Bone metastases

Robert E. Coleman[1] ✉, Peter I. Croucher[2,3], Anwar R. Padhani[4], Philippe Clézardin[1,5], Edward Chow[6], Marie Fallon[7], Theresa Guise[8], Simone Colangeli[9], Rodolfo Capanna[9] and Luis Costa[10]

Abstract | Bone is the most frequent site for metastasis for many cancers, notably for tumours originating in the breast and the prostate. Tumour cells can escape from the primary tumour site and colonize the bone microenvironment. Within the bone, these disseminated tumour cells, as well as those arising in the context of multiple myeloma, may assume a state of dormancy, remaining quiescent for years before resuming proliferation and causing overt metastasis, which causes bone destruction via activation of osteoclast-mediated osteolysis. This structural damage can lead to considerable morbidity, including pain, fractures and impaired quality of life. Although treatment of bone metastases and myeloma bone disease is rarely curative, disease control is often possible for many years through the use of systemic anticancer treatments on a background of multidisciplinary supportive care. This care should include bone-targeted agents to inhibit tumour-associated osteolysis and prevent skeletal morbidity as well as use of appropriate local treatments such as radiation therapy, orthopaedic surgery and specialist palliative care to minimize the impact of metastatic bone disease on physical functioning. In this Primer, we provide an overview of the clinical features, the pathophysiology and the specific treatment approaches to prevent and treat bone metastases from solid tumours as well as myeloma bone disease.

Bone resorption
The breakdown or dissolution of bone by osteoclasts.

Osteoclasts
Multinucleated cells derived from granulocyte–macrophage precursors that break down (resorb) bone.

Osteoblast
A bone-forming cell derived from mesenchymal, fibroblast-like cells that forms bone and usually works in close collaboration with osteoclasts to ensure bone resorption and formation are linked and balanced.

✉e-mail: r.e.coleman@sheffield.ac.uk

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Cancer is a major cause of death worldwide and does so through the ability of malignant cells to leave the site of the primary tumour and spread to other parts of the body via a complex process known as metastasis[1]. Metastases, also referred to as secondary cancers, progressively overwhelm normal organ function and, ultimately, result in death of the patient.

Bone is a particularly common site for metastases and affects many patients with advanced cancer[1] (FIG. 1). Bone metastases can be classified as osteolytic or osteoblastic according to the characteristic radiographic appearances of the lesions, based on the predominance of lysis or sclerosis in the bone. When bone resorption mediated by osteoclasts dominates, as in many patients with lung cancer or multiple myeloma, focal bone destruction occurs, resulting in what are often described as 'punched out' lytic lesions. Conversely, in bone metastases characterized by increased osteoblast activity, such as in patients with prostate cancer, the metastatic bone appears as dense osteosclerotic lesions. Although one component may seem to predominate, both processes are usually accelerated within the bone metastasis, resulting in 'mixed' lesions in which both lytic and sclerotic components are visible. Mixed lesions occur in many tumour types but are especially frequent in patients with metastatic breast cancer.

Bone metastases often lead to skeletal morbidity, usually referred to as skeletal-related events (SREs) that point to the five major objective complications of tumour bone disease[1,2]. These major complications include pathological fracture, the need for radiotherapy to relieve bone pain or reduce structural damage within the bone, surgery to bone to prevent or repair a fracture, spinal cord compression and hypercalcaemia[1]. Typically, SREs reduce overall survival and are associated with loss of mobility and social functioning, decreased quality of life and substantial increases in medical costs[2,3].

The treatment of bone metastases is aimed at preventing disease progression and symptom palliation, with cure only rarely a realistic aim (for example, in lymphoma). The median survival after a diagnosis of bone metastases ranges from ~1 year for patients with lung cancer to 3–5 years for those with breast cancer, prostate cancer or multiple myeloma[4]. External beam radiotherapy (EBRT), endocrine therapy, chemotherapy, biologically targeted therapy and immunotherapy as well as systemically administered radioisotopes are all important treatment modalities that may be recommended. In some cases, surgical intervention is necessary to manage structural complications associated with bone destruction or nerve compression. Additionally, bone-targeted agents (BTAs) such as bisphosphonates

Author addresses

[1]Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK.
[2]Garvan Institute of Medical Research, Darlinghurst, New South Wales, Australia.
[3]St Vincent's Clinical School, Faculty of Medicine, UNSW Sydney, Sydney, New South Wales, Australia.
[4]Paul Strickland Scanner Centre, Mount Vernon Cancer Centre, Northwood, UK.
[5]INSERM, Research Unit UMR_S1033, LyOS, Faculty of Medicine Lyon-Est, University of Lyon, Lyon, France.
[6]Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada.
[7]Edinburgh Cancer Research Centre (IGMM), University of Edinburgh, Edinburgh, UK.
[8]Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA.
[9]Department of Translational Research on New Surgical and Medical Technologies, University of Pisa, Pisa, Italy.
[10]Hospital de Santa Maria and Instituto de Medicina Molecular, Faculdade de Medicina, Centro Hospitalar de Lisboa Norte, Lisbon, Portugal.

Bisphosphonates
A class of drugs that prevent bone loss by disrupting osteoclast-mediated bone resorption.

Denosumab
A fully humanized monoclonal antibody that binds to receptor activator of nuclear factor-κB ligand (RANKL) and inhibits osteoclast-mediated bone resorption.

and denosumab have been shown to complement the cancer-specific treatments by improving bone structure and quality to minimize the risk of skeletal morbidity[2,4,5].

Owing to the high prevalence of bone metastases and the substantial morbidity associated with the disease, the clinical burden on patients, carers and health-care systems is very large. Further research into prevention and treatment of bone metastases is therefore of great importance to improve this major unmet medical need[1].

In this Primer, we review the epidemiology and pathophysiology underlying metastatic bone disease and describe the specific treatment approaches that help prevent disease progression. Additionally, we summarize the role of current technologies that are used for diagnosis and to monitor response to treatment. Finally, we discuss the various potential therapeutic targets that might be suitable for novel treatment approaches in the future.

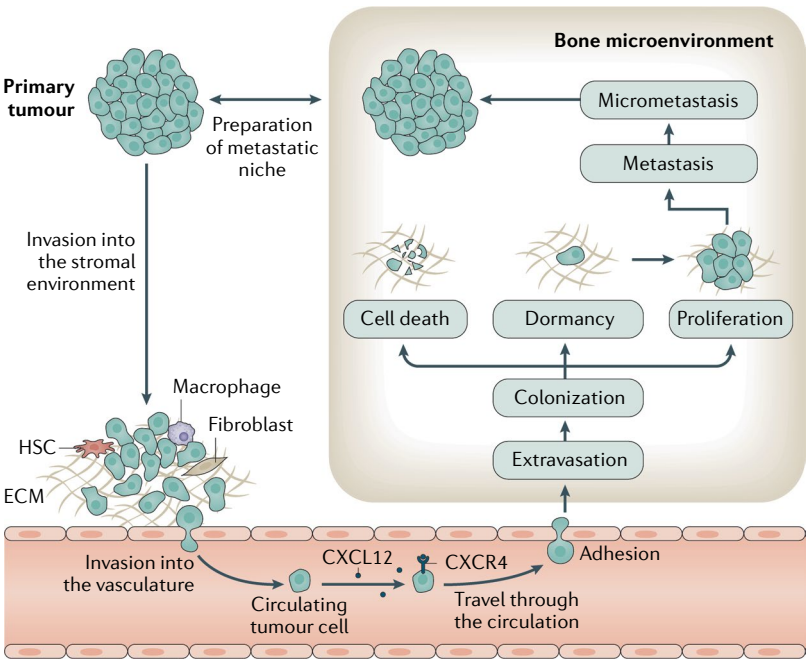

Fig. 1 | **Metastatic invasion of cancer cells to the bone.** The stages of metastasis from preparation of the metastatic niche, invasion, circulation, extravasation and colonization of the metastatic site, tumour dormancy and progression to overt metastases. The early stages of metastasis usually take place even before cancer diagnosis. However, the phenomenon of tumour dormancy, particularly in breast cancer and prostate cancer, suggests that progression to overt metastases often does not take place for many years after diagnosis and treatment of the primary cancer. CXCL12, C-X-C motif chemokine receptor ligand 12; CXCR4, C-X-C motif chemokine receptor 4; ECM, extracellular matrix, HSC, haematopoietic stem cell. Adapted from REF.[260], Springer Nature Limited.

Epidemiology

Globally, >18 million cancers are registered each year and >50% of cases will develop metastatic disease[6]. The vast majority of individuals with metastatic cancer will die because of cancer rather than other causes. In 2018, 9.6 million cancer deaths were recorded worldwide; cancers of the lung (2.1 million cases; 1.8 million deaths), breast cancer (2.1 million cases; 627,000 deaths) and prostate cancer (1.3 million cases; 359,000 deaths) were the most common types[6].

Prevalence of bone metastases

Metastatic bone disease is most commonly seen with specific cancer types, notably those with metastases arising from the breast (70%), prostate (85%), lung (40%) and kidney (40%), as well as multiple myeloma (95%)[4]. Given the high prevalence of carcinomas of the breast, lung and prostate, these carcinomas account for >80% of patients with metastatic bone disease[4,6]. Most tumours predominantly metastasize to the axial skeleton[1,7], particularly the spine (87%), pelvis (63%), skull (35%) and ribs (77%) as well as the proximal humeri and femora (53%), rather than to the distal appendicular skeleton (1%)[7]. This pattern of metastatic spread to bone reflects the distribution of the so-called red bone marrow, a highly vascular tissue containing haematopoietic stem cells and an active microenvironment that promotes cellular growth.

Prevalence of SREs

Skeletal morbidity is most common in the context of osteolytic bone metastases. Amongst all tumour types, patients with breast cancer[8] and multiple myeloma[9] have the highest incidence of SREs. In studies conducted in the 1990s, the proportion of patients with bone metastases who experienced at least one SRE after a median follow-up of 21–24 months was 64% in those with breast cancer[8], 49% in those with prostate cancer[10], 46% in patients with other solid tumours (including lung cancer)[11] and 51% in patients with multiple myeloma[9]. Data collected from routine clinical practice in the 2010s continues to support the relevance of SREs as an important clinical issue in patients with bone metastases, with a high proportion of patients still experiencing SREs despite advancements in primary cancer treatment that have emerged since the 1990s[12].

Breast cancer. The prevalence of bone metastases is highest in breast cancer owing to the high frequency of skeletal involvement and the long clinical course. Before the introduction of bone-targeted treatments, at 1-year follow-up of patients with bone metastases from breast cancer, 49% experienced fractures, 33% needed radiotherapy, 12% developed hypercalcaemia, 10% required orthopaedic surgery and 4% demonstrated spinal cord compression[8]. The median survival in breast cancer after the tumour has metastasized to bone is ~2–3 years[4,5].

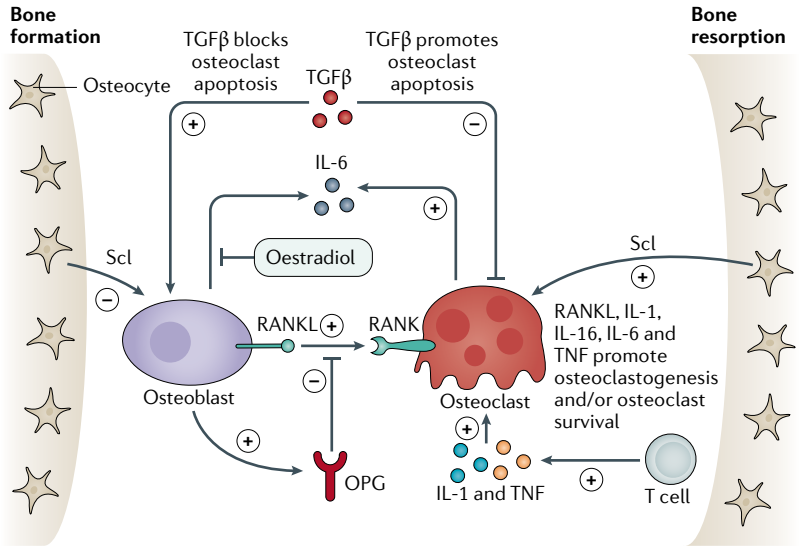

Fig. 2 | **Physiological bone remodelling.** The cellular interactions and key regulators underpinning the bone remodelling process, necessary for maintenance of healthy bone. In addition, other circulating hormones such as parathyroid hormone and vitamin D regulate the calcium balance, within the bone and at other body sites. OPG, osteoprotegerin; RANK, receptor activator of nuclear factor-κB; RANKL, receptor activator of nuclear factor-κB ligand; Scl, sclerostin; TGFβ, transforming growth factor-β; TNF, tumour necrosis factor. Adapted from REF.[261], Springer Nature Limited.

Prostate cancer. In prostate cancer, metastatic disease is often confined to the skeleton and is the main cause of symptoms and premature death. Histological examination of bone metastases from prostate cancer has shown the characteristic association of an osteoblastic response. However, a wide variation in the osteoclast response is present from patient to patient and, consequently, in the amount of structural damage[13]. Bone resorption rates, determined by measuring collagen breakdown products, are often high in patients with prostate cancer[14]. SREs are frequent in prostate cancer, notably 33% of cases experience pain requiring radiotherapy, 25% develop a fracture and 8% develop spinal cord compression[10].

Lung cancer. In patients with bone metastases from lung cancer, ~25% of patients present with an SRE as the first sign of skeletal involvement and 40% have been shown to experience an SRE during the clinical course of their metastatic disease[12]. With new treatments improving overall survival in patients with lung cancer, the relevance of skeletal morbidity in lung cancer is becoming increasingly important[15].

Multiple myeloma. Bone pain, most often in the back due to vertebral fractures, is a presenting feature in ~75% of patients with multiple myeloma[16]. SREs are frequent even after initiating treatment, with 37% experiencing a fracture, 34% requiring radiotherapy for pain relief and 9% developing hypercalcaemia. Extensive lytic bone destruction is observed in >90% of patients and, typically, myeloma bone disease does not heal despite successful antineoplastic treatment[17]. Risk for fracture is also increased in patients with the precursor of myeloma, known as monoclonal gammopathy of unknown significance[18].

Axial skeleton
The central portion of the skeleton comprising the skull, spine, pelvis, shoulders, hips and ribs.

Mechanisms/pathophysiology

The evolution of solid tumour metastases to bone is a complex process. The metastatic dissemination of tumour cells involves pre-metastatic niche formation, tumour cell dissemination through the circulation, and chemotactic attraction and homing of tumour cells to the metastatic site as well as reciprocal interactions with local stromal cells and immune cells within the bone microenvironment[19] (FIG. 1). The unique milieu of specialized bone cells (osteoclasts, osteoblasts and osteocytes), mineralized bone matrix and other cell types within bone provides a fertile soil, promoting cancer growth[19].

Bone remodelling

Bone is a highly specialized, vascularized and innervated connective tissue containing an unmineralized matrix, known as osteoid, composed predominantly of type I collagen and a mineralized matrix of hydroxyapatite crystals[20]. The mineralized compartment encompasses the marrow space containing marrow-residing cells, including osteoblasts, osteoclasts, bone marrow stromal cells, immune cells, mesenchymal stem cells, adipocytes, fibroblasts, endothelial cells and haematopoietic cells, all within a fibrous stroma interspersed by fat and interstitial fluid.

In general, bone undergoes a constant finely balanced and coupled remodelling process, orchestrated by bone-destroying osteoclasts, bone-forming osteoblasts and mechanosensory osteocytes. In a healthy person, bone resorption and bone formation are perfectly balanced in location, time and amount and are regulated by complex interactions of hormones, paracrine growth factors and cytokines with the different cell types within the bone microenvironment[21,22] (FIG. 2).

Bone is uniquely responsive to mechanical stress such as weight bearing and exercise, and the resultant remodelling process continues throughout life, with up to 20% of the skeleton undergoing remodelling at any time to repair damage from mechanical stresses and to maintain skeletal integrity[20]. As a person ages, the coupling between bone formation and resorption is less effective than in the normal healthy young adult owing to age-related changes in hormones and a progressive decline in mobility with age. As a result, bone resorption predominates and 0.5–1% loss of bone per annum occurs, which reduces skeletal strength and its resilience to structural damage from diseases such as malignant infiltration[20].

Bone as a preferred site for metastases

The distribution of bone metastases preferentially in the highly vascular red marrow-containing axial skeleton suggests that slow blood flow at these sites could support the attachment of metastatic tumour cells to the endosteal bone surface. However, anatomical characteristics do not adequately account for the distribution of metastases, and the molecular properties of the malignant cells (that is, the seed) and their reciprocal interactions with the bone microenvironment (the soil) are of greater importance in enabling the metastatic spread of tumour[23].

Bone is a rich source of calcium, which is released as a consequence of bone destruction. Extracellular calcium has been shown to promote tumour growth in the bone via cancer cell expression of extracellular calcium-sensing receptors[24]. For example, high expression of extracellular calcium-sensing receptor in patients with renal cell carcinoma was associated with a higher incidence of bone metastases than in those with low extracellular calcium-sensing receptor expression. Furthermore, the addition of tumour-derived calcium from patients with renal cell carcinoma bone metastases to tumour cell cultures stimulated their migration and proliferation[24].

In addition to calcium, bone is a large storehouse for growth factors, such as transforming growth factor-β (TGFβ), which can promote tumour growth[19]. Osteoblasts deposit growth factors, which are then released and activated by osteoclastic bone destruction. This release of bone-derived factors can stimulate tumour growth, thereby establishing a vicious cycle, leading to enhanced osteolysis stimulated by tumour-derived factors and release of additional growth factors that further stimulate tumour cell proliferation[25].

The immune system also exerts multiple inhibitory and stimulatory effects on host cells within the bone microenvironment that might facilitate metastasis to bone[26]. Osteoclasts are derived from progenitor cells, which can also differentiate into macrophages and lymphocytes. Many of the cytokines involved in regulating bone cell activity have effects on immune cells and the immune response. For example, the main regulator of osteoclast function, receptor activator of nuclear factor-κB (RANK) ligand (RANKL), is produced not only by osteoblasts but also by lymphocytes and has a range of effects, including activation of dendritic cells. Many chemokines involved in the homing of immune cells to sites of action also influence the homing and colonization of tumour cells to the bone microenvironment. These immune cells might have regulatory effects on the phenomenon of tumour dormancy discussed below[26].

Establishment of the pre-metastatic niche

The initiation of metastatic spread is an early event in cancer, occurring before the primary tumour becomes clinically detectable[27]. Evidence from preclinical studies supports the notion that primary tumours need to prepare the microenvironment of a target organ to create a favourable environment for tumour cells to colonize and establish a 'successful' metastatic spread[28]. For example, cancer-associated stromal fibroblasts in primary breast cancer secrete C-X-C motif chemokine receptor ligand 12 (CXCL12), which primes the tumour cells to preferentially migrate to organs expressing its receptor, C-X-C motif chemokine receptor 4 (CXCR4), via selection for high SRC kinase activity[29].

Autocrine secretion of the lysyl oxidase family of enzymes by primary tumour cells has been shown to modulate the extracellular matrix at metastatic sites including bone to facilitate future colonization by tumour cells[30]. Additionally, exosomes and microRNAs produced by the primary tumour have been shown to have systemic stimulatory effects on bone remodelling and can be associated with the development of metastasis in different sites, including bone[31,32].

Proteolytic enzymes, including matrix metalloproteinases (MMPs) and cathepsin K, might also be involved in the early phases of bone metastasis formation[33]. Studies have demonstrated that MMPs can degrade basement membranes to facilitate tumour cell dissemination. Furthermore, MMPs have also been shown to promote the release and activation of growth factors and cytokines bound to the osteoid, thereby further augmenting bone destruction[34] and tumour cell proliferation.

Tumour colonization and dormancy

Metastasis is usually a very inefficient process, with most tumour cells leaving the primary site destroyed before establishing a metastatic focus[35]. However, a small fraction of the tumour cells shed from the primary tumour survive and are chemotactically attracted to 'metastatic niches' in the haematopoietic bone marrow[36]. The precise characteristics of the metastatic niche remain to be established, but model systems have demonstrated that tumour cells reside in the haematopoietic stem cell niche and the perivascular niche[37].

Once established in the metastatic niches, disseminated tumour cells might remain dormant for many years, regulated by the adjacent bone microenvironment[38]. The signals that trigger tumour cells to evolve from the dormant state to subsequently establish overt, clinically detectable bone metastases are under intense study. However, these molecular players are not yet defined with sufficient granularity to be applied in the clinic[39].

Classification of bone metastases

Osteolytic bone metastases are typically observed in breast cancer, lung cancer and renal cancer, whereas osteoblastic disease is predominantly associated with prostate cancer but can also occur in breast cancer. In osteolytic disease, tumour cells produce factors that stimulate osteoclast formation and activation. The osteoblastic phenotype is the result of tumour secretion of factors that stimulate osteoblast proliferation and differentiation, such as endothelin 1 (REFS[40,41]). Although these phenotypes represent two ends of a spectrum, most solid tumour metastases to bone have components of both accelerated bone destruction and new bone formation. Indeed, autopsy studies show that bone metastases can be heterogeneous within a single patient, that is, osteolytic at one site and osteoblastic or mixed at another site[42,43]. Renal cell carcinoma and multiple myeloma are exceptions as these tumours are often entirely osteolytic. Moreover, tumour cell suppression of osteoblast activity is a clinical feature that distinguishes multiple myeloma from most other solid tumour bone metastases[17].

Osteolytic bone metastases

Osteolytic bone metastases are associated with bone destruction resulting from tumour cell secretion of osteolytic factors, such as parathyroid hormone-related protein (PTHrP)[44], IL-11 (REF.[45]) and Jagged 1 (REF.[46]). PTHrP and IL-11 enhance the local production of RANKL[47], which stimulates osteoclast formation and activation, whereas

Exosomes
Extracellular vesicles that may contain proteins, RNA or DNA.

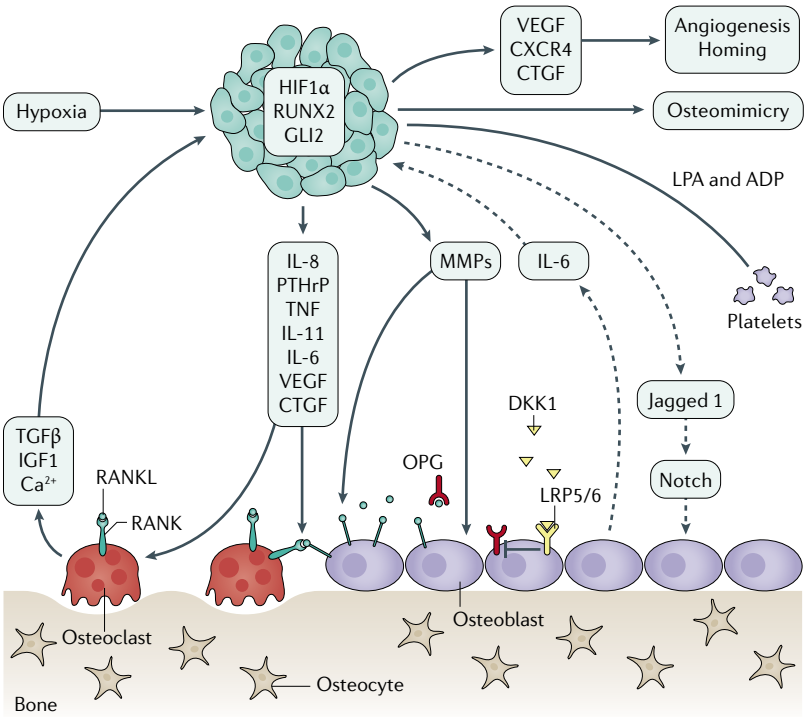

Fig. 3 | **Osteolytic bone metastases.** Circulating tumour cells are attracted to the bone surface, where tumour cells secrete a range of cytokines and growth factors that stimulate bone cell function with predominant effects on osteoclastic bone resorption. The release of bone-derived growth factors and calcium creates a more favourable environment for the tumour cells to survive and proliferate. Other microenvironmental factors, such as hypoxia, can also influence tumour cell survival. ADP, adenine diphosphate; Ca^{2+}, ionized calcium; CTGF, connective tissue growth factor; CXCR4, C-X-C motif chemokine receptor 4; DKK1, Dickkopf-related protein 1; GLI2, GLI family zinc finger 2; HIF1α, hypoxia-inducible factor 1α; IGF1, insulin-like growth factor 1; LPA, lysophosphatidic acid; LRP, low-density lipoprotein receptor-related protein; MMP, matrix metalloproteinase; OPG, osteoprotegerin; PTHrP, parathyroid hormone-related protein; RANK, receptor activator of nuclear factor-κB; RANKL, receptor activator of nuclear factor-κB ligand; RUNX2, Runt-related transcription factor 2; TGFβ, transforming growth factor-β; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor. Adapted from REF.[35], Springer Nature Limited.

Jagged 1 promotes fusion of osteoclast precursor cells by directly binding to monocytes (FIG. 3). Tumour-induced osteoclastic bone destruction triggers the release of growth factors, which promote tumour cell growth and further enhance tumour secretion of osteolytic factors, augmenting bone destruction and, thereby, driving a feedforward cycle to fuel tumour growth in bone[25] (FIG. 3).

Breast cancer metastases to bone. Breast cancer, one of the common osteolytic metastases, has been shown to exploit the bone microenvironment through various mechanisms to survive and proliferate in the bone. Breast cancer cells selected for a high bone metastatic capacity (by sequential cell passage experiments of human-derived cell lines) were shown to express a toolbox of genes that encode osteolytic factors (IL-11), angiogenic factors (connective tissue growth factor, CTGF), CXCR4 and invasive factors (MMP1), all of which act on different parts of the metastatic cascade[45]. For example, IL-11 stimulates osteoclastic bone destruction; CTGF stimulates angiogenesis, which helps tumour growth and osteoblast proliferation; and CXCR4 on tumour cells binds to its ligand, CXCL12, which is expressed by organs, including the bone microenvironment niches[48]. Furthermore, MMP1 promotes cancer cell invasion, which is further enhanced by the RANK/RANKL signalling pathway[49]. This signalling cleaves the collagen molecules at the bone extracellular matrix to prime the endosteal bone surface for osteoclastic bone resorption[34] to initiate the feed-forward cycle of bone destruction. Collectively, these findings suggest that tumour cells acquire a set of functions through which they exploit the bone microenvironment and grow into a functional metastatic lesion[45].

Breast cancer cells have also been shown to hijack the osteogenic niche to absorb calcium, which helps their survival. For example, in preclinical model systems, breast cancer cells utilize the bone cells to increase intracellular calcium concentration by forming connexin-43 gap junctions with osteoblasts[50,51]. Additionally, studies have also implicated the importance of the Wnt pathway in the establishment of breast cancer in bone through its known effects on cancer stem cell maintenance and interactions with IL-1β[52]. Furthermore, crosstalk between muscle and bone is now appreciated, that is, changes induced by hormones, cytokines and growth factors in one tissue might affect the other and vice versa[53]. For example, one study showed that muscle weakness associated with breast cancer might promote the development of bone metastasis[54].

Systemic effects of physiological changes, cancer treatments and, potentially, the cancer itself on the bone microenvironment might also promote breast cancer (and other tumour) growth in bone. In mouse models of oestrogen deprivation (frequently used to treat breast cancers), tumour growth was enhanced in bone and this increased development of bone metastases could be blocked by inhibitors of osteoclastic bone resorption, such as zoledronate[55,56]. Systemic activation of the sympathetic nervous system, as would be observed through anxiety and depression in patients with breast cancer, promotes breast cancer localization to bone by inducing RANKL expression in bone marrow osteoblasts. One study demonstrated that pharmacological stimulation of the β2 adrenergic receptor increased the migration of breast cancer cells in vitro, independently of CXCL12–CXCR4 signalling. These migratory effects could be hampered by either blocking the β-adrenergic receptor or by inhibiting RANKL[57].

Lung cancer metastases to bone. Lung cancer bone metastases, particularly those from non-small-cell subtypes such as adenocarcinoma, are often osteolytic. Lung cancer shares some common pathophysiological mechanisms of metastases with breast cancer and multiple myeloma. In the setting of lung cancer bone metastases, increased bone turnover markers such as collagen fragments and bone alkaline phosphatase, increased tumour expression of various microRNAs (for example, miR-335, miR-33a and miR-21) and increased expression of Dickkopf-related protein 1 (DKK1) and IGFBP3 have all been associated with a poor prognosis in patients with lung cancer[58]. In addition, osteolytic factors such as PTHrP, IL-11 and other downstream mediators of TGFβ signalling have been implicated in lung

Bone turnover
A measure of the speed of bone resorption and formation as determined by biomarkers or bone biopsy.

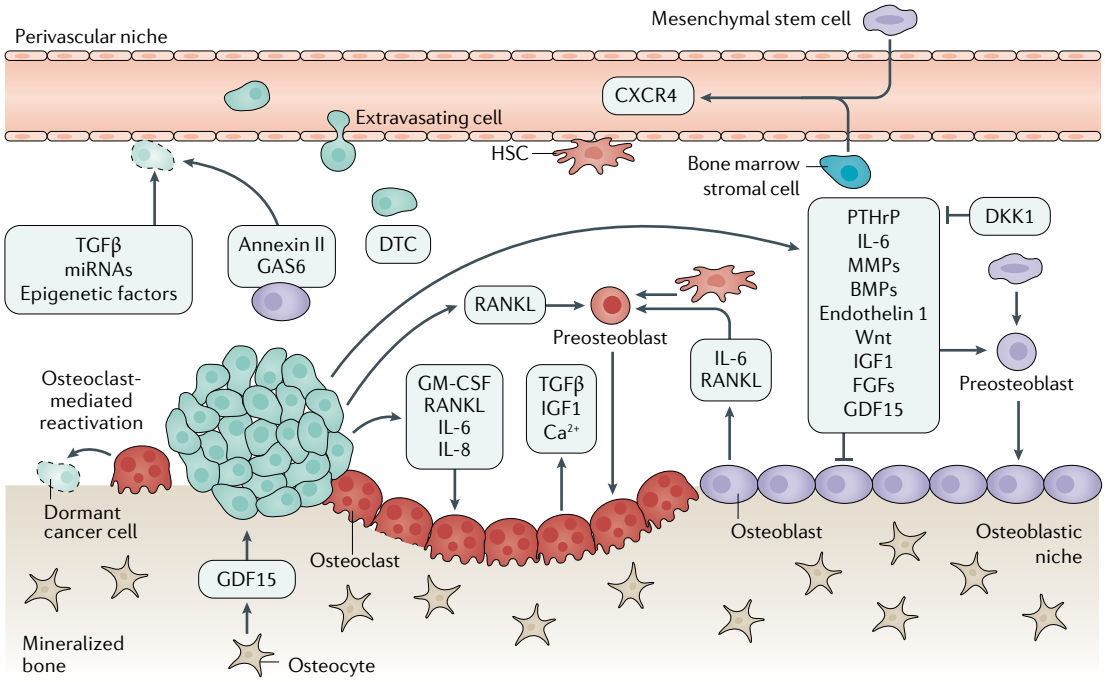

Fig. 4 | **Osteoblastic bone metastases.** Circulating tumour cells are attracted to the bone surface, where they secrete a range of cytokines and growth factors that stimulate bone cell function with predominant effects on the osteoblasts, resulting in increased bone formation. BMP, bone morphogenetic protein; Ca^{2+}, ionized calcium; CXCR4, C-X-C motif chemokine receptor 4; DKK1, Dickkopf-related protein 1; DTC, disseminated tumour cells; FGF, fibroblast growth factor; GAS6, growth arrest-specific protein 6; GDF15, growth differentiation factor 15; GM–CSF, granulocyte–macrophage colony-stimulating factor; HSC, haematopoietic stem cell; IGF1, insulin-like growth factor 1; miRNA, microRNA; MMP, matrix metalloproteinase; PTHrP, parathyroid hormone-related protein; RANKL, receptor activator of nuclear factor-κB ligand; TGFβ, transforming growth factor-β. Adapted from REF.[262], Springer Nature Limited.

cancer-associated bone destruction[59,60]. Furthermore, activation of the canonical Wnt pathway has been shown to mediate bone metastases and brain metastases via HOXB9 and LEF1, which enhances chemotactic invasion and colony outgrowth[61]. One study has reported higher concentrations of serum DKK1 in patients with non-small-cell lung cancer-associated bone metastases than in those without bone metastases[62]. DKK1 has been shown to inhibit osteoblast activity by suppressing β-catenin and Runt-related transcription factor 2 (RUNX2) in small-cell lung cancer[63]. Thus, targeting Wnt signalling, specifically DKK1, might be an effective method to treat bone metastases from lung cancer.

Other molecules such as a disintegrin and metalloproteinases (ADAMs) have been associated with poor prognosis in lung cancer. Specifically, the truncated forms of ADAM8 have been shown to increase the expression of IL-8 and IL-6 as well as osteolytic bone metastases in mouse models[64]. Hypoxia (via hypoxia-inducible factor 1α (HIF1α)) has been shown to induce ADAM17 and Semaphorin 4D (an osteogenic inhibitory factor overexpressed in lung cancer), which strongly correlate with osteolytic bone destruction[65]. One study showed that TNFSF14 (also known as LIGHT), which regulates innate and adaptive immune responses, was increased in the serum and monocytes of patients with non-small-cell lung cancer-associated bone metastases. LIGHT increases RANKL and inhibits bone formation and seems to be an important control mechanism for bone homeostasis during metastatic invasion[66]. Furthermore, RANKL inhibitors as well as zoledronate has been shown to reduce lung cancer osteolysis in mouse models[67,68].

Osteoblastic bone metastases

Osteoblastic bone metastases are associated with tumour production of osteoblastic factors, which stimulate osteoblast proliferation and differentiation[69,70]. These factors include endothelin 1, growth differentiation factor 15 (GDF15) and bone morphogenic proteins (BMPs), effects of which are often mediated by the Wnt signalling pathway. The osteoblastic process adds a layer of complexity to the common element of osteolysis, which is present across all tumour types.

Osteoblast precursors in the bone microenvironment are hypothesized to be the source of tumour-induced bone formation. However, studies have provided evidence for tumour osteomimicry[71] as well as tumour-induced endothelial-to-osteoblast conversion[72] as the source of bone forming activity. Osteomimicry is defined as the ability of cancer cells or associated microenvironment cells to express bone-specific proteins, such as osteocalcin, osteopontin and RANKL, which support cancer cell growth and survival in the bone microenvironment. Osteomimicry can occur at primary tumour or metastatic sites[71] and similar mechanisms have been described in breast cancer[73] (FIG. 4).

Endosteum
A thin vascular membrane of connective tissue that lines the inner surface of the bony tissue that forms the medullary cavity of long bones.

Prostate cancer metastases to bone. Prostate cancer is unique in its ability to stimulate abnormal new bone formation. Wnt signalling and fibroblast growth factor receptors activated by tumour-secreted endothelin 1 have been shown to have a crucial role in this process[74]. Tumour cells can induce osteocytes to secrete GDF15, which stimulates prostate cancer growth and invasion[75]. Additionally, the mechanical effects of tumour-induced pressure in the bone microenvironment cause osteocytes to promote bone remodelling and tumour growth[76]. Prostate cancer cells have been shown to displace the haematopoietic stem cells (HSCs) from their niche within the bone marrow to create an empty niche for metastasis formation[77]. Furthermore, one study showed that prostate cancer cells interact with the HSC niche and switch on a wide repertoire of genes to maintain tumour cell dormancy[78].

In support of the osteomimicry hypothesis, tumour-associated endothelial cells isolated from mouse prostate cancer were shown to express haematopoietic stem cell and mesenchymal stem cell markers and differentiated to form cartilage and bone tissues, with an associated upregulation of a chondrocytic marker (SOX9) and the osteoblast marker, osteocalcin[79]. These changes also promoted the formation of blood vessels that facilitate tumour cell intravasation necessary for metastasis formation. Prostate cancer-associated endothelial cells can also undergo mesenchymal-like transition, suggesting that these tumour-derived cells are pluripotent with the ability to differentiate into various cell types[72].

Myeloma bone disease

Bone disease associated with multiple myeloma, a malignancy of plasma cells arising in the bone marrow, is characterized by osteolytic bone lesions and a generalized bone loss or osteoporosis.

In the bone marrow, myeloma cells localize to specialized niches on the endosteal bone surface, which include cells of the osteoblast lineage[80,81]. A unique myeloid gene signature is activated in myeloma cells, which maintains these cells in a long-term dormant state[82]. Subsequently, as the disease progresses, a subset of dormant myeloma cells are released from niche-dependent control and are reactivated, forming actively growing myeloma colonies within the bone marrow that modify the bone microenvironment[38]. Although selective reactivation is poorly understood, osteoclastic resorption, which can remodel the dormant cell niche on the endosteum, can reactivate dormant tumour cells, suggesting that reactivation is under extrinsic control[81]. Increased osteoclast resorption is also associated with the progression from monoclonal gammopathy of unknown significance to myeloma[82] (FIG. 5).

Myeloma cells have been shown to increase the expression of RANKL, the key osteoclastogenic factor, and decrease the expression of RANKL decoy receptor,

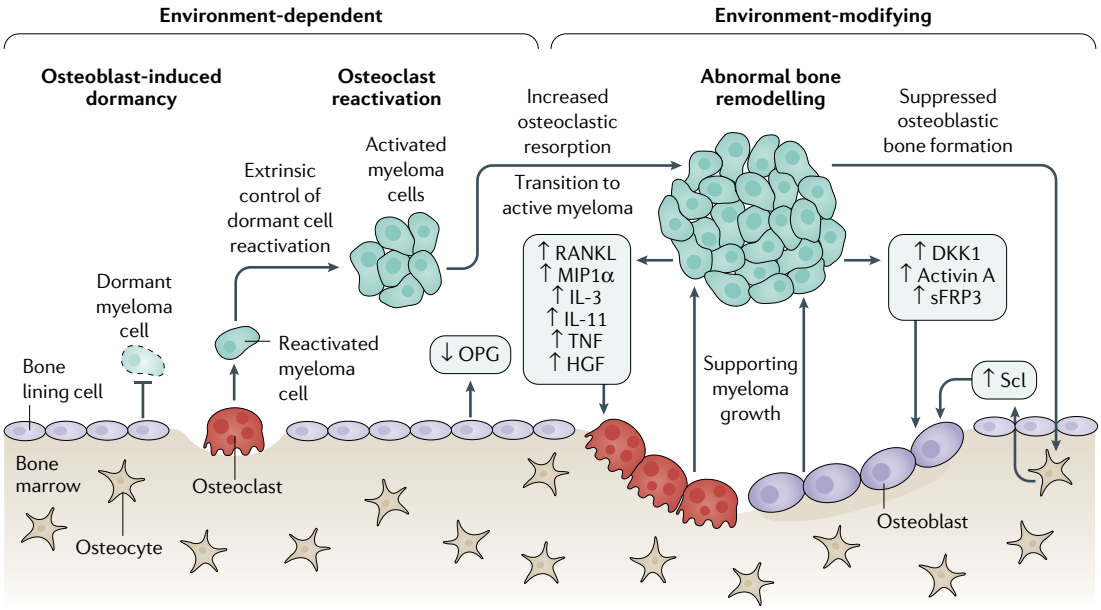

Fig. 5 | **Myeloma bone disease.** Dormant myeloma cells are usually found associated with the endosteal bone surface. Remodelling of the endosteal bone surface by osteoclasts releases these dormant cells from niche-dependent control. Reactivated myeloma cells produce a range of molecules, including receptor activator of nuclear factor-κB ligand (RANKL), macrophage inflammatory protein 1α (MIP1α), IL-3, IL-11, tumour necrosis factor (TNF) and hepatocyte growth factor (HGF), that either directly and/or indirectly stimulate osteoclast formation and bone resorption. These molecules often function by upregulating RANKL and downregulating osteoprotegerin (OPG) expression in the bone microenvironment. Myeloma cells also produce molecules, such as Dickkopf-related protein 1 (DKK1), activin A and soluble frizzled-related protein 3 (sFRP3), that suppress Wnt signalling and inhibit osteoblast differentiation and function, thereby blocking bone formation. Myeloma cells can also interact with osteocytes, either directly or indirectly, to increase sclerostin (Scl) production, which can also inhibit bone formation. This combination of increased resorption and decreased bone formation leads to an uncoupling of the normal process of bone remodelling and the development of osteolytic bone disease. Adapted from REF.[38], Springer Nature Limited.

Leukoerythroblastic anaemia
Anaemia resulting from a structural or neoplastic problem in the bone marrow and the resultant appearance of immature erythrocyte and white cell precursors in the peripheral blood.

osteoprotegerin[83,84]. Myeloma cells and activated T cells in the myeloma microenvironment have also been shown to express RANKL[83,85,86]. Aberrant expression of RANKL leads to an increase in osteoclastic bone resorption and the development of lytic bone lesions. One study reported increased serum levels of soluble RANKL and decreased serum levels of osteoprotegerin in patients with myeloma, consistent with accelerated osteolysis[87]. In experimental models, inhibiting RANKL hindered osteoclast formation, prevented the development of osteolytic bone metastases and reduced myeloma burden[83,88].

Alternative pathways implicated in promoting bone resorption include interactions of tumour cells with stromal cells and the production of CCL3, IL-3, IL-11, TNF and hepatocyte growth factor (HGF) by myeloma cells[89–91]. These molecules likely also stimulate osteoclastic bone resorption by upregulating RANKL expression and downregulating osteoprotegerin expression[92] (FIG. 5).

Myeloma cells secrete soluble Wnt antagonists, including DKK1 and soluble frizzled-related protein 3 (sFRP3), which suppress osteoblastic bone formation, even when myeloma is in remission following effective treatment[93,94]. In experimental models, DKK1 blockade prevented osteoblast inhibition and myeloma bone disease[95,96]. In patients with multiple myeloma, serum levels of DKK1 are elevated and are associated with the extent and progression of bone disease[97]. Furthermore, myeloma cells also interact with osteocytes embedded in the bone matrix and stimulate the expression of soluble Wnt antagonist, sclerostin[98]. In experimental models, inhibiting sclerostin prevented the development of osteolytic bone disease[99–101] and increased the bone strength and resistance to fracture[102]. In addition, activin A, a member of the TGFβ superfamily, was overexpressed in the bone marrow of patients with myeloma[103]. Indeed, inhibiting activin A and/or blocking TGFβ prevented the development of myeloma bone disease in mouse models[101]. The mechanisms behind the largely irreversible inhibition of bone formation (even in the absence of active myeloma cells) are poorly understood and age-related changes and/or epigenetic changes in bone marrow stromal cells might be involved[17].

In addition to the direct effect on bone cells, myeloma cells also interact with T cells, stromal cells and adipocytes in the bone microenvironment to amplify the effect on bone[92]. As a result, the skeleton of patients with multiple myeloma remains abnormal and at increased risk for SREs throughout the clinical course of the disease.

Box 1 | **Challenges and priorities for bone metastases in developing regions**

Challenges

- Late diagnosis
  - Many patients have metastatic disease at diagnosis
- Younger population
  - Fewer cancers associated with old age
  - Younger patients have a different range of cancer diagnoses
- Highly constrained health-care budgets
  - Lack of specialist cancer services and equipment
  - Very limited infrastructure and facilities for imaging
  - Focus on generic drugs
  - Limited access to radiotherapy, specialist orthopaedics and modern targeted treatments
  - Potential for generic bisphosphonates to reduce health-care demands and improve patient quality of life largely unrecognized

Priorities

- Burden of associated disease
  - Infections (HIV, malaria, tuberculosis)
  - Maternal and child health needs
  - Malnutrition
- Prevention
  - Smoking cessation to reduce lung, oropharyngeal and other cancers
  - Hepatitis B vaccination to prevent hepatocellular carcinoma
  - Condom use to prevent cervical cancer
- Earlier diagnosis
  - Patient education on healthy living and concerning symptoms
  - Cervical screening
- Treatment
  - Focus on curable cancers
  - Palliative care, the main priority for advanced malignancies

Diagnosis, screening and prevention

The clinical burden of cancer is vast and rapidly expanding worldwide. In different parts of the world, the main focus is on prevention of primary cancer through tobacco cessation, vaccination against oncoviruses, earlier diagnosis through patient education and screening, and curative, relatively inexpensive treatments including surgery and generic medications. In the developing world, the diagnosis of metastatic disease is less of a priority than in developed jurisdictions. Furthermore, the treatment options are also limited in regions with low socio-economic status compared with affluent regions with well-developed and funded health-care systems (BOX 1).

Presentation

Patients with bone metastases most often present with bone pain[1], which is often poorly localized and worse at night. In some patients, pathological fractures, hypercalcaemia of malignancy and spinal cord compression are also occasional presenting features. In addition, infiltration of the malignant cells within the bone marrow space might result in anaemia, thrombocytopenia or leukopenia. A full blood count in such cases may show leukoerythroblastic anaemia. Patients may also experience general, non-specific symptoms of advancing malignancy such as malaise, loss of appetite and weight loss, especially if the underlying diagnosis is lung cancer. Although these general symptoms in a patient with a past history of malignancy should prompt investigation, they are not specific to the presence of bone metastases.

Diagnosis

A diagnosis of metastatic bone disease has major clinical consequences for the patient concerned and, therefore, a timely and definite diagnosis is crucial. Within current guidelines, the standard of care imaging methods for bone metastases detection include plain X-ray, CT scan and radionuclide bone scintigraphy. These modalities assess the stromal reaction to the presence of cancer cells within the bone marrow rather than depicting the cancer foci themselves (FIG. 6). This

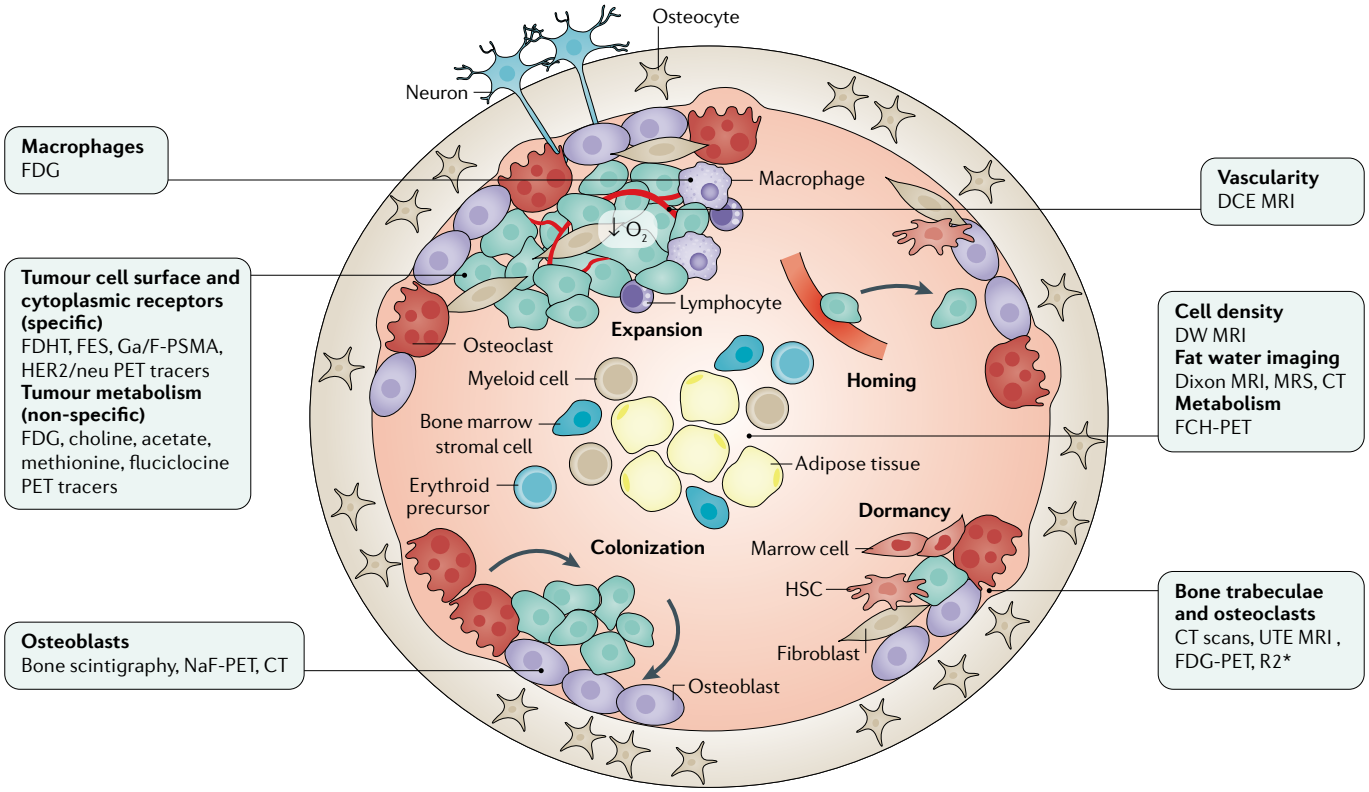

Fig. 6 | **Relationships between imaging technologies and cellular biology of bone metastasis.** Bone is a complex structure consisting of the bone matrix, mesenchymal cells and various haematopoietic bone marrow cells, within which tumour cells remain dormant, proliferate and manipulate the microenvironment. Morphological, functional and molecular imaging methods interrogate aspects of bone, depending on their biophysical basis. Some techniques are able to evaluate the intactness of the bone structure (bone formation and destruction) and reflect the functioning of osteoblasts and osteoclasts. Other techniques report on the displacement and composition of the normal marrow elements. Uniquely, PET techniques report on tumour metabolism, tumour cell surface receptors and tumour cell cytoplasmic receptors. DCE, dynamic contrast enhancement; DW, diffusion weighted; FCH, fluorocholine; FDG, fluorodeoxyglucose; FDHT, fluoro-dihydrotestosterone; FES, fluoroestradiol; HSC, haematopoetic stem cell; HER2/neu (also known as ERBB2), human epidermal growth factor receptor 2; NaF, sodium fluoride; MRS, magnetic resonance spectroscopy; PSMA, prostate-specific membrane antigen; R2*, susceptibility weighted MRI; UTE, ultrashort echo time. Adapted from REF.[35], Springer Nature Limited.

lack of direct depiction of tumour foci limits early metastatic detection and assessment of the response of bone metastases to treatment. Hence, the use of high-sensitivity imaging methods such as a PET scan with various radiotracers and whole-body MRI (including diffusion weighted imaging, bone marrow fat imaging and contrast enhancement) to improve the assessment of metastatic bone disease (TABLE 1) is growing.

Bone metastases in asymptomatic patients are usually diagnosed during imaging investigations that are performed to stage (that is, assess the extent of spread) a cancer or when evaluating metastases at other sites. For example, a CT scan in a patient with liver metastases may reveal asymptomatic bone lesions. In some cases, symptoms or complications from bone metastases might be the first manifestation of malignancy due to a hitherto unnoticed or undetectable primary cancer, referred to as metastatic cancer of unknown primary.

Bone scintigraphy. The detection of bone metastases using bone scintigraphy is based on increased osteoblast activity in the vicinity of the metastases, which results in increased tracer accumulation at sites of bone formation. A meta-analysis showed a combined sensitivity and specificity of 79% (95% CI 73–83%) and 82% (95% CI 78–85%), respectively, on a per-patient basis and a combined sensitivity and specificity of 59% (95% CI 55–63%) and 75% (95% CI 71–79%), respectively, on a per-lesion basis in men with prostate cancer[104]. This finding implies that the ability to detect patients and lesions within bone metastases is limited and that the detected lesions might not always represent bone metastases owing to false-positive observations[104]. However, despite these limitations, bone scintigraphy remains the method of choice for the initial investigation of patients with clinically suspected bone metastases, with the exception of multiple myeloma, renal cancer and thyroid cancer, owing to minimal tracer uptake in purely osteolytic lesions.

CT imaging. CT imaging has reduced diagnostic accuracy compared with MRI as the distinction of tumour cells within the fatty bone marrow surrounded by a calcified bone might be difficult; significant bone destruction and/or new bone formation must occur before a lesion becomes perceptible in a CT scan (FIG. 7). The diagnostic performance of CT for detecting bone metastases is reported to have a sensitivity of 73% and a specificity of 95% in prostate cancer[105]. However, similar to bone

Diffusion weighted imaging
A form of MRI based upon measuring the random Brownian motion of water molecules within a voxel of tissue. Highly cellular tissues or those with cellular swelling exhibit lower diffusion coefficients.

Table 1 | **Strengths and weaknesses of whole-body imaging methods for evaluation of metastatic bone disease**

Method	Strengths	Weaknesses
CT	Widely available	Does not directly evaluate malignant bone disease when soft tissue is absent
	Easily standardized	Radiation exposure
	Low cost	Inability to visualize infiltrative (non-sclerotic) bone disease
	Fast acquisitions	CT 'flare' phenomenon (cannot reliably distinguish osteoblastic healing response from tumour progression)
	Quantitative assessments (Hounsfield units)	
	Ability to discern the full spectrum of metastatic bone disease, from sclerotic to lytic disease	
	Soft-tissue and lytic bone metastasis detection and assessment of response to treatment	
	Incorporated into clinical practice and trial guidelines	
Bone scintigraphy	Widely available	Does not directly evaluate malignant bone disease; reactive osteoblastic uptake only
	Easily standardized	Longest examination times
	Low cost	Pre- and post-examination care precautions
	Incorporated into clinical practice and trial guidelines	Radiation exposure of patients and the public owing to the longer half-life of technetium-99m
		Inability to assess soft-tissue disease
		Lower sensitivity and specificity than CT–MRI
		'Flare' phenomenon (cannot reliably distinguish osteoblastic healing response from tumour progression)
		No disease improvement criteria (progression criteria only)
Fluorine-18 NaF PET–CT	High sensitivity and good specificity for bone metastases (CT scan increases specificity)	Does not directly evaluate malignant bone disease; reactive osteoblastic uptake only
	Medium-length examination times	Limited availability of tracer
		Expensive
		Multiple sources of radiation exposure (CT scans and radiotracer)
		Some post-examination care precautions (not burdensome)
		Limited ability to assess soft-tissue disease owing to lower quality of the CT component (used for attenuation correction)
		'Flare' phenomenon (cannot reliably distinguish osteoblastic healing response from tumour progression or immunotherapy-associated pseudo-progression)
		No positive benefit criteria (progression criteria only)
PET–CT with metabolite radiotracers[a] and cell surface and cytoplasmic receptors[b]	Directly evaluates malignant bone marrow disease	Tracer availability may be limited
	High sensitivity and good specificity for detection of bone and soft-tissue metastases compared with bone scintigraphy or CT alone	Expensive
		Multiple sources of radiation exposure (CT scans and radiotracers)
	Ability to assess response of bone and soft-tissue disease to treatment	Some post-examination care precautions (not burdensome)
	Objective response parameters (specific uptake values)	Potentially influenced by bone marrow-stimulating factors that increase proliferation of haematopoietic progenitor cells, resulting in false-positive and false-negative findings
	Medium-length examination times	
Whole-body MRI with diffusion weighted imaging	Directly evaluates malignant bone marrow disease	Competing demands for MRI resource
	Potential wide availability	Scanner-dependent performance
	No radiation exposure	Longer acquisition time
	Flexible imaging times and adaptable (possible to tailor examinations according to disease location)	Susceptible to artefacts arising from patients (metal implants, bowel gas and patient habitus) and due to data acquisition methods
	Bone disease detection and assessment of response to treatment	Influenced by bone marrow-stimulating factors and blood transfusions resulting in false-positive and false-negative findings
	Objective response parameters (linear dimensions, volumes and ADC measurements)	Radiological expertise required for some aspects of image analysis is limited
		Challenging data analysis
		Higher cost (equal to combined cost of bone scintigraphy and CT scans) and medical insurance reimbursement challenges

Adapted with permission from REF.[244], Elsevier. ADC, apparent diffusion coefficient; NaF, sodium fluoride. [a]Metabolite tracers include glucose, choline and fluciclovine. [b]Cell surface receptors include prostate-specific membrane antigen (PSMA), human epidermal growth factor receptor 2 (HER2/neu; also known as ERBB2), testosterone and oestrogen receptors.

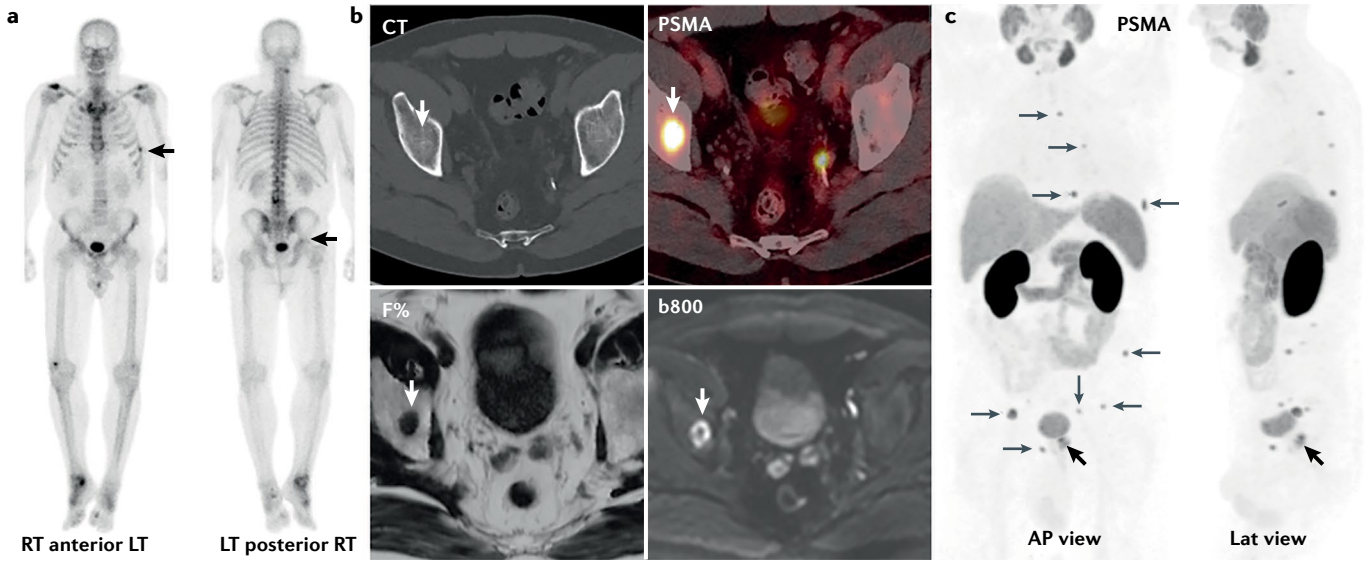

Fig. 7 | **Comparison of imaging techniques used for the diagnosis of bone metastases.** An example of relatively poor detection of bone metastases with conventional imaging. A 55-year-old man with locally advanced prostate cancer (Gleason score 4 + 5) with oligo-secretory disease (prostate-specific antigen (PSA) 3.3 ng/ml) and at high risk for metastasis, undergoing standard-of-care bone scintigraphy and CT scan for staging purposes. **a** | Planar bone views obtained from the anterior and posterior directions. Two abnormalities are seen (left eighth rib and right acetabulum (arrows)). This seems to represent synchronous oligometastatic disease and modern imaging methods are recommended to clarify the malignant nature of the bone scan abnormalities. **b** | Whole-body MRI (bottom row) and gallium-prostate-specific membrane antigen (PSMA)-PET–CT (top row) were performed. The right acetabula lesion (vertical down arrows) is clearly visible on the colour PSMA scan (top right) and on the diffusion (labelled b800; bottom right) and the bone marrow fat (labelled F%, bottom left) whole-body MRI images. This lesion is invisible on the CT scan (top left). **c** | Both modern imaging methods (whole-body MRI and gallium-PSMA-PET–CT) reported poly-metastatic bone disease (horizontal arrows on the PSMA scan) (left panel). The PSMA-PET study (right panel) also shows the primary tumour and a left-sided pelvic sidewall lymph node (slanting arrow and down-pointing arrow). AP, anteroposterior; LAT, lateral; LT, left; RT, right.

scintigraphy, studies analysing the performance of CT were mostly conducted without a reliable pathological standard and in patients with advanced disease, biasing the results towards higher diagnostic performances than would be achieved normally. The number of equivocal lesions on bone scintigraphy is reduced by combination with CT; when SPECT is used, greater anatomical information is provided for each area of increased tracer uptake[106,107].

Whole-body imaging. Owing to their enhanced sensitivity and specificity, modern imaging techniques such as MRI and combined PET–CT imaging are increasingly used and are recommended as alternatives to conventional diagnostic methods for the detection of bone metastases[107–109]. However, in many health-care settings, such state-of-the-art technologies are typically not available. Numerous PET isotopes, including fluorine-18 sodium fluoride (a bone turnover-specific radiotracer with probably the highest sensitivity), are currently being used to detect the presence of metastases[110]. However, fluorine-18 sodium fluoride is a bone-seeking radioisotope and does not detect extra-skeletal disease.

Metabolite imaging with radiotracers such as fluorodeoxyglucose, choline or fluciclovine using PET–CT is more sensitive than CT or bone scintigraphy at detecting metastases. PET–CT identifies fewer indeterminate and false-positive bone lesions than CT or bone scintigraphy[111,112]. Other clinically available radiotracers that target cell surface receptors include prostate-specific membrane antigen (PSMA), which can be labelled by radioactive gallium. In the setting of biochemical recurrence after prostatectomy, the performance of gallium-68-PSMA-PET–CT for detecting bone metastases is highly dependent on serum prostate-specific antigen (PSA) levels[113]. Nevertheless, membrane-bound gallium-68-PSMA-PET–CT has higher metastasis detection rates than metabolite imaging with choline or fluciclovine even at low PSA levels[114].

MRI has also been shown to be highly accurate in detecting bone metastases[115] and whole-body MRI has been shown to have higher sensitivity than bone scintigraphy and CT, with diagnostic performance similar to choline-PET–CT[108]. Whole-body MRI consists of visually evaluating imaging appearances in combination with corresponding water diffusivity values and bone lesion fat measurements. Image contrast on diffusion weight imaging emanates from the degree of free water motion within the tissues, being relatively impeded by the chaotic arrangements of tumour cells. The addition of diffusion weight imaging increases the diagnostic accuracy over the use of morphological features alone for bone metastases detection (by highlighting potential abnormalities) and characterization (diffusivity and percentage of bone marrow fat provide tissue type-specificity)[115,116].

Biopsy. When bone lesions identified during imaging are accompanied by definite metastases at other body sites, tissue confirmation for bone involvement is usually not

required. However, in patients whose metastases seem to be confined to the skeleton (bone-only disease), as is frequently observed in breast cancer or prostate cancer, and when few lesions are present or if imaging tests are equivocal, histological confirmation of metastatic disease is strongly recommended[3]. In a patient with bone metastases and an unknown primary cancer, histological evaluation of the biopsy specimen might indicate a likely primary site.

CT-guided biopsy of the suspected area followed by pathological assessment should be performed by a specialist familiar with the technical challenges of working with bone biopsies. In addition to confirming or refuting a secure diagnosis of metastatic disease, the biopsy provides an opportunity to reassess tumour-specific biomarkers that might help guide future treatment recommendations. In multiple myeloma, a bone marrow aspiration and trephine biopsy (usually taken from the iliac crest) is essential to detect clonal expansion of plasma cells in the bone marrow to establish a diagnosis.

Biomarkers. Bone formation and resorption result in the release of biochemical markers that are amenable to non-invasive measurement in blood or urine[117]. These biomarkers include the breakdown products of osteolysis, for example, the amino-terminal and carboxy-terminal cross-linked telopeptides of type I collagen. Other biomarkers include terminal peptides cleaved from procollagen (for example, procollagen type I N-terminal peptide and procollagen type 1 C-terminal peptide) before its integration into new bone matrix as well as the osteoblast-derived enzyme bone alkaline phosphatase, which regulates bone mineralization[117].

Biochemical markers of bone metabolism reflect the ongoing rates of bone resorption and formation in the body as a whole. Thus, bone marker measurements do not provide information specific to individual lesion sites. For example, elevated levels of bone alkaline phosphatase might support a diagnosis of bone metastases but its sensitivity and specificity are low and, therefore, bone biomarkers do not have a routine role in diagnosis. However, biomarkers can provide meaningful insights into prognosis and the likelihood of a patient developing an SRE[14].

Screening

Currently, no imaging tests are recommended for screening for bone metastases. During follow-up after cancer diagnosis, the diagnostic accuracy and frequency of positive metastases detection with bone scintigraphy performed every 6–12 months are insufficient for routine clinical practice[118].

Measurement of the prostate cancer-specific marker PSA is routinely performed in patients with prostate cancer to identify disease progression. Increasing levels of PSA may prompt initiation of or a change in treatment[119]. Serial measurement of tumour markers such as CA15.3 in the setting of breast cancer or non-specific enolase in patients with lung cancer to screen for metastases is not recommended. Importantly, with the exception of some men with prostate cancer, diagnosing metastatic bone disease before symptom development or earlier initiation of treatment through surveillance tests was not shown to have an impact on overall survival or quality of life in patients with advanced cancer.

Metastasis prevention

Evidence from animal models has underscored the importance of the interactions between multiple cell types within the bone microenvironment in maintaining tumour dormancy and its subsequent escape from quiescence, leading to the development of metastasis[120]. Treatments that modify these complex interactions could therefore potentially modify the course of primary cancer and potentially inhibit its metastatic spread[3]. BTAs including bisphosphonates and denosumab provide one potential strategy for metastasis prevention.

Breast cancer. Bisphosphonates have been the focus of clinical trials for >20 years for the treatment of early-stage breast cancer. Initial studies reported inconsistent results that were difficult to interpret[121] but, in 2011, one study showed significantly improved disease-free survival (DFS) from the addition of 6-monthly zoledronate to adjuvant endocrine therapy that included ovarian suppression for premenopausal women with oestrogen receptor (ER)-positive disease[122]. Subsequently, however, the larger AZURE study, with broader inclusion criteria and a more intensive treatment schedule of zoledronate, showed no overall benefit in DFS[123]. However, the AZURE study did identify potential benefits in the subgroup of women who were postmenopausal at the time of study entry and led to the hypothesis that only women with low levels of reproductive hormones were the likely target population for clinical benefit from adjuvant bisphosphonates[122,124].

This hypothesis was investigated further in a detailed meta-analysis of individual patient data from 18,766 patients with breast cancer involved in randomized controlled trials (RCTs) of adjuvant bisphosphonates. The meta-analysis showed that adjuvant bisphosphonates (intravenous zoledronate, daily oral clodronate or daily oral ibandronate specifically) reduced both breast cancer metastasis to bone and deaths from breast cancer, but these benefits were relevant only in postmenopausal women (natural and induced)[125] (TABLE 2). Clinically, important benefits in overall breast cancer recurrence, fewer bone recurrences and fewer breast cancer deaths were observed. Breast cancer deaths were reduced by nearly one-fifth at 10 years after diagnosis, with survival benefits similar across the different biological subtypes of breast cancer and seemingly independent of the type of bisphosphonate administered[125,126].

Studies have also assessed the disease-modifying effects of denosumab in early-stage breast cancer. In one study performed exclusively in postmenopausal women with ER-positive breast cancer, using denosumab at a dose schedule approved for the treatment of osteoporosis resulted in a significant improvement in DFS. However, the development of metastasis from breast cancer was unaffected; the DFS benefits related to fewer second non-breast primary cancers and deaths

Table 2 | **Results of EBCTCG meta-analysis of trials of adjuvant bisphosphonates for metastasis prevention in early-stage breast cancer**[125]

End point	All patients ($n = 18,766$)			Postmenopausal patients ($n = 11,767$)			Premenopausal or perimenopausal patients ($n = 6,171$)		
	Risk ratio (95% CI)	P[a]	Change in outcome[b] (%)	Risk ratio (95% CI)	P[a]	Change in outcome[b] (%)	Risk ratio (95% CI)	P[a]	Change in outcome[b] (%)
All recurrences	0.94 (0.87–1.01)	0.08	1.1	0.86 (0.78–0.94)	0.002	3.0	1.02 (0.91–1.15)	0.69	−0.8
Distant recurrence	0.92 (0.85–0.99)	0.03	1.4	0.82 (0.74–0.91)	0.0003	3.4	1.02 (0.90–1.15)	0.81	−0.9
Bone recurrence	0.83 (0.75–0.94)	0.004	1.1	0.72 (0.60–0.86)	0.0002	2.2	0.92 (0.75–1.12)	0.42	0.0
Non-bone recurrence	0.98 (0.89–1.08)	0.69	0.5	0.90 (0.79–1.02)	0.1	1.6	1.08 (0.92–1.26)	0.35	−1.1
Breast cancer mortality	0.91 (0.83–0.99)	0.04	1.7	0.82 (0.73–0.93)	0.002	3.3	1.00 (0.86–1.15)	0.96	0.1

CI, confidence interval; EBCTCG, Early Breast Cancer Trialists' Collaborative Group. [a]Statistical significance in two-sided log-rank test. [b]Absolute change in outcome after 10 years.

without recurrence — effects that seem biologically implausible[127]. In a larger RCT, performed in a broader population of women with early-stage breast cancer (premenopausal and postmenopausal women; ER-positive and ER-negative disease), the addition of denosumab to standard adjuvant breast cancer treatments had no significant effect on bone metastasis-free survival, DFS or overall survival[128]. In contrast to the benefits observed with adjuvant bisphosphonates, outcomes in the postmenopausal subgroup were not improved. The apparent differences between the efficacy of adjuvant denosumab and bisphosphonates might be owing to the broader biological effects of bisphosphonates on other aspects of the metastatic process, rather than on bone cell function alone[121].

Prostate cancer. Prostate cancer provides another ideal clinical setting for evaluating the efficacy of BTAs in metastasis prevention. Several RCTs have been conducted in men with early-stage prostate cancer, without clinical evidence of bone involvement at randomization. However, none of the trials with the bisphosphonates (zoledronate or clodronate) demonstrated a beneficial effect on disease recurrence or metastasis[129]. In men with increasing levels of PSA, despite androgen deprivation therapy but no evidence of overt metastases, denosumab increased median bone metastasis-free survival by 4.2 months compared with placebo; the time to first symptomatic bone metastases was delayed but survival was unaffected[130]. Although the trial met its primary end point, the disease benefits were not considered sufficient to justify the 5% cumulative incidence of osteonecrosis of the jaw that occurred with the prolonged delivery of monthly denosumab over a 5-year schedule tested within the trial.

Lung cancer and multiple myeloma. The potential impact of BTAs on the natural history of lung cancer has also been evaluated. However, neither zoledronate[131] nor denosumab[132] seem to have any measurable impact on overall disease recurrence, time to bone metastasis or survival. The possibility that BTAs might affect the progression of monoclonal gammopathy of unknown significance to multiple myeloma has been considered but appropriate trials to test this hypothesis have not yet been performed.

Management

Treatment decisions for patients with bone metastases depend on the nature of the underlying malignancy, the presence or absence of extra-skeletal metastases and whether the bone disease is localized or widespread. The specific choices and order of systemic anticancer treatments for patients with bone metastases or myeloma bone disease are broadly similar to those used for the underlying metastatic disease and tumour subtype as a whole. Chemotherapy, biologically targeted therapies, immunological therapies and endocrine treatments are all potentially important. Resistance to systemic treatments can be expected to develop, necessitating multiple sequential changes of therapy in an effort to regain control of the disease. EBRT is used for pain relief and, in some cases, surgical intervention might be necessary. BTAs are used complementary to other systemic therapies to minimize the risk of skeletal morbidity (FIG. 8).

Optimal patient management requires a multidisciplinary team, which includes medical oncologists (haematologists for multiple myeloma), radiation oncologists, orthopaedic surgeons, radiologists and nuclear medicine physicians as well as palliative medicine specialists and a supportive therapies team with expertise in cancer-associated bone complications[2].

Assessment of response to treatment

The evaluation of the effects of treatments used in the management of metastatic bone disease is important for routine clinical practice. Bone is the only metastatic site with distinct criteria for evaluating response to treatment, which are based on bone repair and destruction rather than on changes in tumour volume.

Imaging is essential for assessing treatment benefits, especially when serum biomarkers are not available or perform poorly. Sclerosis within lytic bone metastases without radiologic evidence of new lesions is generally accepted as an indication of tumour regression, but these changes take several months to appear on radiographs or CT imaging. Additionally, confounding factors include the appearance of sclerosis on the radiograph or CT scan in a previously seemingly normal area; this change could represent the development of a new metastasis (progression) but can also denote healing within a lesion that existed but was not sufficiently destructive or large enough to be radiographically visible (response).

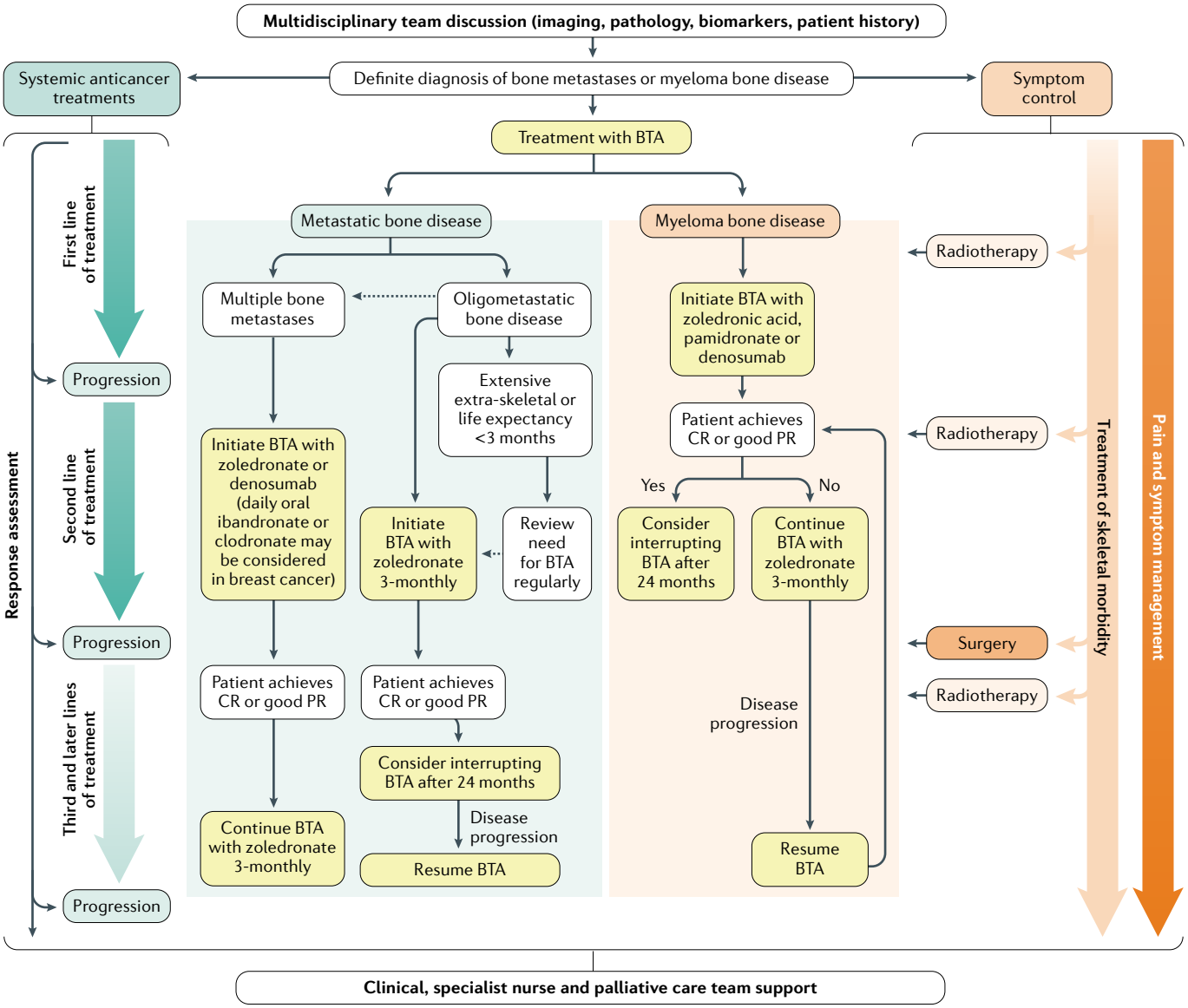

Fig. 8 | **Schematic algorithm for multidisciplinary treatment of bone metastases and myeloma bone disease.** Sequential systemic treatments for the underlying cancer are dependent on tumour biology and clinical features and are accompanied by regular imaging for assessment of treatment response to guide treatment changes. Bone-targeted treatments are recommended following diagnosis of bone involvement and continued throughout the clinical course of the disease. In addition to these treatments, symptom control incorporating pain management, treatment of skeletal-related events if and when they occur with radiotherapy and/or surgery, and specialist clinical, nursing and palliative care support are necessary to reduce the clinical impact of the underlying disease, preserve quality of life and maintain physical functioning for as long as possible. BTA, bone-targeted agent; CR, complete remission; PR, partial remission. Adapted with permission from REF.[3], Elsevier.

The evaluation of response in osteosclerotic lesions is more challenging and decisions about the efficacy of treatment usually rely on symptom improvement such as pain alleviation, changes in tumour markers, or the growth or shrinkage of metastatic disease (if present) in soft tissues or viscera.

The use of bone scintigraphy for assessment of response to therapy has always been contentious and is certainly unreliable when lytic metastases predominate. After initiating therapy for metastatic disease, the healing processes of new bone formation cause an initial increase in tracer uptake and, therefore, scans performed during this phase are likely to show increased intensity within known metastases and visualize previously unseen lesions because they were small or purely osteolytic in nature. Six months following treatment, the appearances of bone metastases in the scan 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 scintigraphy images after successful therapy, known as the 'flare response', is now a well-recognized phenomenon in both breast cancer and prostate cancer[133]. To assess response to treatment objectively in patients without CT-evaluable soft-tissue disease, this flare reaction can contribute to an incorrect assessment that treatment has been ineffective and lead to premature treatment discontinuation.

Although of limited value, bone scintigraphy is still widely used to assess response to treatment in prostate cancer owing to the lack of other comprehensively validated imaging modalities for the assessment of osteosclerotic bone metastases[134]. Criteria to determine disease progression have been defined to support clinical decisions after initiation of therapy. These criteria require identifying at least two new lesions on the first assessment following a baseline bone scan and at least two further lesions on a subsequent confirmatory scan before progressive disease is confirmed. The criteria are reproducible, easy to apply and allow for the potential confounding elements associated with the flare response[135,136].

The International Myeloma Working Group has developed specific response criteria to measure response to treatment. These criteria require a reduction in the percentage of malignant plasma cells within the bone marrow and a decrease in the concentrations of serum monoclonal protein or urinary light chain paraproteins. An absence of osteoblast response with successful therapy is known to occur in myeloma, implying that changes in bone lesions on bone CT or scintigraphy are not required to assign a successful response to treatment but increases in the number or size of lytic bone lesions indicate progression of disease[137].

Emerging approaches to assess treatment response. New approaches are being evaluated to improve the assessment of treatment response in patients with bone metastases (FIG. 9). The first approach involves quantitative assessment of bone scintigraphy images using computer-assisted image processing to estimate the number, size, shape and intensity of bone scan lesions to create a bone scan index, which gives an estimate of the proportion of the skeleton affected by disease[138]. The other approaches involve the use of quantitative MRI and PET–CT imaging techniques and the evaluation of blood biomarkers of treatment response and disease prognosis such as changes in the number of circulating tumour cells[139] or the amount of tumour-derived DNA in a blood sample[140]. Currently, substantial efforts are being made to standardize PET–CT imaging[141,142] and whole-body MRI[143] to validate their use for measuring therapy response. However, the lack of standardization of imaging techniques, the heterogeneity of imaging expertise, limited availability of these advanced imaging technologies and financial constraints prevent their routine clinical use across different parts of the world and health-care systems. Thus, currently, most clinicians continue to rely on suboptimal tests and clinical response such as pain, mobility and analgesic consumption to estimate treatment efficacy in patients with bone metastases.

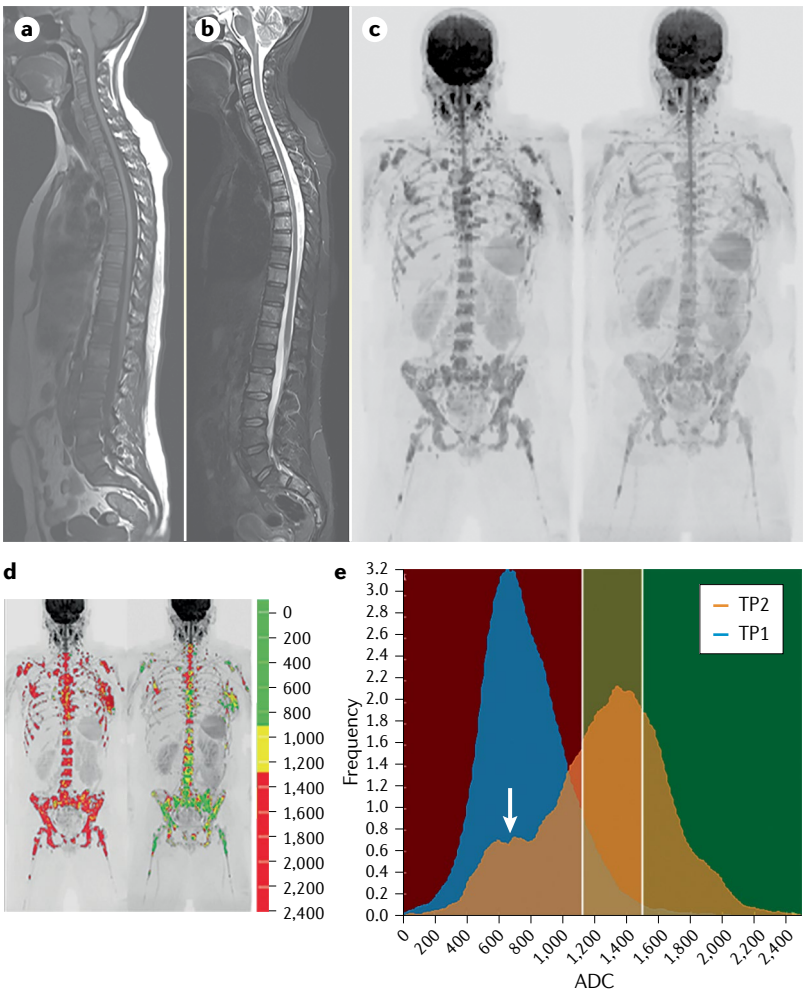

Fig. 9 | **Bone metastasis response assessments on whole-body MRI.** A 38-year-old woman with a node-positive, oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2/neu)-negative (also known as ERBB2), invasive ductal carcinoma of the left breast (5 cm, grade 3). Examinations at baseline and after 11 weeks of palbociclib and letrozole therapy with zoledronate infusions. Morphological images: T1-weighted MRI image of the spine shows extensive bone marrow infiltration with no morphological changes to indicate response (baseline image not shown) (part **a**); T2-weighted image of the spine shows extensive bone marrow infiltration with subtle increase in signal intensity in the lumbar spine (baseline scan not shown), indicating increased bone marrow water (part **b**). Both parts **a** and **b** indicate radiologically stable disease. Functional images: anterior projections of high *b*-value diffusion weighted images (inverted grey scale) show decreased signal intensity consistent with therapy response of the primary tumour in the left breast, in the left axillary lymph nodes and in the bone marrow (part **c**); diffusion weighted images for both time points were analysed using signal-intensity threshold-based segmentation on Syngio.via Frontier MR Total Tumour Load software (Siemens Healthineers, Erlangen, Germany) (part **d**). Pretreatment apparent diffusion coefficient (ADC) histogram (coloured blue) showing a unimodal distribution of ADC values (part **e**). During therapy, a pronounced rightward shift of the histogram occurs, indicating less impeded water diffusion. These ADC histogram changes are consistent with a favourable therapy response. Responding voxels are colour-coded as yellow and green voxels and are projected onto the diffusion weighted images (part **d**) to provide anatomical localization information. Note that there are some voxels that retain a red colour, indicating non-responding voxels, which are widely distributed in the bone marrow and are visible on the histogram as a small non-moving peak (down arrow). TP, tumour profile.

Bone-targeted agents

BTAs have been shown to decrease the incidence of SREs in patients with multiple myeloma and in those with bone metastases (regardless of tumour type)[2,3]. These benefits continue to be observed despite the evolution of anticancer therapies since the 1990s[2,3]. BTAs are also effective in delaying the progression of bone pain, indicated by lower pain scores and analgesic use in treated patients[144]. Additionally, in a meta-analysis of patients with metastatic cancer, SREs were shown to significantly increase the risk of pain progression and need for

Castration-resistant prostate cancer
(CRPC). A phase in the evolution of advanced prostate cancer that progresses despite androgen deprivation therapy.

Castration-sensitive prostate cancer
Prostate cancer that can be controlled by lowering androgen levels.

strong opioids, further underlining the importance of SRE prevention[145].

Bisphosphonates. The use of bisphosphonates has changed the natural history of metastatic bone disease. Bisphosphonates are internalized by bone-resorbing osteoclasts, thereby inhibiting osteoclast function[146]. Specifically, nitrogen-containing bisphosphonates impair the mevalonate pathway, which further inhibits the prenylation of small GTPase signalling proteins. Consequently, osteoclasts are no longer capable of resorbing bone. Pamidronate, ibandronate and zoledronate are the nitrogen-containing bisphosphonates that have been extensively tested in patients with bone metastases[8–11,147]. Non-nitrogen-containing bisphosphonates lead to intracellular accumulation of cytotoxic non-hydrolysable ATP analogues, impairing osteoclast activity[146]. Clodronate is the most studied first-generation non-nitrogen-containing bisphosphonate in clinical trials[2,5,148].

Several RCTs have reported a decreased incidence of SREs in patients receiving bisphosphonates and standard anticancer therapy compared with those receiving anticancer agents alone[8,9,148]. Although several bisphosphonates have proven efficacious in preventing SREs in patients with breast cancer bone metastases, zoledronate remains the only bisphosphonate approved for castration-resistant prostate cancer[10] (CRPC) and for patients with bone metastases from other solid tumours, such as lung cancer, kidney cancer and bladder cancer[11] (TABLE 3). In multiple myeloma, beyond SRE prevention, an anti-myeloma effect was additionally proposed as in the Myeloma IX trial, zoledronic acid achieved a progression-free survival (PFS) benefit and reduced mortality with a median overall survival improvement of 5.5 months compared with clodronate[149].

In patients with metastatic castration-sensitive prostate cancer, current hormonal treatments for the underlying malignancy are so effective that the risk of SREs during this earlier phase of the illness is low. Currently, evidence proving that bisphosphonates can reduce the risk of SREs in castration-sensitive prostate cancer as the disease progresses is unavailable[150]. In this setting, the use of BTAs should be restricted to the prevention of treatment-induced bone loss and fragility fractures in line with current bone health guidelines[3].

Denosumab. Denosumab has been shown to achieve almost complete osteoclast inhibition in patients with solid tumour bone metastases as well as in those with multiple myeloma[151]. Three large RCTs compared denosumab with zoledronate in 5,723 patients with different types of cancer[152–154] — the first study recruited patients with breast cancer[152], the second study included men with CRPC[153] and the third study included patients with a range of solid tumours including lung

Table 3 | **Studies of bone-targeted agents for solid tumours with bone metastases or multiple myeloma**

Treatment	SRE (%)	Median time to first SRE (days)	Other end points	Refs
Breast cancer				
Clodronate[a] vs placebo	NE	NE	SMR: 219 vs 305	8,147,148, 152,249–252
Pamidronate vs placebo	43 vs 56	399 vs 213	Improved QOL and pain	
Pamidronate vs placebo	56 vs 67	317 vs 210	Improved QOL and pain	
Zoledronate vs placebo	30 vs 50	NR vs 364	Improved pain	
Zoledronate vs pamidronate	43 vs 45	310 vs 174	SRE: 20% risk reduction	
Oral ibandronate[a] vs placebo	NE	632 vs 454	SMPR: 0.99 vs 1.15	
Intravenous ibandronate[a] vs placebo	51 vs 62	354 vs 232	SMPR: 1.19 vs 1.48	
Denosumab vs zoledronate	NE	NR vs 804	SRE: 23% risk reduction	
Prostate cancer (CRPC)				
Zoledronate vs placebo	33 vs 44	NR vs 321	Significant pain relief	10,153
Denosumab vs zoledronate	36 vs 41	520 vs 630	Similar PFS and OS	
Solid tumours[b]				
Zoledronate vs placebo	39 vs 46	236 vs 155	31% overall SRE reduction	11,154
Denosumab[c] vs zoledronate	NE	627 vs 496	Similar PFS and OS	
Multiple myeloma				
Zoledronate vs clodronate	27 vs 35	NR vs NR	Zoledronate improved OS by 4 months	9,149,155, 253,254
Zoledronate vs pamidronate	47 vs 49	NE	Similar efficacy	
Clodronate[a] vs placebo	NE	Improved	Progression: 12% vs 24%	
Pamidronate vs placebo	24 vs 41	693 vs 730	SMR: 1.3 vs 2.4	
Denosumab vs zoledronate	44 vs 45		Denosumab improved PFS by 9 months	

Only includes treatments with regulatory approval in the United States and/or Europe for the prevention of skeletal-related events. CRPC, castration-resistant prostate cancer; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival; QOL, quality of life; SMPR, skeletal morbidity period rate; SMR, skeletal morbidity rate; SRE, skeletal-related event. [a]European approval only. [b]Excluding breast and prostate cancers. [c]Study included a cohort of patients with multiple myeloma.

Box 2 | **Key adverse effects associated with use of bone-targeted agents in patients with metastatic bone disease**

Bone-targeted agents such as bisphosphonates and denosumab have been associated with adverse effects that range in prevalence from common (in >1% of patients) to uncommon (in 0.1–1% of patients) or rare (in <0.1% of patients). This list is not exhaustive but illustrates those adverse events most clearly associated with the use of bone-targeted agents.

Oral bisphosphonates
These drugs include daily oral clodronate and ibandronate.

Common adverse effects
Asymptomatic hypocalcaemia, diarrhoea, abdominal pain, nausea and/or dyspepsia, vomiting, constipation and oesophagitis

Uncommon adverse effects
Iritis, gastritis, dysphagia, duodenitis, oesophageal ulcer and osteonecrosis of the jaw

Rare adverse effects
Symptomatic hypocalcaemia, increased serum parathyroid hormone levels, atypical femoral fractures and oesophageal stricture

Intravenous bisphosphonates
These drugs include zoledronate, pamidronate and ibandronate.

Common adverse effects
Influenza-like illness, headache, bone and/or joint pain, myalgia, increased serum creatinine levels, symptomatic hypocalcaemia, hypophosphataemia, hypomagnasaemia, increased serum parathyroid hormone levels, osteonecrosis of the jaw, conjunctivitis, diarrhoea, abdominal pain, nausea, dyspepsia and vomiting

Uncommon adverse effects
Uveitis, cataract, atrial fibrillation, rash and pruritis

Rare adverse effects
Atypical femoral fractures, focal segmental glomerulosclerosis and nephrotic syndrome

Denosumab
This human monoclonal antibody is a specific inhibitor of receptor activator of nuclear factor-κB ligand (RANKL) that inhibits osteoclast function and activity.

Common adverse effects
Rash, symptomatic hypocalcaemia, osteonecrosis of the jaw, increased serum parathyroid hormone levels, urinary tract infection and upper respiratory tract infection

Uncommon adverse effects
Eczema and cataracts

Rare adverse effects
Atypical femoral fractures

cancer and a subset of patients with multiple myeloma[154]. In patients with metastatic breast cancer and CRPC[152,153], denosumab was superior to zoledronate plus standard cancer therapies in the time to the first and subsequent SREs. However, in the third RCT investigating other solid tumours and myeloma, denosumab was shown to be statistically non-inferior to zoledronate but not statistically superior[154]. Despite the additional benefits of denosumab on skeletal morbidity, the time to disease progression and the overall survival of patients treated with denosumab or zoledronate were similar (TABLE 3).

The role of denosumab in preventing SREs in myeloma bone disease was recently clarified in a RCT that only recruited patients with myeloma. Denosumab was shown to be non-inferior to zoledronate in delaying time to first SRE[155]. Although overall survival was similar for both treatments (49.5 months), the median PFS was improved by 9 months with denosumab compared with zoledronate. As a result, denosumab is now approved for the prevention of SREs in myeloma and is particularly appropriate for patients with renal impairment as bisphosphonates are contraindicated in such patients.

Clinical guidelines on use of BTAs. Current clinical guidelines recommend the inclusion of a BTA, typically denosumab or zoledronate, in patients with metastatic bone disease from solid tumours or multiple myeloma[3]. Treatment should be initiated following a confirmed diagnosis of bone metastases and continued throughout the course of the disease, alongside sequential systemic treatments. The frequency of zoledronate administration can be reduced during periods of disease remission[3]. However, data are currently lacking on the efficacy of reduced frequency of denosumab administration and, therefore, adherence of monthly therapy is recommended. Bisphosphonates have a prolonged duration of action as they attach to the bone surface and, therefore, treatment interruptions — for example, to allow safer completion of dental treatment or during remission — are unlikely to greatly influence any ongoing risk of SRE[156]. By contrast, denosumab has a short half-life and, therefore, discontinuation for any reason would be associated with rebound osteolysis that might lead to rapid bone loss and an increased risk of vertebral fractures[157]. In the cancer setting, interrupting denosumab might also increase bone pain and the rate of SREs. As a result, finishing a course of denosumab with an infusion of a potent bisphosphonate is now recommended to reduce the clinical consequences of this rebound phenomenon[3,158].

Adverse effects of BTAs. Adverse events associated with BTAs are often preventable and usually only mild in severity[3,159] (BOX 2). Intravenous bisphosphonates can adversely affect renal function, and progressive dosing reductions are necessary when creatinine clearance is <60 ml/min; bisphosphonate use is contraindicated when creatine clearance is <30 ml/min. Denosumab, however, is not associated with renal toxicity and, therefore, is safe to use in patients with renal impairment. Hypocalcaemia may occur, especially with the use of denosumab, and particularly in patients with prostate cancer and extensive osteoblastic disease or in those with renal impairment, highlighting the importance of vitamin D supplementation and adequate calcium intake through diet and/or supplements[3,160].

Osteonecrosis of the jaw is a potentially serious adverse event associated with BTAs; the risk of developing this condition increases with treatment duration, at a rate of ~1% per year on treatment[161]. Thus, maintaining good dental hygiene, avoiding bone trauma and treating dental infections before and during bone-targeted therapy are vital[162]. Long-term treatment over several years with BTA might be associated also with the development

of atypical femoral fractures[163]. Current evidence suggests that de-escalation of zoledronate just after a few months of monthly treatment is equally effective in SRE prevention[164,165] and might reduce the frequency of adverse effects.

External beam radiotherapy

Radiotherapy is used to treat a wide range of primary tumours and, in some disease settings, can be curative. However, in advanced metastatic cancers, the primary aim of treatment is palliation. For patients with bone metastases, EBRT is most effective for pain relief but can also induce bone healing and improve the structural integrity of the treated bone surface via its effects on the underlying tumour. Up to 80% of patients report a reduction in bone pain[166], with pain relief occurring as early as 10 days after treatment in 40% of patients[167]. A single 8-Gy fraction of EBRT has been proven to be equally as effective as multi-fractionated radiotherapy for relieving pain from bone metastases not complicated by fracture or nerve entrapment[168,169]. Although there may be an increased need for retreatment with a single-fraction regimen, EBRT is widely recommended owing to its simplicity and convenience, especially for patients with a short life expectancy[170]. In addition, single-fraction radiotherapy was associated with fewer adverse events[171].

Some patients may require retreatment for further worsening of bone pain and pain relief can be achieved in ~50% of patients receiving retreatment. This palliative effect was observed in patients who initially responded to radiotherapy and in those who did not[172]. Among pain responders, re-irradiation also improved quality of life[173].

For patients receiving EBRT to the dorso-lumbar spine, pelvis and skull, prophylactic antiemetics are recommended[171]. Patients may also experience transient irritation of the oesophagus and other mucosal surfaces in the radiated area. These adverse effects are severe when large radiation field sizes are needed. Approximately 40% of patients will experience pain flare (a brief augmentation of pain intensity before subsequent pain relief)[174], which can be managed by prophylactic administration of dexamethasone[175].

Palliative EBRT can also be utilized to address some of the structural complications associated with bone metastases. For patients with impending fractures who are not surgical candidates, radiotherapy (alongside bone-targeted therapies) may also be indicated for tumour control to prevent worsening of the structural damage. However, radiotherapy alone does not restore bone stability; orthopaedic surgery is preferentially recommended for established pathological fracture and most cases of impending fractures[176]. Postoperative radiotherapy after surgery to a limb lesion is shown to be effective in reducing the need for subsequent surgeries by controlling metastatic spread and preventing prosthesis displacement[177,178]. In patients receiving surgery for spinal metastases, postoperative EBRT can be administered to improve local control and ambulation[179].

Stereotactic body radiotherapy (SBRT) is a radiation technique that utilizes sophisticated 3D image guidance to deliver extremely precise, intense doses of EBRT to a tumour or metastasis while minimizing damage to healthy tissues and is particularly effective after spinal surgery[180]. SBRT has also been shown to improve outcomes in patients with spinal metastases who do not require surgery, with up to 80% of patients achieving local tumour control and reporting pain relief[180]. SBRT is a safe and effective option for patients with bone metastases, with potentially better outcomes than traditionally conformed EBRT techniques. Patients receiving SBRT achieved pain relief more quickly during the 4 weeks after treatment and had more durable pain relief assessed at 6 months compared with those receiving standard conformal EBRT[181]. However, no differences in quality of life, fatigue or emotional distress were found between the two treatment approaches[182]. Although bone healing was similar between the two approaches, a slightly higher rate of subsequent pathological fractures was observed in patients receiving SBRT, reflecting the effects of high localized doses of radiation on bone quality[183]. Additionally, long-term control rates for disease within the irradiated fields were higher with single-fraction SBRT than standard EBRT[184].

EBRT for spinal cord compression. Spinal cord compression is a medical emergency that should be examined immediately by MRI to establish the diagnosis and initiate treatment. Following dexamethasone, EBRT is typically recommended on its own or after surgical decompression. Combined surgery and radiotherapy should be considered for patients with good mobility prior to developing spinal cord compression and favourable disease characteristics[185]. However, for those with poor performance status and unfavourable characteristics (compression at multiple spinal segments, extensive visceral metastases or severe co-morbidities), the functional outcome, duration of survival and recovery times from surgery are poor. In these cases, EBRT alone, using a single fraction of radiotherapy to reduce the need for hospital visits in patients who are often close to the end of life, is recommended[186,187].

Radionuclide therapy

The therapeutic use of radiolabelled tracers has theoretical advantages that radiation may be delivered more specifically to the tumour than EBRT, sparing unnecessary irradiation to normal tissues. Originally developed for the treatment of metastatic thyroid cancer, the use of iodine-131 is now well established, and long-term palliation is usually possible when uptake of iodine-131 into the bone metastases is substantial[188]. Bone-seeking radionucleotides such as strontium-89 chloride and samarium-153-labelled ethylene diamine tetramethylene phosphonate (EDTMP) localize within bone metastases[189] and can be used to treat cancer-induced bone pain (CIBP). However, significant bone marrow suppression may occur that can limit subsequent use of chemotherapy[189].

The bone-seeking radiopharmaceutical, radium-223 chloride (Ra-223), an alpha-emitting pharmaceutical with preferential uptake into areas of increased bone formation, is now in clinical use for men with prostate cancer. Ra-223 produces high, linear energy transfer

radiation with ultra-short penetration (2–10 cell diameters), resulting in a highly localized antitumour effect on adjacent bone metastases while limiting damage to the surrounding normal tissue[190]. In a placebo-controlled trial, Ra-223 increased the overall survival of patients by 3.6 months and reduced SREs both overall and in those men receiving a bisphosphonate[191]. Ra-223 is approved for use as a single agent for men with CRPC and symptomatic bone metastases as the dominant site of disease. Concomitant denosumab or zoledronate are recommended in patients, especially when Ra-223 is used with other treatments, for example, androgen receptor-targeted therapy, such as abiraterone acetate or enzalutamide, to avoid detrimental interactions[192,193].

Theranostics

Theranostics refers to the combination of an imaging biomarker that predicts response and a second radioactive-labelled drug to target the main tumour and any metastases and is an emerging new treatment approach[194]. For example, the overexpression of PSMA in metastatic prostate cancer has led to the development of PSMA-PET imaging isotopes as potential imaging biomarkers to guide therapy using PSMA ligand-directed treatments[195]. PSMA-targeting of lutetium-177 or actinium-225 offers a new treatment option in some men with treatment-refractory CRPC[196]. Lutetium-177-PSMA-617 can lead to biochemical responses in PSA and delay disease progression[197]. Improving patient selection using a combination of fluorodeoxyglucose and PSMA-PET–CT will more accurately predict the treatment benefit from such approaches compared with PSMA-PET imaging alone[198].

Surgery

The aim of surgical intervention in bone metastases is to maintain patient functionality and mobility, prevent impending fractures or stabilize a pathological fracture, manage spinal cord compression and improve quality of life by alleviating pain. Patient selection for surgery is critical, particularly in the setting of fracture prevention. Besides the size of the bone lesion, the degree of bone destruction and the presence or absence of a fracture, one must take into consideration the high risk of bleeding associated with highly vascular tumours (such as renal cell carcinoma or thyroid cancers), the likely prognosis and co-morbidities of the patient and an estimate of the likely efficacy of available systemic treatments.

For solitary or oligometastasis and small lesions, the tumour should be excised completely with clear margins to avoid further local recurrence and complications. However, in most cases, an intralesional approach (without clear margins) such as curettage of the lesion is unavoidable and should ideally be supplemented by the use of either argon coagulation, cryotherapy or radioablation of the metastatic area.

Long bone metastases. In the proximal femur or humerus, a long-stem cemented endoprosthesis or a modular tumour endoprosthesis is usually recommended for rapid mobilization. This technique has a lower complication rate than the use of intramedullary nails or plates. However, in patients with a short life expectancy, intramedullary nailing with locking screws introduced by a minimally invasive technique and, if necessary, augmented by bone cement may be preferred as this also allows immediate full weight bearing. In the diaphysis of a long bone, the surgeon may implant a plate, intramedullary nail or prosthesis. Tumour spread along the nail track needs to be considered and, unless the prognosis is very poor, surgery should be followed by EBRT upon wound healing[199,200].

Impending fractures. For impending fractures, prophylactic stabilization is generally preferred as it is associated with better outcomes, fewer surgical complications, quicker functional recovery and shorter hospitalization[201]. Predicting which metastatic lesions will ultimately progress to fracture is imprecise. Prophylactic surgery is recommended for lesions ≥30 mm in diameter involving the neck, subtrochanteric or supracondylar regions of the femur, lytic destruction of 50% of the cortex (outer or inner layer) of a long bone and/or continued pain with weight bearing after radiotherapy[202]. Risk stratification using fracture probability scores can be clinically useful and incorporates symptoms and functional limitations with radiographic findings[203].

Spinal metastases. The indications for surgery for spinal metastases depend on symptoms, findings from imaging on the extent of disease and the overall prognosis. Operative techniques differ according to the site and size of the spinal metastases. Palliative decompression through a posterior approach supplemented by a stabilization procedure and EBRT upon wound heading is generally recommended[204]. For slow-growing tumours or, in patients with relatively good prognosis, more aggressive interventions including total en bloc resection can be justified[204]. Immediate surgical intervention should be considered for spinal cord or cauda equina nerve root compression with neurological symptoms or uncontrollable pain[185]. Instability of a vertebral body may cause intractable pain but is often misdiagnosed by oncologists and, therefore, a low threshold for assessment by a spinal specialist is recommended before fracture and/or neurological damage occurs. The Spinal Instability Neoplastic Score is an easy-to-use algorithm that incorporates six clinical features for the evaluation of instability associated with spinal metastases. These features take into consideration the location of metastases in the spine, the presence of pain, the patterns of lesions, radiographic spinal alignment, the presence of vertebral segment collapse and posterolateral involvement of the spinal elements. Patients with Spinal Instability Neoplastic Score scores between 7 and 18 (indicative of impending or active instability) warrant surgical consultation[205].

Pain inflicted by vertebral body fractures can also be treated by vertebroplasty or kyphoplasty. Vertebroplasty involves injecting medical-grade cement into a fractured vertebra, which then hardens in the bone space to form an internal cast. Kyphoplasty involves the use of an inflatable balloon catheter to create a cavity in which bone cement can be injected and provides an opportunity to

Oligometastasis
A single site or a few (<5) sites of metastasis within up to three different metastatic sites.

Curettage
Removal of tissue by scraping or scooping rather than surgical resection.

restore the height of the collapsed vertebra. Pain relief with both techniques is usually seen within 1–3 days and functional outcomes are good[206]. Care should be taken to avoid cement leakage outside the targeted vertebral body and kyphoplasty has been reported to cause less cement extravasation. Tumour cells may also be spread by the procedure and it is often best followed up with radiotherapy if tissue tolerance allows.

Cancer-induced bone pain

CIBP can have a profoundly negative impact on patients' lives and its management is one of the greatest challenges in cancer care. CIBP remains under-reported and under-treated, owing to the inherent therapeutic challenges associated with this pain syndrome and the failure to use well-proven treatment strategies such as the World Health Organization (WHO) analgesic ladder.

Types of CIBP. Bone pain can be subdivided into background pain, pain associated with movements and spontaneous pain at rest[207]. Breakthrough pain, defined as sudden flare-ups of bone pain severe enough to be perceived in spite of pain medication being taken, is highly prevalent in CIBP and often leads to significant functional impairment[208]. Breakthrough pain is often of severe intensity, rapid onset and short duration[209].

Need for an interdisciplinary approach. The basic principles of the WHO analgesic ladder remain the key to managing bone pain. The neurobiology of CIBP is complex and involves neuropathic and inflammatory components as well as unique molecular players (BOX 3). Owing to this complexity, the usefulness of the WHO analgesic ladder, which is effective in other types of cancer pain, is often unable to achieve adequate pain relief. Although opioids and radiotherapy form the current standard of care, these modalities might not be effective in all patients. Thus, optimal relief requires a multidisciplinary team and different strategies at each disease stage and for different types of CIBP. Carefully listening to patients and understanding their concerns is inherently therapeutic and essential for planning tailored management. Physiotherapy and occupational therapy input are important to optimize function and independence. Various clinical and biological markers have been explored as potential predictors of pain response, although no specific marker has been identified as a reliable marker for use in daily clinical practice to date[210].

Box 3 | **Neurobiology of cancer-induced bone pain**[207,208]

The key components of the neurobiology of cancer-induced bone pain include the following.

- Disruption of bone homeostasis
- Direct infiltration of nerves by tumour
- Release of neurochemicals that modulate pain
- Release of prostaglandins by tumour cells
- Increased expression of nerve growth factor
- Transient receptor potential vanilloid 1 (TrpV1) receptor sensitization
- An acidic bone microenvironment
- Microglia activation

Analgesics used in CIBP. In patients with moderate to severe background pain, the standard WHO ladder analgesics have been shown to be effective in relieving pain. NSAIDS are usually prescribed unless there are contraindications[211]. Treatment of breakthrough pain, such as pain escalation on movement and spontaneous pain at rest, is challenging. These episodes of spontaneous pain can occur between two and eight times per day. The use of opioids for spontaneous pain is usually associated with adverse effects and, in some cases, dangerous opioid toxicity. Movement-related pain or spontaneous pain usually peaks within 5 min and resolves after 15 min. Even with oral short-acting opioids, the onset of analgesia only begins after 30 min but lasts for up to 4 h. In these situations, oral opioids can only make the patient feel drowsy and are irrelevant for alleviating pain. Rapid-acting opioid preparations such as fentanyl, with an onset of action of 15 min, have been developed. However, even such rapid-acting opioids are still not optimum for managing the time course of breakthrough pain[212].

Patients with CIBP might develop opioid tolerance, requiring steadily escalating doses for pain relief. Conversely, in patients on opioids that can be discontinued owing to effective cancer treatment or surgical intervention, reducing the opioid doses steadily is important to avoid physical dependency and withdrawal symptoms. However, psychological dependence and addiction are rarely an issue.

The neuropathic component of CIBP suggested a potential role for drugs such as pregabalin and gabapentin in alleviating pain[213]. The results of RCTs investigating these drugs have been variable; a systematic review reported only minimal efficacy of pregabalin and gabapentin for managing CIBP[214]. Nevertheless, a neuropathic agent is generally indicated in patients with neuropathic pain symptoms.

Auxiliary modalities for pain relief. Radiotherapy[171], BTAs[215] and bone-seeking radiopharmaceuticals[190] are all useful for the management of bone pain. When CIBP remains severe and/or a pathological fracture occurs in patients receiving end of life care, an interventional technique, such as an external spinal catheter inserted into the epidural space, might be appropriate[216]. In patients who are not in the terminal phase of their illness, implanted intrathecal pumps are preferred instead of external spinal catheters. The empirical use of glucocorticoids might be helpful in patients with opioid-refractory CIBP, especially in patients with advanced disease[210]. Additional strategies include transcutaneous electrical stimulation of the painful area, an underused but very useful approach for some patients[217]. Other topical treatments include lidocaine (a local anaesthetic) or high-dose (8%) capsaicin patches. Current evidence supports the use of capsaicin patches, particularly when a substantial neuropathic pain component with overlying allodynia and hyperalgesia is present[218].

The complexities of central processing of pain are slowly being understood. For example, in those patients who have poor activation of the descending inhibitory pathways to the spinal cord, pain perception might be influenced by emotional input. Such clinical situations should encourage a holistic approach to pain management, ensuring that anxiety, depression, sleep deprivation and sources of distress are minimized alongside the appropriate use of analgesics[219].

As patients approach the end of life, interventions required to preserve quality of life during the terminal phase of the illness will take over as mobility becomes more limited and higher doses of opioids become necessary for control of a range of symptoms including agitation, breathlessness and general distress. Nonetheless, a small number of patients will have bone pain that is difficult to manage or experience pathological fracture at this time. Radiotherapy can be utilized effectively to help maintain quality of life in the last 3 months of life[220]. However, in the final days of life, pain from metastases and/or fractures can be better managed with analgesic titration and adjuvant analgesics such as anti-inflammatory drugs.

Quality of life

Bone metastases are associated with significant morbidity that impacts on quality of life, social functioning and mobility[221]. Owing to their beneficial effects on the bone structure, BTAs are shown to greatly reduce skeletal morbidity. In addition, BTAs also lead to reduced patient demands on both carers and health-care systems[2,5].

Before the introduction of BTAs into routine clinical care, the frequency of SREs was high, and many SREs required hospital admission. Now the incidence of SREs is <1 event per year per patient with bone metastases, and the need for hospital admission has been substantially reduced. Although survival is severely compromised by a diagnosis of bone metastases, the quality of life of patients has markedly improved, with many patients continuing to work, care for their families and enjoy an active life until the end stages of the disease[222]. Support and advice from experienced health-care practitioners can be invaluable in helping patients make the best use of available treatments.

Functional assessments of bone pain are a crucial part of the overall pain assessment. Routine pain assessment using patient-reported outcome measurements, such as a pain score, is important to monitor response and adverse effects to treatment. Informing the patient about which strategy to use in different pain situations is important. The Brief Pain Inventory (BPI)[223] and the European Organization for Research and Treatment of Cancer Bone Metastasis 22 questionnaire[224] are valuable tools for evaluating quality of life. In addition to providing details of breakthrough pain, these questionnaires provide a useful assessment of efficacy and could help bring emerging therapies into clinical practice. Future research, with an aim of improving pain management, should include appropriate functional outcomes as well as detailed pain assessments to capture all aspects of breakthrough pain[225].

Analgesic titration
A stepwise increase in analgesics, especially opioids, to achieve pain control without excessive toxicity.

Outlook

Mechanisms

Despite several years of research, the complex biology of metastasis is only just being understood. We need to deepen our knowledge of the critical stages of metastasis that could potentially be therapeutically targeted. The early stages of metastasis, such as establishment of the pre-metastatic niche, escape from the primary site and colonization of the bone microenvironment, occur even prior to treatment of the primary tumour. Thus, early diagnosis is probably the only strategy by which these early events can be disrupted.

A greater understanding of tumour dormancy is a priority and holds tremendous therapeutic potential. Delineating the factors that induce and maintain tumour dormancy might lead to therapeutic approaches that could eliminate these quiescent cells that are so difficult to target with current strategies. Tumour dormancy can be influenced by modifying the cellular interactions between the host cells within the microenvironment and the disseminated cancer cells. Preclinical models that truly recapitulate the metastatic processes as seen in patients are warranted for a better understanding of the disease processes[226]. Currently, a reliable biomarker for tumour dormancy is not available for clinical use. However, single-cell analysis of disseminated tumour cells and circulating biomarkers such as cell-free tumour DNA[139,140] may, in the future, give us valuable insights and are an area for further research. Additionally, our knowledge of the immunological control of cancer is improving and a wide range of immunomodulatory treatments may provide additional options for maintaining tumour dormancy and preventing the emergence of overt metastases[227].

Emerging therapies for bone metastases

Advances in our understanding of the signalling mechanisms between bone cells and tumour cells have resulted in the emergence of numerous therapies, which target osteoclasts, osteoblasts and/or the bone microenvironment. Some of these drugs are at an early stage of development in clinical trials, whereas others are already approved for clinical use in other indications and are beginning to have an impact on the care of patients with bone metastases (TABLE 4).

Bone resorption inhibitors. In addition to bisphosphonates and denosumab, a wide range of agents can block osteoclast-mediated bone resorption[228]. These agents include everolimus (mTOR inhibitor)[229,230], cathepsin K (a protease that degrades collagen during bone resorption) inhibitors[231,232], SRC tyrosine kinase inhibitors[233] and cabozantinib (an inhibitor of receptor tyrosine kinases including VEGFR2 and MET)[234–237].

The BOLERO II study reported a significant increase in PFS in patients receiving a combination of everolimus and exemestane (12.9 months) compared with patients receiving exemestane (5.3 months)[230]. In animal models of prostate cancer bone metastasis, inhibition of cathepsin K has been shown to reduce bone destruction and skeletal tumour burden[231]. In patients with breast cancer bone metastases, the

Table 4 | **Potential therapeutic targets and drugs in development for bone metastases and multiple myeloma**

Drug	Targets	Results	Trial ID	Refs
Everolimus[a]	mTOR	Improvement in PFS in patients with breast cancer bone metastases Approved for treatment of metastatic breast cancer, renal cell carcinoma and neuroendocrine tumours	NCT00863655 (BOLERO II) NCT01783444 (BOLERO 6)	230
Cabozantinib[a]	MET and VEGFR2	Decreases tumour burden Reduces osteoblastic lesions Improvement in PFS in patients with CRPC Improvement in OS and PFS in patients with advanced RCC and bone metastases Approved for use in patients with renal and thyroid cancers	NCT01605227 (COMET-1) NCT01865747 (METEOR)	235–237
Dasatinib[a]	BCR–ABL and SRC	Inhibits bone turnover markers in patients with prostate cancer Responses in patients with prostate cancer seen on PET–CT imaging Approved for use in haematological malignancies	NCT00410813 NCT00918385	256,257
Abiraterone[a]	CYP17A	Improvement in OS and increase in time to first SRE in patients with metastatic CRPC Approved for use in patients with prostate cancer Anabolic and antiresorptive effects in patients	NCT00638690 NCT00887198	258,259
Romosozumab[a]	Sclerostin	Reduces osteolytic lesions in mouse models of breast cancer or multiple myeloma Approved for use in postmenopausal women with severe osteoporosis	Preclinical studies only for effects on cancer NCT01575834	238
Bortezomib[a]	26S proteasome	Stimulates bone formation and improves bone healing in patients with multiple myeloma Approved for use in patients with multiple myeloma	NCT01286077 NCT00972959	239
Atrasentan[b], zibotentan[b]	Endothelin 1	Promising phase II data in prostate cancer Atrasentan failed to achieve the primary end point of improved OS in phase III trials	SWOG S0421, ENTHUSE M1C	241
Tanezumab[b]	NGF	Attenuates cancer pain in animal models of prostate and breast cancer bone metastasis and sarcoma Provides additional sustained analgesia in patients with metastatic bone pain who are taking opioids; failed to achieve the primary end point of lowering opioid usage	NCT00545129 NCT02609828	243
Odanacatib[c]	Cathepsin K	Inhibits the formation of osteolytic lesions in vivo Reduces bone resorption in the clinic Development halted owing to potential cardiac adverse events	NCT00399802	231,232
Saracatinib[c]	SRC and BCR–ABL	Limited activity in solid tumours Minimal effects on bone pain	NCT00558272 NCT02085603	228,255
BHQ880[c]	DKK1	Reduces osteolytic lesions in mouse model of multiple myeloma Improves bone mineral density in patients with relapsed or refractory multiple myeloma	NCT01302886 NCT01337752 NCT00741377	228
Sotatercept[c]	Activin A	Improves bone mineral density Inhibits myeloma bone disease in animals Ongoing studies in patients with multiple myeloma	NCT01562405 NCT00747123	102,240
Galunisertib[c]	TGFβ	Inhibitory effects on metastasis number and growth in experimental models of bone metastasis Ongoing study in patients with CRPC	NCT02452008	242
BMS777607[d] or ASLAN002[d]	RON	Inhibits the formation of osteolytic lesions in animal models Reduces bone resorption in patients with advanced cancer	NCT01721148 NCT00605618	228

Table 4 (cont.) | **Potential therapeutic targets and drugs in development for bone metastases and multiple myeloma**

Drug	Targets	Results	Trial ID	Refs
JQ1[e]	BET family bromodomain proteins	Inhibits osteoclastogenesis and bone destruction in experimental models of osteosarcoma	Preclinical only	228
IVD11[e]	Jagged or Notch	Inhibits osteoclastogenesis and bone metastasis formation in vivo	Preclinical only	228
C21[e]	DOCK5	Reduces osteoclast activity in vitro and bone destruction in a mouse model of melanoma	Preclinical only	228

ABL, tyrosine-protein kinase ABL1; BCR, breakpoint cluster protein; BET, bromodomain and extra-terminal domain; CRPC, castration-resistant prostate cancer; CYP17A, cytochrome P450 17α hydroxylase; DOCK5, dedicator of cytokinesis 5; DKK1, Dickkopf-related protein 1; MET, *N*-methyl-*N*′-nitroso-guanidine human osteosarcoma transforming gene; mTOR, mammalian target of rapamycin; NGF, nerve growth factor; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; RON, macrophage-stimulating 1 receptor; SRC, proto-oncogene tyrosine kinase SRC; SRE, skeletal-related event; TGFβ, transforming growth factor-β; VEGFR2, vascular endothelial growth factor receptor 2. [a]Has regulatory approval in the United States and/or Europe for use in patients with cancer or other indications as indicated. [b]Drug in phase III trials. [c]Drug in phase II trials. [d]Drug in phase I trials. [e]Drug investigated in preclinical studies.

cathepsin K inhibitor, odanacatib, reduced circulating levels of bone resorption markers, implicating possible useful clinical activity[232]. However, phase III trials of odanacatib were discontinued owing to possible cardiovascular adverse events reported in trials conducted in women with osteoporosis.

In animal models of prostate cancer, cabozantinib decreased skeletal tumour burden and the formation of osteoblastic lesions[234]. Additionally, in patients with CRPC bone metastases, a single-arm phase II study showed a 68% rate of normalization of bone scans with cabozantinib treatment, suggesting significant clinical activity[235]. However, in the subsequent phase III trial (COMET-1), cabozantinib failed to achieve the primary end point of improved overall survival, although secondary end points including PFS and time to first SRE were significantly improved with cabozantinib treatment compared with the prednisone-treated group[236]. In renal cell carcinoma, cabozantinib seemed to be particularly effective in the subgroup of patients with bone metastases[237].

Anabolic agents. Although bisphosphonates and denosumab inhibit tumour-induced osteolysis, they do not replace the bone lost as the result of the metastatic disease and, therefore, patients remain at risk of developing fractures. Inhibitors of androgen biosynthesis, such as abiraterone, are well established in the management of advanced prostate cancer and might have some direct bone anabolic activity that contributes to their efficacy in metastatic bone disease. Specific bone anabolic agents that promote bone formation by targeting osteoblasts offer a new therapeutic approach, although they are not approved for routine clinical practice. Targeting the Wnt–DKK1–sclerostin pathway is currently being investigated; for example, romosozumab, an anti-sclerostin antibody, has been shown to increase bone mass and reduce the fracture risk in patients with osteoporosis[238]. Additionally, an anti-sclerostin antibody decreased the extent of osteolytic lesions in a mouse model of breast cancer bone metastasis and multiple myeloma[102] but has yet to be tested in patients.

Bone anabolic agents can also potentially repair existing bone lesions. For example, proteasome inhibitors such as bortezomib stimulate bone formation and are associated with evidence of bone healing in some patients[239]. Alternative strategies include inhibition of activin A[240] or endothelin 1 (REF.[241]) and regulators of TGFβ signalling[242], all of which have shown promising activity in preclinical settings.

Other therapeutic strategies. Insights from animal models into the mechanisms that drive CIBP have also provided opportunities to develop new targeted therapies. These include tumour-directed osteoclast-mediated osteolysis, tumour cells themselves, tumour-induced nerve injury, transient receptor potential vanilloid 1 (TrpV1) potentiation, endothelin 1 release and nerve growth factor (NGF) expression by both immune cells and tumour cells[243]. A combination of therapies that target these mechanisms is likely to be superior to any single therapy for CIBP.

Advancements in imaging

Modern imaging techniques such as PET–CT imaging and whole-body MRI have limited clinical availability and resources to make them more widely available are needed. In addition, clinical acceptance of next-generation imaging technologies is lacking in the management of patients by clinicians who are not working in specialist centres.

Metastatic bone disease is increasingly recognized as a heterogeneous disease, with biological differences between tumour lesions as well as the potential for discordant responses to therapy within an individual. Functional bone imaging may be used to study genomic heterogeneity, both within tumours and between bone lesions. The ability of functional imaging techniques to characterize tumour biophysical properties could be harnessed to inform precision treatments including radiotherapy planning (metastasis-directed therapy) and for tumour sampling for genomic assays[244]. Additionally, the increasing use of whole-body MRI and PET–CT in the metastatic setting provides an opportunity to perform serial tumour measurements of both size and function and/or obtain serial tumour samples. These approaches can provide earlier evidence of treatment resistance, thereby reducing unnecessary toxicities and enabling earlier use of alternative treatment options[245].

Biomarkers

Biomarkers are of great importance in assessing prognosis and are particularly valuable if they can predict therapeutic benefit from an intervention. In early cancer, efforts are ongoing to identify biomarkers that may predict benefit (and potential harm) that results from manipulating the bone microenvironment. Preliminary data from a study of adjuvant zoledronate suggest that the co-expression of macrophage-capping protein and PDZ domain-containing protein GIPC1 is not only a prognostic factor in early breast cancer but can also predict treatment benefit, such as the time to first distant recurrence in bone, from zoledronate[246]. In tissues collected from the same trial, increased copy number expression of the transcription factor MAF was found to predict recurrence and survival benefit up to 10 years. MAF is amplified in ~20% of tumours and predicts bone recurrence[247]. In those with normal MAF amplification status, marked disease benefits from zoledronate were observed, whereas in those with increased MAF expression the addition of zoledronate to adjuvant treatments resulted in worse survival, especially in premenopausal women, than with adjuvant treatments alone[124,248]. Nevertheless, validation of these results is needed before any of these biomarkers could be considered for routine clinical use.

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Competing interests
R.E.C. has received honoraria from Amgen and Novartis, and has stock options with Inbiomotion related to a patented biomarker. P.I.C. is the recipient of a grant from Amgen, and received honoraria and participated in advisory boards from Amgen. P.C. has received honoraria from Amgen. L.C. has received research grants from Amgen, Bayer, Novartis and Roche, speaker honoraria from Amgen, Bayer, Janssen, Lilly and Roche, and is also a consultant for Amgen, Novartis and Servier. All other authors declare no competing interests.

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