriate treatment can present challenges in caring for these patients.

Osteoporosis can lead to a higher risk of fracture with resultant loss of quality of life and greater dependence on health care resources; as such, optimal management of skeletal health is an increasingly important part of cancer care. Certain cancer treatments themselves are also implicated in resulting in osteoporosis, including aromatase inhibitors, gonadotrophin-releasing hormone agonists, selective oestrogen receptor modulators, androgen deprivation therapy, luteinising hormone-releasing hormone (LHRH) analogues, LHRH antagonists, antiandrogens and glucocorticoids. This information must be borne in mind when planning treatment for each patient and is an important reason why establishing close and harmonious communication with a patient's referring oncologist will ensure that any treatment is compatible with bone management.

Pain is experienced by 60%–84% of patients with bone metastases. Initially, the pain may be dull and continuous, but it becomes more severe as the cancer progresses. In terms of management, it is essential to understand the pain location, whether it is related to bone metastases and which particular lesion. This is especially true for multiple vertebral lesions.

All these factors bring a significant burden, in both monetary and social terms, as well as an impact on patients and their carers in terms of quality of life and deterioration in mental health. They have also provided a real impetus to improve and develop the management of bone metastases, not least the accompanying damage to bone. Indeed, significant advances in cancer treatment have been made in recent years, with hormone therapies, targeted small molecules, monoclonal antibodies, and immune checkpoint inhibitors added to conventional chemotherapy protocols. Nevertheless, significant challenges still face clinicians tasked with the care of people with metastatic cancer. Numerous factors must be considered when deciding on a management plan, including assessing the risk of complications, whether the disease is early or late stage, patient characteristics such as



comorbidities, age, previous treatment, and a patient's willingness to adhere to their treatment.

The complexity of managing bone metastases, particularly with the additional layer of complications that osteoporosis and the risk of fractures bring, means that a holistic approach to managing patients with bone metastases is vital. A precise, personalised goal for each patient and optimisation of care also depend on clinicians and healthcare professionals thoroughly appreciating the complementary benefits of the various management strategies and their limitations.

Management, especially in complex cases, requires multidisciplinary input from specialists to determine the best treatment options for the individual patient. The team should comprise a medical oncologist, radiation oncologist, radiologist, pathologist, an orthopaedic surgeon interested in bone metastasis, a palliative care specialist, and, most importantly, have input from the patient and the family/carers. Multidisciplinary consultation alongside regular oncology meetings optimise bone-related care and overall treatment coordination.

As we continue our mission of producing compelling and impactful educational content, *Hospital Pharmacy Europe* hopes this latest handbook will precisely achieve that goal and support you in optimising management and prevention strategies to ensure the best possible outcomes for patients with secondary bone cancer and skeletal fragility under your care.



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