Cancer Metastasis – Biology and Treatment 21

Vassilios Vassiliou
Edward Chow
Dimitrios Kardamakis *Editors*

Bone Metastases

A translational and Clinical Approach

Second Edition

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Bone Metastases

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Preface

The impact of cancer on the skeleton can be devastating and typically results in a major decline in quality of life as well as reduced survival. Over the last decade or more, we have learnt a great deal about the cellular interactions that lead to the colonisation of bone by tumour cells and subsequent formation of metastases. This improved knowledge has helped the development of a range of bone-targeted treatments that have profoundly affected the clinical course of metastatic bone disease across the range of primary tumours that can affect the skeleton. These agents have complemented the improvements in specific drug treatments for cancer, radiation treatments and orthopaedic surgery and become part of the standard of care for patients with spread of cancer to bone.

Drs. Vassiliou, Chow and Kardamakis are to be congratulated on the production of this excellent textbook containing contributions from some of the leading authors in the field from around the world. Following discussion of the pathophysiology, clinical features and epidemiology of bone metastases, the strategies for investigation and subsequent therapeutic management of bone metastases are discussed. These chapters cover all of the relevant treatment modalities including surgery, radiotherapy, systemic anti-cancer treatment and bone-targeted therapies. Valuable contributions on the assessment of therapeutic response and on the cost of managing metastatic bone disease complement this comprehensive, highly useful textbook that will be of value to all oncologists and other clinicians dealing with advanced cancer patients.

Through better diagnostic tools, advancing surgical techniques, improved systemic and local anti-cancer treatments and particularly the introduction of bone-targeted therapies, the management of metastatic bone disease has been transformed for the better. The cascade of frequent skeletal complications experienced by patients with metastatic bone during the latter part of the last century, often requiring inpatient care and occurring on average every 3–4 months, has been replaced by a disease that can be largely managed in an outpatient setting with relatively minor disruption from the skeletal component of the disease. In many cancers, this has resulted in the possibility of disease control over years rather than months with excellent quality of life and social functioning.

This book fills an important niche for all of us involved in cancer management to help ensure that we implement the variety of available treatments in the most effective and efficient manner and thereby help our patients live better and, ideally, longer lives despite their advanced malignancy.

Sheffield, England Robert Coleman

Contents

Part III Therapeutic Management

Part I
Fundamental Concepts

Chapter 1
Pathophysiology of Bone Metastases

John M. Chirgwin and G. David Roodman

Abstract Bone metastases are a late event in tumor progression, contributing to morbidity and mortality and decreasing patient quality of life. Cancer colonization of the skeleton is characteristic of advanced tumors of breast, prostate and other sites and of multiple myeloma. The pathophysiology of cancer in the skeleton can be conceptualized as a *vicious cycle*, where cancer-secreted factors activate bone cells to release factors that encourage further growth of tumor, which in turn secretes more factors into the microenvironment. Bone provides unusual physical conditions favorable to tumor growth: low pH and oxygen tension and high concentrations of calcium, phosphate and many growth factors. It also houses stem cells, bone marrow and immune cells, which can encourage the establishment, growth and survival of metastases. A plethora of bone and tumor factors contributes to the vicious cycle: too many to be individually targeted in the clinic. However, inhibition of bone resorption is invariably effective and may oppose the initial development of cancer in bone. Central pathways, such as hypoxia and TGFβ signaling, are important for both tumor and bone functions; they are promising targets for improved therapies, while other pathways may yield future treatments to decrease bone metastases and myeloma bone disease.

Keywords Bone metastasis • Multiple myeloma • Bone resorption • Osteoblast • Osteoclast • Osteocyte • Vicious cycle

1.1 Introduction

Bone metastases occur late in tumor progression, toward the end of a multi-stage process. First, cancer cells must detach from the primary tumor and invade blood vessels. Once in the bloodstream, they are attracted to preferred target tissues.

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Tumor cells reaching the skeleton adhere to the endosteal surface and colonize bone. The early steps in the metastatic cascade remain experimentally challenging to study. However, the final colonization of bone can be reproduced in animal models, which enable testing of mechanisms and development of treatments. Tumor cells housed in the skeleton subvert the cellular processes of normal remodeling, causing bone pathology [1].

Bone is the preferred site for breast and prostate cancer metastases; many other cancers, including lung and renal tumors and melanomas also colonize the skeleton. Carcinomas of the thyroid, kidney, and bronchus metastasize to bone with an incidence at autopsy of 30–40 %, while gastrointestinal tumors rarely metastasize to the skeleton [2, 3]. Hematological malignancies do not by definition metastasize, but among them multiple myeloma (MM) consistently grows in bone and stimulates severe, destructive osteolysis. Bone metastases and myeloma bone disease cause skeletal-related events (SREs), complications that include bone pain, pathologic fractures, spinal cord and nerve compression syndromes and derangements of calcium and phosphate homeostasis [2], covered in subsequent chapters. SREs increase morbidity, contribute to mortality and diminish quality of life, as discussed in Chap. 24. Virtually all patients dying from advanced prostate cancer or myeloma and the majority succumbing to advanced breast cancer have tumor-induced bone lesions. Tumor in bone may also contribute, by presently unknown mechanisms, to systemic muscle cachexia.

Among the solid tumors, those of the breast and prostate are characterized by multi-year survival from first diagnosis of bone metastases. They are leading causes of cancer death among women and men—second only to lung cancer. If detected at an early stage their prognosis is favorable, with 5-year survivals—for death from the cancer—greater than 90 %. However, when initial diagnosis is of advanced metastatic disease, the 5-year survivals decrease to around 30 % [4]. At least 80 % of patients with advanced breast and prostate cancers have bone metastases, and survival from time of first diagnosis of skeletal involvement in prostate cancer patients, for example, is approximately 40 months [3]. Multi-year survival times provide the need and opportunity for treatments to decrease metastatic growth. Lung cancers and melanoma also metastasize to bone with high incidence. The short survival time of patients with these tumors may improve, creating addition needs for effective treatment of bone metastases. The diagnosis of bone metastases is not thought to be cost-effective for many cancer types, so diagnosis is inconsistent, but skeletal metastases could be the largest single cause of death from adult cancers [5].

1.2 Pathophysiology of Bone Metastases

Bone metastases are classified as osteoblastic, when bone formation overcomes bone resorption, or osteolytic, when focal decreases in bone occur via increased bone resorption [1]. Osteoblastic lesions are characteristic of advanced prostate cancer, while in breast cancer osteolytic lesions are found in 80 % of patients with stage IV metastatic disease [6]. Bone lesions span a spectrum, shown in Fig. 1.1, from osteolytic

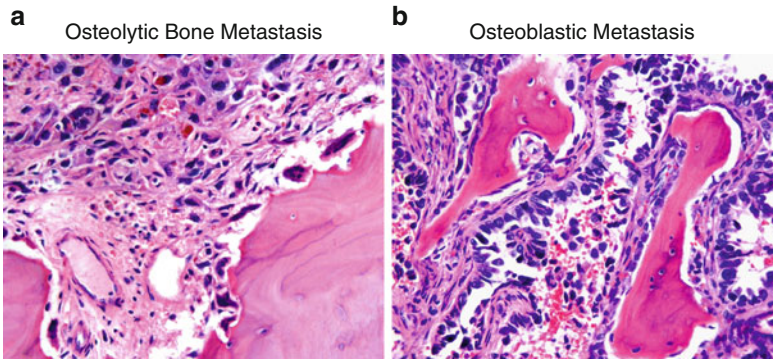

Fig. 1.1 Osteolytic (a) and osteoblastic (b) metastases. *Panel A* shows osteolytic bone metastasis due to renal carcinoma invading the bone marrow. Osteoclasts (*arrows*) are actively resorbing bone adjacent to tumor cells, causing scalloped excavations in the bone surface. *Panel B* shows osteoblastic metastasis. Thickened trabeculae have large numbers of osteoblasts next to the bone surfaces. Lung adenocarcinoma tumor cells are growing between the two large trabeculae (*pink-stained*), in which dark-staining osteocytes are embedded. Tumor angiogenesis is visible in both panels (Images (hematoxylin and eosin, X200) graciously provided by Dr. Brendan Boyce, University of Rochester, Rochester, New York)

(**A**) to osteoblastic (**B**). Although bone lesions from breast cancer metastases are mostly osteolytic, up to 15 % are osteoblastic or mixed. Regardless of tumor type, most patients with bone metastases have evidence of both abnormal bone resorption and formation. At autopsy of men with prostate cancer, bone metastases are histologically heterogeneous within and among lesions [7], while multiple metastatic foci in an individual appear to be genetically monoclonal [8]. The phenotypic heterogeneity may be due to progressive but asynchronous changes in tumor-bone interactions. The bone destruction in osteolytic disease is due to increased number and activity of osteoclasts in the vicinity of tumor. Focal loss of bone causes lesions to be visible on x-ray contributes to loss of bone strength and integrity and may result in hypercalcemia and cancer-induced bone pain. Osteoblasts appear to be the primary agents of osteoblastic metastases, producing disorganized new bone of poor biomechanical quality. Osteoblastic metastases are not as readily assessed by x-ray and are accompanied by markers of bone resorption (Chap. 6) even higher than those seen in osteolytic disease.

1.3 Interactions Between Tumor Cell and the Bone Microenvironment: The Seed and Soil and the Vicious Cycle

The basic pathophysiological mechanism of local tumor-induced bone disease can be conceptualized as a vicious cycle between tumor and bone. The foundation of this model is the Seed & Soil hypothesis proposed by Stephen Paget in the Lancet

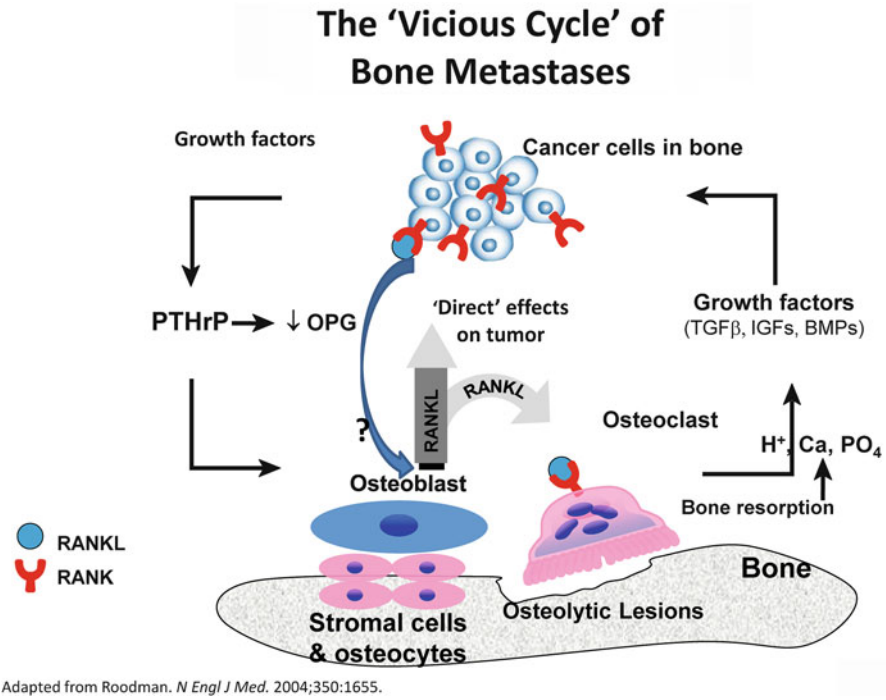

Fig. 1.2 The vicious cycle. Osteolytic metastases, most common in multiple myeloma and breast cancer, are shown. There is an excess of bone resorption relative to bone formation. In breast cancer metastases the tumor cells commonly produce PTHrP to promote the differentiation and maturation of osteoclasts through increased RANKL production. PTHrP also decreases production by osteoblasts of Opg, which neutralizes RANK ligand. The imbalance between bone resorption and formation is responsible for the bone lesions and bone loss observed in Osteolytic bone diseases associated with cancer. RANK ligand may also be produced by osteocytes, which are more abundant than osteoblasts. Bone acts as a large depository of inactive growth factors (TGFβ, IGFs, FGFs, PDGFs, and BMPs), which are released and may be activated during the bone resorption process. The release of Ca^{++}, phosphate, acid and growth factors induce further growth and proliferation of tumor cells, which produce more factors to promote bone resorption to release even more growth factors to stimulate tumor cell growth. This stimulatory circle of interactions between tumor cells and osteoclasts and other bone cells fuels the vicious cycle of osteolytic metastases

in1889 [9]. Paget suggested that cancer cells scatter throughout the body as premetastatic 'seeds', which grow best when they encounter a specific fertile 'soil': bone in the case of tumors of the breast. This model has been expanded in the molecular era into the 'vicious cycle' model (Fig. 1.2), in which factors from bone stimulate tumor activity, which in turn makes the bone environment more fertile by two mechanisms: (a) bone turnover releases growth factors immobilized in mineralized bone matrix; (b) bone cells secrete factors that can act on tumor cells. Crosstalk between tumor cells and the microenvironment thus fuels a vicious cycle of tumor growth and bone remodeling [10], which relies on factors secreted by

tumor cells that stimulate osteoblast and osteoclast proliferation and maturation, leading to a net increase in osteoclast-mediated bone destruction or disorganized new bone formation. The resorption of bone matrix leads to the release of immobilized growth factors that stimulate tumor growth (Fig. 1.2). The locally enriched factors surrounding the tumor cells not only encourage their growth but also alter their phenotype, frequently making them resistant to standard cytotoxic anti-tumor treatments. The mutual stimulation between tumor and bone drives the vicious cycle, which may be the rate-limiting step for tumor growth and contributes to resistance to chemotherapy at the metastatic site.

The bone microenvironment is comprised of mineralized bone matrix and many cell types: osteoblasts, osteoclasts, osteocytes (much more abundant than the previous two types and embedded within bone), endothelia, immune cells, bone marrow components and nerves. Signals from bone activate numerous intracellular tumor pathways that drive the vicious cycle. The vicious cycle paradigm is supported by experiments with the tumor-secreted factor, parathyroid hormone-related protein, PTHrP, which stimulates osteolysis via activation of the RANK ligand pathway (discussed below). Osteolysis in turn releases active transforming growth factor, TGFβ, from the bone matrix. TGFβ signaling then increases tumor secretion of PTHrP. The cycle has been validated by extensive animal experiments with the osteolytic breast cancer line MDA-MB-231; the prostate cancer line PC3 and others behave similarly. TGFβ inhibitors are now in clinical trials [11]. The important prediction of the two heuristic models is that agents that target bone will significantly inhibit bone metastases, decrease SREs and in the long run could eliminate tumor in bone or turn bone metastases into a non-lethal complication of cancer. In this review we focus on the roles of local and secreted factors, secreted proteases, and physical and chemical properties of bone as potential targets for advanced metastatic bone disease.

Animal models and limitations: There are no animal models in which specific tumors arise spontaneously and cause reproducible skeletal metastases with enough frequency to be usefully studied. A few mouse tumor lines (4T1 breast cancer, B16 melanoma and 5TGM1 myeloma lines, for example) can be transplanted into genetically matched hosts and will colonize bone. Most researchers transplant human tumor lines into immunodeficient mice, where many tumor types will grow upon direct injection into bone. Some but not all of these will also home to bone and establish metastatic lesions from the arterial circulation, generally after inoculation into the left cardiac ventricle [12]. These models do not duplicate the metastatic cascade but do reproduce appropriate responses to treatments. They are thus centrally important for development of novel therapeutics. It is challenging to introduce transgenic or knockout genetic changes into these models because of the complex mouse breeding required. Co-cultures of tumor with bone cells line are presently too simplified a system to reproduce the metastatic microenvironment [13].

Bone may be a special site for tumor metastases for three reasons: (1) Bone is a unique chemical and physical environment rich in calcium, phosphate and collagen with low oxygen tension; (2) Bone houses marrow, providing stem cell niches and many hematopoietic and immune cells; (3) Bone matrix is degraded by an unusual cell

type, the osteoclast, which is the target of antiresorptive treatments (Chaps. 11 and 12). Other mesenchymally derived tissues, such as fat and muscle, do not have a osteoclastic cell specialized for tissue catabolism. These three specialized properties of bone provide most of the targets for therapeutic interventions against cancer bone diseases.

Stem cell niche: Bone marrow provides major niches for mesenchymal and hematopoietic stem cells. Disseminating tumor cells may competitively usurp this niche [14] and remain dormant within bone, giving rise to micrometastases, which subsequently develop into macroscopic metastases and may seed distant metastatic sites [15]. Future agents to prevent tumor stem cell occupancy of niches in bone or to prevent escape from dormancy could prevent the development of bone metastases.

Metastatic signatures: A series of studies beginning a decade ago show that a single cell line, although apparently genetically homogeneous, consists of subclones that vary in patterns of stable gene expression. Using their behavior in mice, it is possible to isolate aggressive versus indolent subclones and ones that metastasize to specific target tissues such as bone [16]. Analysis of gene expression between subclones identified a molecular signature that contributed to bone-selective metastasis by breast cancer. The signature consists of a handful of genes that serve as a "molecular toolbox" to facilitate tumor growth in bone. Knockdown of a single gene in the handful does not decrease bone metastasis, but blockade of combinations of three or four does. The identified genes include ones for secretory proteins that stimulate angiogenesis, osteoblast growth, bone matrix proteolysis, osteoclast activity and the CXCR4 receptor involved in homing to bone.

Signaling from primary tumor site to bone: The presence of a primary tumor may alter the properties of bone to create a pre-metastatic niche [17]. For example, primary breast cancers in experimental animals can cause substantial damage to bone structure and strength [18]. Such changes can be caused by tumor-produced parathyroid hormone-related protein [19], which is a causal agent in osteolytic bone metastases as well as humoral hypercalcemia of malignancy—where it stimulates bone resorption and inhibits tubular reabsorption of calcium in the kidney. Another contributor is heparanase secreted from breast cancer, myeloma and other tumors, which can activate growth factors in extracellular matrix and enhance bone metastases [20].

Changes in tumor: bone interactions over time, exosomal communication and epigenetics: Bone metastatic lesions change over time, with prostate cancer metastases being able to become more osteoblastic due to changes in the Wnt signaling pathway [21]. It seems likely that as a metastatic lesion evolves, local signaling interactions will change tumor cells and bone cells. Such interactions may involve bidirectional transfer of exosomal vesicles [17] and epigenetic changes (via DNA methylation and demethylation to alter transcription for example) in tumor and in bone cell lineages.

Immune effects on metastasis: T cells, myeloid-derived suppressor cells and other components of the immune system are natural components of the bone marrow and control the growth of tumor in bone [22]. These cells offer future targets for potential therapeutic intervention.

Tumor effects on osteolysis: Cancer-induced bone diseases, both solid tumor bone metastases and myeloma bone disease, are characterized by pathologically increased bone destruction and elevated markers of bone resorption. The central pathway for the regulation of osteoclast formation, activity and survival is that of RANK ligand (RANKL). Hematopoietic precursor cells in the presence of M-CSF express receptor activator of NFκB (RANK), which binds RANKL, followed by intracellular signaling and differentiation into active, multinucleated osteoclasts. The effects of RANKL are opposed by osteoprotegerin, Opg, which is a soluble binding protein for RANKL. Blockade of the RANKL pathway with the neutralizing antibody denosumab effectively blocks the formation of osteoclasts and consequent bone destruction. Bisphosphonates are metabolic toxins that bind to the bone surface and are ingested by actively-resorbing osteoclasts, thus blocking their activity and survival. Cathepsin K and Src inhibitors inhibit specific functions necessary for osteolysis, without killing osteoclasts. The RANK ligand pathway and the classes of antiresorptive drugs are discussed in detail in other chapters.

RANKL Is produced in soluble and membrane-anchored form by cells in the early osteoblast lineage in response to pro-osteolytic factors such as interleukin-11 and PTHrP, which is also the main causal agent of hypercalcemia of malignancy [19]. High concentrations of 1,25-dihydroxyvitamin D also increase RANKL and osteoclasts. It has recently been found that osteocytes, which are the most abundant bone cell type, are a major source of RANKL [23]. There are also a variety of RANKL-independent factors that stimulate osteoclasts, including interleukins 3, -8 -6, -17, -18, macrophage-induced protein MIP-1α and activin A [24].

Tumor effects on osteoblastic responses: Markers of activity of both osteoblasts and osteoclasts are high in most cancer metastases, although osteoblast activity is strikingly depressed in multiple myeloma. In prostate cancer the majority of bone metastases are osteoblastic, presumably due to tumor secretion of factors that tip the balance between bone resorption and formation in favor of the latter. It is unclear if the major problem in osteoblastic disease is too much bone laid down in the wrong place, or if the bone is of different quality from normal. Many candidate osteoblast-stimulatory factors have been identified, such as the insulin-like growth factors, IGFs, platelet-derived growth factor B (PDGF-B), bone morphogenetic proteins, BMPs, and the small peptide vasoconstrictor endothelin-1 (ET-1), which can stimulate bone formation by suppressing the Wnt inhibitor Dkk-1 [25]. Endothelin was an unexpected stimulator of bone formation and causal agent in osteoblastic metastasis of prostate and breast cancers [26]. However, several endothelin A receptor antagonists have failed phase III clinical trials in men with advanced prostate cancer, and it remains unclear what is the major mechanism(s) driving abnormal bone formation in osteoblastic disease. Wnt signaling (discussed below) is a fundamental driver of normal and pathological bone formation, as well as acting on tumor cells [27]. Two endogenous soluble inhibitors of Wnt signaling are Dkk1 and sclerostin. The former is a specific product of osteocytes, while the latter is more widely expressed and is a major product of multiple myeloma (MM) cells [28], which suppress osteoblast activity, causing purely osteolytic disease. MM may also produce sclerostin. Antibodies neutralizing sclerostin or Dkk1 have

been developed as therapies for osteoporotic bone loss, and are in clinical trial for myeloma, but it is unclear that these would be appropriate for use in cancer patients.

Pathways active in tumors and bone: A challenge to the treatment of cancer bone disease is that the list of factors (from tumors acting on bone and from bone acting on tumor) is long, and treatments to block single factors are expensive (Chap. 25). Thus treatments need to target centrally important factors (such as RANK ligand) or pathways that control the production of multiple factors, such as the signaling pathways for TGF or hypoxia. Additional multifunctional signaling targets include the Wnt (discussed above) and Notch [29] pathways, Src [30], RANKL, the transcription factors NF-κB and Runx2 [31] and p38MAP kinase, all of which offer future possibilities for therapeutic intervention.

1.4 Effects of the Bone Microenvironment on Tumor Cells

The development of skeletal metastases depends on the reactions of the cancer cells to the bone microenvironment, whose milieu contains a multitude of growth factors, cytokines, chemokines and interleukins. It is also characterized by low pO_2, low pH and high Ca^{2+} and phosphate, which contribute to the physical properties of the bone microenvironment, reviewed in detail by Kingsley [32].

Hypoxia is a major contributor to tumor metastasis, regulating secreted products that drive tumor cell proliferation and spread. Hypoxia also contributes to resistance to radiation and chemotherapy in primary tumors. Solid tumors are particularly susceptible to hypoxia because they proliferate rapidly, outgrowing the inefficient tumor vasculature. Bone is a hypoxic microenvironment ($pO_2 = 5$ %) capable of potentiating tumor metastasis and growth. Hypoxia regulates normal marrow hematopoiesis and chondrocyte differentiation. Cancer cells continue to grow at low oxygen levels in the hypoxic bone microenvironment and contribute to the vicious cycle, where oxygen-regulated genes [33] include glycolytic enzymes, glucose transporters, and vascular endothelial growth factor (VEGF, which is important for angiogenesis). Many others are pro-metastatic [34], supporting a role for hypoxia in the vicious cycle.

The regulatory subunit for hypoxic transcription, HIF-1α, increases the expression of factors that could accelerate the vicious cycle of skeletal metastases, such as the MET receptor tyrosine kinase that binds hepatocyte growth factor and is associated with invasion and metastasis in advanced breast cancer. HIF-1 also regulates adrenomedullin, CXCR4, and connective tissue growth factor, CTGF, factors with known roles in bone growth and turnover and homing of tumor metastases. HIF-1α and TGFβ signaling have parallel roles in a model of breast cancer bone metastases by acting on many of the same prometastatic target genes [34].

Low pH: Bone resorption acidifies the bone microenvironment, which potentiates the vicious cycle of bone metastasis. Acidification increases osteoclastic resorption

pit formation, with maximal stimulation below pH 6.9. The ability of osteoblasts to catalyze mineralization and form bone is inhibited by acid pH. Tumor metastasis leads to localized regions of acidosis within the skeleton via increased glycolysis and lactic acid production from cancer cells. Acidosis can promote apoptosis in adjacent normal cells such as osteoblasts and increase extracellular matrix degradation by proteolytic enzymes. Unlike normal cells, cancer cells are not susceptible to acid-induced apoptosis, nor are acid-producing osteoclasts. Hypoxia further promotes acidosis within tumor cells through overexpression of glycolytic enzymes, increased lactic acid production and release and activation of proteinases, which degrade the extracellular matrix and facilitate metastasis [35]. Hypoxia-mediated acidosis also activates numerous stress signaling cascades within tumor cells, including the NFκB and AP-1 pathways, which in turn regulate the transcription of pro-metastatic factors such as interleukin-8, a causal factor in osteolytic bone metastases [36].

Extracellular calcium and phosphate released from the mineralized bone matrix may contribute to the vicious cycle of metastasis by several mechanisms. Calcium phosphate is the primary inorganic component of the bone matrix. In the circulation, calcium levels are maintained within a narrow physiologic range (~1.2 mM), while active osteoclastic bone resorption causes local extracellular calcium (Ca^{2+}) levels to rise up to 40 mM [37]. Extracellular phosphate in bone should parallel calcium. Phosphate concentrations are systemically regulated by the endocrine hormone FGF23 released from bone osteocytes and acting on the kidney [38], but the roles of phosphate and FGF23 have been little studied in cancer and bone metastases.

Some effects of calcium are mediated through the extracellular calcium sensing receptor (CaSR), a G-protein coupled receptor that is overexpressed in many cancers, which respond to low Ca^{2+} by increasing PTHrP, which activates bone resorption and release of further calcium from bone matrix. The vicious cycle of bone metastasis includes contributions by the CaSR: TGF-β and calcium released during osteolysis activate the CaSR to increase PTHrP release, perpetuating osteolysis and bone matrix destruction. Bone matrix calcium may act through this receptor to help cancer cells localize to and attach to bone during metastasis. The CaSR also signals in part through the MAP kinase signaling pathway to stimulate PTHrP release, which is blocked by a variety of kinase inhibitors.

Factors secreted from osteoclasts, osteoblasts, osteocytes include interleukin 6 and annexin II from osteoclasts. These two molecules are discussed in detail in Roodman [24]. Many factors are made by osteoblasts. More recently, factors specifically secreted by osteocytes, which are cells derived from the same mesenchymal lineage as osteoblasts, have been identified: sclerostin and FGF23, discussed above. Factors secreted by osteoblasts with significant activities in cancer:bone disease include Wnt and Notch family members (both ligands and receptors), TGFβ superfamily members (including BMPs, activins and TGFβ itself), the RANKL inhibitor osteoprotegerin and the insulin-like growth factors. The secretory osteoblast is also the main source of these same growth factors when they become immobilized in bone matrix and released and activated during resorption.

The Wnt signaling pathway The Wnt pathway uses a large number of ligands and antagonists acting through complex receptors and signaling pathways in both bone and cancer cells [39]. Wnt ligand proteins released by metastatic prostate cancers stimulate osteoblasts and have autocrine effects on tumor proliferation [21]. An inhibitor of Wnt signaling dickkopf-1, Dkk1, can regulate metastatic progression by opposing osteogenic Wnts early in metastasis and later controlling the phenotypic switch from osteolytic to osteoblastic lesions. Increased Dkk1 is an early event in prostate cancer, but it declines in advanced bone metastases, relieving Wnt inhibition and increasing osteoblast activity. In contrast, Wnt inhibition may be one of the mechanisms through which multiple myeloma induces bone destruction via inhibiting bone formation [40]. Multiple myeloma cells secrete and multiple myeloma patients with advanced osteolytic lesions have high levels of the Wnt inhibitors Dkk1, frizzled-related protein-2 (sFRP-2), and sclerostin.

Bone morphogenetic proteins (BMPs): are growth factors that stimulate bone formation and are members of the TGFβ superfamily. Different BMPs may have different actions on cancer cells. The BMP antagonist noggin decreased osteolytic and osteoblastic lesions due to prostate cancer in mice [41]. Noggin plus a RANKL inhibitor delayed the radiographic development of lesions and decreased bone loss and tumor burden in models of prostate cancer bone metastases [42]. However, testing BMPs and their signaling in bone metastases is complicated by the wide variety of ligands and secreted antagonists in the family, as well as multiple receptors. It is not presently clear that the BMPs offer a viable target for therapeutic development against skeletal metastases, especially given their central role in normal bone homeostasis.

TGFβ is not the most abundant growth factor in bone [43], but its role in skeletal metastases is established. It is deposited in the bone matrix by osteoblasts, is released and activated during osteoclastic resorption and regulates bone development and remodeling. Advanced cancers frequently escape growth inhibition by TGFβ, which also activates epithelial-mesenchymal transition and invasion, promoting metastases. TGFβ also increases angiogenesis and suppresses immune surveillance. It specifically stimulates bone metastases by inducing pro-osteolytic gene expression in cancer cells, such as parathyroid hormone related protein (PTHrP). Its concentration is higher at sites of bone metastases compared to non-osseous metastases. The consequent increase in bone resorption releases more bone matrix factors to act on cancer cells, sustaining the vicious cycle [41]. TGFβ also increases COX-2 and interleukin-8 (IL-8), which induces osteoclast formation and activity independently of RANK ligand, and can also induce IL-11, which increases osteoclasts via RANK ligand, although IL-11 does not increase bone metastases in the absence of other pro-metastatic factors such as osteopontin. TGFβ inhibitors decrease bone metastases in mouse models [34]. They may effectively decrease osteolytic metastases by braking the vicious cycle, while having positive effects on the skeleton.

IGFs: The most abundant non-structural proteins in mineralized bone matrix are insulin-like growth factor (IGF) II and then I [43]. They act through the IGF

receptor to maintain cell growth, and both are important in bone development. In cancer and metastases, IGF receptor signaling promotes transformation and angiogenesis, induces cell proliferation and invasion and is anti-apoptotic. Inhibition of the IGF receptor decreases experimental bone metastases, although engineered overexpression of IGF-I had no effect in a different model. It remains unclear whether bone-derived IGFs are important drivers of skeletal metastases, but they appear to play an important role in myeloma [44].

Runx2 is a transcription factor essential for skeletogenesis. Runx2 in cancer cells and osteoblasts stimulates the production and release of angiogenic factors like VEGF and matrix metalloproteinases (MMPs) and upregulates adhesion proteins that facilitate tumor:bone cell binding [31]. Runx2 expression by cancer cells may also support tumor-induced osteoclastogenesis. Expression of similar surface proteins and secreted factors by bone cells and tumor cells allows for coexistence of the cell types and promotes the growth of metastatic lesions by double-feeding the vicious cycle. Cancer cells express a number of markers traditionally thought to be osteoblastic, such as osteopontin, bone sialoprotein and osteocalcin; they are regulated by Runx2 in both osteoblasts and cancer cells. Runx2 up-regulates RANKL expression and decreases Opg. Thus Runx2 is a potential therapeutic target for suppression of multiple genes driving bone metastasis.

Proteinases responsible for remodeling the extracellular matrix of the bone microenvironment include the matrix metalloproteinases (MMPs), along with other proteinases, proteinase inhibitors, clotting factors, chemotactic molecules, latent growth factors, growth factor binding proteins, cell surface receptors, and cell-cell and cell-matrix adhesion molecules. MMPs have important functions in pathologic conditions where excessive degradation of extracellular matrix ECM occurs, such as tumor metastasis to bone. MMP-9 is required to recruit osteoclasts to metastatic sites: treatment with MMP inhibitors abrogated osteoclast recruitment. MMPs may be produced by stromal cells in the vicinity of tumor cells rather than by the tumor itself, although MMPs can be up-regulated in tumor cells in bone. MMP-2 and MMP-13 are highly expressed in metastases to bone compared to brain metastases from breast cancer [45]. MMP-2, besides degrading extracellular matrix components, also activates TGFβ, interleukin 1, MMP-1 and MMP-13, while MMP-13 is responsible for activating MMP-9. Many MMPs are up-regulated in bone metastases and can activate factors important in bone metabolism and tumor development, such as IGFs and soluble RANKL, among others. MMP-1 is a member of the bone-metastatic gene signature [16]. Bone matrix is mostly comprised of mineralized fibrillar type-I collagen, which after demineralization is degraded by interstitial collagenase (MMP-1). Tumors expressing MMP-1 cause increased osteolysis in mice, and tumor-secreted MMP-1 activates osteoclasts in vitro.

Roles of osteoblast-stimulating agents: Stimulation of osteoblast activity should counteract the osteolytic destruction characteristic of MM and metastatic breast cancer. Myeloma can cause bone lesions that fail to heal during tumor remission, and MM cells and osteoblasts inhibit one another [46]. It is less clear whether such

inhibition is important in bone metastases due to solid tumors, where osteoblast stimulation might exacerbate osteoblastic disease, such as seen with prostate cancer. The case may be more complex when agents have effects on both tumor cells and bone cells. For example, proteasome inhibitors have anti-tumor activities and are also anabolic for bone [47]. They are effective clinically against multiple myeloma. Osteoblast activity is directly inhibitory for MM cell growth [48], which may account for the success of these agents in MM, since they have both direct and indirect effects against tumor [49]. Proteasome inhibitors have been less successful in clinical trials with solid tumors, but effects on bone metastases have not been studied. Bortezomib suppresses bone metastases due to osteolytic prostate cells [50], but since prostate cancer bone metastases are predominantly osteoblastic, it is unclear whether osteoblast stimulation would be dangerous or beneficial. Pennisi and colleagues [48] found that intermittent PTH treatment, which is anabolic for bone, suppressed multiple myeloma growth in bone, while Gomes and colleagues [51] reported that the same treatment enhanced growth in bone of C4-2B prostate cancer cells. In breast cancer the aromatase inhibitor exemestane plus the mTOR inhibitor everolimus significantly increased survival of women with ER+ metastatic breast cancer [52]. The combination therapy had direct positive effects on bone (almost certainly due to mTOR suppression), which may contribute to the antitumor effect and the survival benefit.

Systemic antitumor therapies can alter osteoclastic bone resorption, the activity of osteoblasts and the specific bone microenvironment surrounding the tumor (Chap. 13). Tumor cell proliferation is the target for cytotoxic chemotherapy and adjuvant therapies aimed at sex steroid and growth factor receptors (Chap. 13), which are not specific to bone metastases. Most of these treatments increase osteolytic bone destruction [49], which is expected to exacerbate bone metastases by accelerating the vicious cycle. For example, 17-allylamino-17-demethoxy-geldanamycin (17-AAG), decreases growth of prostate and other cancer xenografts. The drug unexpectedly increased bone metastases in a breast cancer model by direct stimulation of osteoclasts [53]. The same response was seen in a prostate cancer model. The side effect of the drug on osteoclasts could be prevented by addition of an antiresorptive bisphosphonate or a Src inhibitor [54], showing that that drug-dependent modulation of the local microenvironment can profoundly affect the efficacy of anti-tumor therapy. This cautionary tale emphasizes the importance of understanding the effects of agents on bone cells as well as on tumor and of considering the role of the vicious cycle.

1.5 Summary

The vicious cycle model (Fig. 1.2) provides an effective paradigm for thinking about the roles of tumor and bone in skeletal metastases and myeloma bone disease. Bone provides unusual physical conditions favorable to tumor growth: low pH and oxygen tension and high concentrations of calcium, phosphate and growth factors.

Bone houses stem cells, bone marrow elements and immune cells that alter the growth of tumor in bone. Protein factors made by the many cell types in bone act upon tumor cells, and in turn tumors secrete factors acting upon bone cells. The list of these factors is clearly too long for many of them to be targeted in patients. Many of the factors that participate in the vicious cycle are also activators of pain, which is the subject of Chap. 3. Inhibition of bone resorption (Chaps. 11 and 12) is consistently efficacious and may oppose initial steps in the development of cancer in bone. Central pathways, such as hypoxia and TGFβ signaling, are important for both tumor and bone functions; they are likely to lead soon to improved therapies, and other pathways may be added to the list of promising future treatments to decrease bone metastases and myeloma bone disease.

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Chapter 2
Natural History, Prognosis, Clinical Features and Complications of Metastatic Bone Disease

Vassilios Vassiliou, Edward Chow, Dimitrios Kardamakis, and Natalie Lauzon

Abstract The survival and prognosis of cancer patients with metastatic skeletal disease varies widely and depends on many factors including the histologic type and grade of the primary tumor, performance status and age of patients, presence of extraosseus metastatic disease, level of tumor markers and extend of skeletal disease. Bone metastases are inevitably associated with considerable morbidity and suffering, and severe complications such as pain, pathological fractures, spinal cord or nerve root compression, impaired mobility, bone marrow infiltration and hypercalcemia of malignancy. In the current chapter all aforementioned complications are thoroughly discussed, giving emphasis to associated symptomatology, clinical features and patient evaluation. Symptom clusters that occur in patients with bone metastases before and after treatment are also presented. Such symptoms include pain, depression, fatigue, drowsiness, anxiety, shortness of breath, nausea, poor sense of well being and poor appetite.

Keywords Bone metastases • Natural history • Complications • Clinical features • Spinal cord compression • Symptom clusters • Hypercalcemia • Quality of life • Pathologic fractures

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2.1 Introduction

Bone metastases are not only common in the event of malignancy, but their development is of particular clinical importance, since they can bring about severe complications such as pain, pathological fractures, spinal cord compression and hypercalcemia [1, 2]. Such events may be detrimental not only for the quality of life and performance status of affected patients, but may also be life threatening [3]. In this chapter we discuss the natural history, prognosis, clinical picture and complications of metastatic bone disease. Symptom clusters occurring in cancer patients with metastatic bone lesions are also presented.

2.2 Natural History and Prognosis

Due to the high prevalence, marked osteotropism and the relatively long clinical course of breast and prostate cancer, bone metastases are most often seen in patients with such malignancies. Bone metastases are also frequent in other tumors such as lung, kidney and thyroid. The survival from the time of development of bone metastases varies considerably among the different types of tumors. In the case of prostate and breast cancer, the median survival from the time that bone metastases are diagnosed is measured in years [4–6], whereas the corresponding survival in patients with advanced lung cancer is measured in months [7, 8].

Through several studies it was shown that certain tumor characteristics were associated with an increased risk of developing either bone or extaosseus metastases. In breast cancer patients the incidence of metastases to bone was found to be significantly higher in tumors which produce parathyroid hormone related peptide (PTHrP) [9] and are either estrogen receptor positive [10] or well differentiated [4, 11]. A significant association between histological high grade tumors and a development of intrapulmonary, liver and para-aortic lymph node metastases has also been reported [11]. In a different study by James JJ et al., a significant correlation between the development of skeletal metastases and the degree of lymph node involvement by the primary tumor was also found [12].

In a trial involving 2,240 consecutive patients with localized breast carcinoma, 30 % relapsed after a median follow up period of 5 years, with 8 % developing metastasis to bone. The median survival after the recurrence in bone was 20 months, whereas the survival in women who developed metastasis to liver was only 3 months [4]. The survival of patients with bone metastases from breast cancer was also influenced by the subsequent formation of extraosseus metastases. The median survival of such patients was shown to be 1.6 years as compared to 2.1 years for patients with metastases confined to the skeleton [13]. In the same study it was found that older, post menopausal women with lobular carcinoma or ductal grade III tumors were more likely to have disease that remains confined to skeleton [13]. The same was true for women with minimal axillary lymph node involvement [13]. In a recent trial

Table 2.1 Prognostic factors in patients with metastatic breast or prostate cancer

Primary cancer	Breast	Prostate
	Extraosseus metastases	Performance status
	Estrogen receptor status	Histologic grade
	Metastasis free survival	Baseline prostatic specific antigen
	Performance status	Hemoglobin level
	Age	Alkaline phosphatise
	Serological tumor marker levels	Lactate dehydrogenase
	Histologic type (lobular versus ductal)	Aspartate aminotransferase
	Histologic grade (ductal)	Extent of bone disease
	Bone metastases at presentation	Age
	Number of bone metastases	Gleason score
	Symptomatic skeletal metastases	Clinical stage

Data from James JJ et al. [12], Coleman RE et al. [13], Niikoura N et al. [14], Robson M et al. [15], Sabbatini P et al. [16], Eisenberger M et al. [17], Matzkin H et al. [18], Armstrong AJ et al. [19], He J et al. [20]

it was reported that the development of SRE's in patients with skeletal disease from breast cancer leads to a decreased 5 year survival as compared to patients with bone metastases alone (8.3 % versus 2.5 %) [6].

Survival in women with bone metastases is also dependent on other clinical and histopathological factors such as the metastasis free survival interval, additional sites of metastatic disease other than bone, estrogen receptor status, symptomatic skeletal disease, number of metastases and serological tumor marker levels [10, 12, 14]. Multivariate analysis has shown that all of these factors independently contributed to survival from the time of bone metastases formation [12]. In a different study by Coleman et al., multivariate analysis showed that age, menopausal status, bone disease at initial presentation and histological grade and type, were also important prognostic factors after the diagnosis of metastatic bone disease [13]. Important factors of good prognostic significance were lobular or ductal grade I or II carcinomas, age <70 years, disease free interval ≥3 years, bone disease at presentation and positive estrogen receptor status [13]. Established prognostic factors in women with bone metastases from breast cancer are presented in Table 2.1.

Patients with prostatic carcinoma also have a relatively long clinical course. In men with metastases confined to the axial skeleton, good performance status and under androgen blockade, the duration of disease control was found to be 4 years [15]. Survival in patients with metastatic prostatic cancer is dependent on several prognostic factors such as tumor grade, baseline prostate specific antigen (PSA), PSA doubling time, hemoglobin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), gleason score, clinical stage, invasion of neighbouring organs, performance status, number of metastatic sites and extent of metastatic bone disease (Table 2.1) [15–20]. It may be worth to note that the extent of metastatic bone disease in prostatic cancer may be quantified by using the bone scan index (BSI). In this system each bone is evaluated individually and assigned a numeric score. The score represents the product of the percentage of the involved bone with

Table 2.2 Complications that may accompany metastatic bone disease

Pathological fracture
Bone pain
Hypercalcemia of malignancy
Nerve root compression
Impaired mobility
Surgery to bone
Radiation to bone
Spinal cord compression
Infiltration of bone marrow

tumor times the known weight of the bone that is derived from the reference man [21]. It has been shown that in patients with BSI values <1.4 %, 1.4–5.1 % and >5.1 %, median survivals were 18.3, 15.5 and 8.1 months respectively [16].

Survival in patients with multiple myeloma ranges from a few months to more than a decade [21]. With modern, intensive therapy involving autologous hematopoietic stem cell transplantation, the median survival is approximately 5 years [22]. Many prognostic factors have been reported in the scientific literature, the most important ones being albumin, beta2-microglobulin, chromosomal karyotype, renal function, hemoglobin, performance status, calcium, interleukin 6 (IL6), C-reactive protein (CRP), low plasma cell percentage in bone marrow and a positive response to treatment [21–23].

Renal cell cancer also shows a predilection to bone. Metastases from renal carcinoma are usually lytic in type, highly vascular and are associated with severe morbidity [24]. In a series with 209 patients with renal cell carcinoma, bone metastases developed in 22 % of patients and bone was the second commonest site of metastases after lung (37 %) [25]. In a recent study by Toyoda Y and co workers it was shown that median survival in patients with bone metastases from renal carcinoma was 12 months and overall survival at 2 years was 37 %. In the same study it was found that clinical features correlating with longer survival were a long interval between the time of diagnosis and development of bone metastases (greater than 24 months) and the absence of extraosseus metastatic disease [26]. The median survival of patients with none of the above favorable factors was 5 months and for those with both factors 30 months [26].

2.3 Morbidity and Complications of Metastatic Bone Disease

Bone metastases are accompanied by considerable morbidity and suffering. About two thirds of patients with breast cancer and metastases to bone will subsequently develop complications such as pain, pathological fractures, spinal cord or nerve root compression, impaired mobility, bone marrow infiltration and hypercalcemia of malignancy [27–29]. Table 2.2 summarizes the potential complications associated with bone metastases. From the presented complications (Table 2.2), pathological fractures, hypercalcemia of malignancy, spinal cord compression, surgery to bone

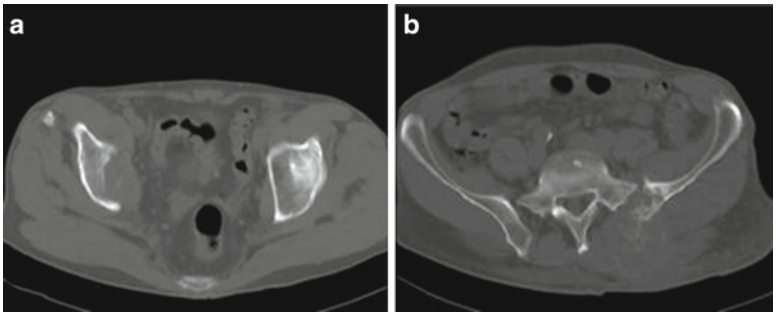

Fig. 2.1 Lytic bone metastases in the *right* (**a**) and *left* (**b**) iliac bones in two patients with renal carcinoma (This figure is reprinted from Clinical and Experimental Metastasis Journal, Vol 24: 49–56, table 1, copyright 2007, with kind permission of Springer Science+Business Media B)

and radiation to bone are known as skeletal related events (SREs). These events are composite end points used in the majority of trials involving treatment with bisphosphonates.

Pain and impaired mobility are evident in 65–75 % of patients with bone metastases [30] and metastatic bone lesions have been reported to be the commonest cause of cancer-related pain [31]. Bone pain may be nociceptive [32, 33], or neuropathic [32–34]. In the former case pain is produced via simulation of nociceptors in the endostium by chemical mediators such as prostaglandins, leukotrienes, substance P, bradykinine, interleukins 1 and 6, endothelins and tumor necrosis factor-a (TNF-a). Nociceptive pain may also result due to stretching of periostium resulting from tumor infiltration or increase in size, or fracture. Neuropathic pain may result from direct infiltration and destruction of nerves by tumors.

In two recent trials pain was found to be the major factor affecting the quality of life and performance status of cancer patients with bone metastases [35, 36]. The level of morbidity differed between patients with different types of metastatic bone lesions (lytic, mixed, sclerotic) [35]. Figures 2.1, 2.2, and 2.3 present typical examples of lytic, mixed and sclerotic bone metastases. Patients with osteolytic lesions had the highest mean pain scores with 8.1 points (visual analogue scale, 0–10) and the least mean scores for quality of life (QOL-EORTC C30, physical functioning scale, 0–100) and Karnofsky performance status (KPS, 0–100) with 31.4 and 58.6 points respectively. This group of patients was also found to have the highest percentage and mean opioid consumption (measured in daily oral morphine equivalents, mg) and the least mean bone density within skeletal lesions with 116.3 Hounsfield units (HU, measured by Computer Tomography). On the contrary the group with osteosclerotic bone lesions had the least mean pain score with 4.6 points, the highest mean scores for QOL and KPS with 61.1 and 66.6 points respectively, the least percentage and mean opioid requirement and the highest mean bone density with 444 HU. Table 2.3 presents the mean values of the clinical and radiological evaluations of the three groups of patients taking part in the study [31]. Interestingly, this study also showed that bone density had a strong, negative,

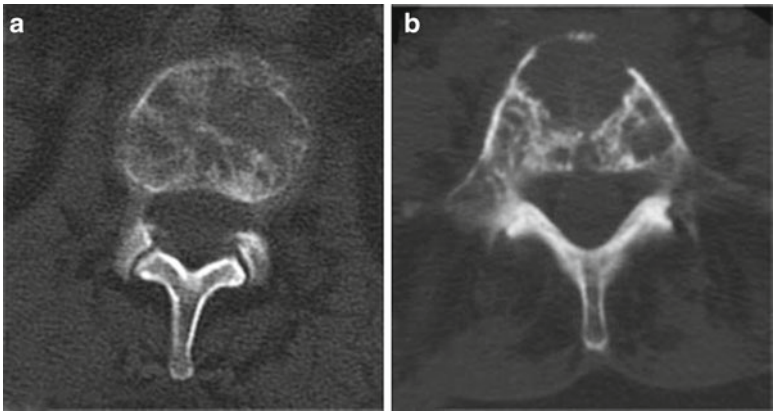

Fig. 2.2 Typical mixed bone lesions in the second (**a**) and fifth (**b**) lumbar vertebrae, due to metastatic breast carcinoma in two separate patients (The above figure is reprinted from Clinical and Experimental Metastasis Journal, Vol 24: 49–56, table 1, copyright 2007, with kind permission of Springer Science+Business Media B)

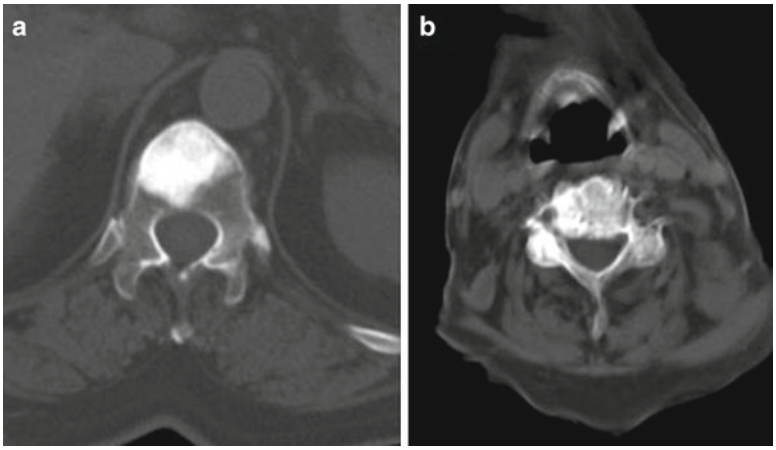

Fig. 2.3 Osteosclerotic bone metastases in two different breast cancer patients, in the eighth thoracic (**a**) and fourth cervical (**b**) vertebrae (This figure is reprinted from Clinical and Experimental Metastasis Journal, Vol 24: 49–56, table 1, copyright 2007, with kind permission of Springer Science+Business Media B)

statistically significant correlation with pain and a strong, positive, statistically significant correlation with QOL (partial correlation coefficients −0.57 and 0.64 respectively) (Table 2.4). These results showed that there is a clear correlation between the clinical status of patients and the type of bone metastases and that the level of bone resorption at sites of bone metastasis is a major determinant of the level of morbidity and suffering [35]. A link between pain and the level of resorption in patients with metastatic bone disease has also been demonstrated in other studies [37].

Table 2.3 Summary of results of clinical and radiological evaluations

	Pts with lytic bone lesions (n = 32)	Pts with mixed bone lesions (n = 30)	Pts with sclerotic bone lesions (n = 18)	p value
Pain score (0–10)	8.1 ± 2.2	6.6 ± 1.7	4.6 ± 1.3	<0.05[a]
Quality of life (0–100)	31.4 ± 14.6	45 ± 10.9	61.1 ± 15.5	<0.05[a]
Performance status (0–100)	58.6 ± 9.7	64.6 ± 7.3	66.6 ± 10	<0.05[a]
Bone density: (Hounsfield units)	116.3 ± 40.4	240.7 ± 69.4	444 ± 86.6	<0.05[a]
Opioid consumption: (%)	100 %	86.6 %	55.5 %	<0.05[b]

This table is reprinted from Clinical and Experimental Metastasis Journal, Vol 24: 49–56, table 1, copyright 2007, with kind permission of Springer Science + Business Media B
Data presented as mean values ± standard deviation
Pts patients
[a]ANCOVA test: All pair wise comparisons between groups were statistically significant, apart from performance status between the mixed and sclerotic groups
[b]X^2 test, followed by the Holm's sequential Bonferroni method

Table 2.4 Partial correlation coefficients between pain score, quality of life, performance status and bone density

Variables	Bone density	Pain	Quality of life
Pain	−0.57[a]	–	–
Quality of life	0.64[a]	−0.78[a]	–
Performance status	0.39[a]	−0.51[a]	0.49[a]

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[a]Statistically significant after controlling for type I error

The location of bone metastases is another determinant of the clinical picture and level of suffering. Patients with vertebral metastases typically present with neck or back pain that may be exacerbated by palpation or local application of pressure or movement. Ten percent of such patients suffer from pain due to spinal instability. In such cases pain may be excruciating, worsening upon patient movement. Base of skull involvement can result in nerve palsies, neuralgias or headache [7]. Finally, hip or femoral metastases commonly cause back or lower limb pain [7] and are associated with marked movement impairment.

Bone metastases are frequently complicated by pathologic fractures and are the second most common cause of such fractures after osteoporosis. Pathologic fractures are a result of bone destruction at metastatic bone sites and are most commonly seen in osteolytic metastases involving the cortex. Bone lysis and the loss of structural integrity at metastatic sites inevitably lead to a reduction of the loading capabilities of the affected bone and ultimately to fracture. Rib fractures and

vertebral collapses are especially frequent [7], but the most detrimental fracture in terms of patient's QOL and performance status are the fractures of weight bearing long bones. Such fractures occur in 10–20 % of patients with metastases to bone [25] and the most commonly affected site is the proximal femur [38].

Many authors have tried to investigate and reveal the risk factors for pathologic fractures. A number of studies have reported that such fractures appear in patients with lesions that exceed 50 % of the diameter of the affected bone [39, 40]. Other studies have shown that lesions >2.5 cm are at greater risk to fracture as compared to metastatic lesions ≤2.5 cm [41]. Bertin and co-workers have also shown that avulsion of the lesser trochanter is another important risk factor for pathologic fractures in the femur [42]. A set of criteria have been proposed for prophylactic internal fixation in patients with peritrochanteric femoral lesions. These criteria are as follows: (a) lesion size >2.5 cm (b) lesion diameter greater than 50 % of the diameter of the affected bone and (c) avulsion of the lesser trochanter [43].

Mirels H has proposed a scoring system for impending pathologic fractures of long bones that is in our opinion very useful. The system incorporates variables such as size of lesion, radiographic appearance, level of suffering (pain), and location of metastasis. Through the assessment of patients, each variable is assigned a score. It was shown that lesions that scored greater than seven points generally required internal fixation and lesions with scores equal or greater than ten had an estimated risk to fracture greater than 50 % [44].

The probability of undergoing a pathologic fracture increases with the duration of metastatic bone disease and this complication is more common in patients with metastases confined to bone. This is rather paradoxical since such patients have a relatively good prognosis as compared to patients with extraosseus metastases [1, 13]. Special attention should be given to the evaluation of patients with impending pathologic fractures in order to prevent this severe complication. Risk factors should be carefully evaluated and patients at risk should be referred to orthopedic surgeons for prophylactic surgery. This need is of uttermost importance if we take into consideration that it was recently reported that pathologic fractures not only deteriorate the QOL of patients, but also correlate with a reduced survival [45].

Bone marrow infiltration by tumor cells is favored by the high blood flow in the red marrow [46], the adhesive molecules of tumor cells that bind them to marrow stromal cells and bone matrix [47] and the large repository of immobilized growth factors that are released during the process of bone resorption [48]. Such factors serve as a fertile ground for tumor cell growth and proliferation [47]. However not all patients with bone marrow infiltration develop bone metastases. It has been shown that 25 % of breast cancer patients were found to have tumor cells in their bone marrow prior to surgery. After a median follow up of 76 months only 48 % of these patients developed bone metastases. Metastatic bone disease was also diagnosed in 25 % of patients who were free of bone marrow tumor cell infiltration prior to surgery [48, 49]. Bone marrow infiltration and tumor growth into the marrow space is in most cases accompanied by extensive fibrosis and may result in reduced haemopoiesis and pain. Useful diagnostic signs are leukoerythroblastosis with immature white and red cells in peripheral blood smears. This is seen in about 50 %

of patients with bone marrow infiltration and is a result of extramedullary haemopoiesis [33]. Early detection of bone marrow metastases enables earlier therapy [50] that may result in alleviation of pain [51] and prevention of complications of metastatic bone disease [52, 53]. Both magnetic resonance imaging (MRI) and bone marrow scintigraphy have proved to be effective in detecting bone marrow involvement, MRI being superior in terms of sensitivity and specificity [54].

Spinal cord compression is a medical emergency that calls for an urgent evaluation and treatment [7], since neurological recovery is probable only in the case that compression is relieved within 24–48 h from the time of diagnosis [55]. This complication generally occurs late in the natural history of cancer and is considered as a pre-terminal event since upon its occurrence prognosis is rather poor. The thoracic spine is most commonly affected.

Local pain and tenderness over the affected cord lesion is the commonest initial symptom in patients with spinal cord compression due to metastatic bone disease and usually precedes neurological manifestations by weeks or months. Pain is more intense with activities such as coughing or straining that increase intradural pressure and may worsen at night time [7]. Metastases with a more lateral localization involving nerve roots bring about radiculopathy with focally sited segmental pain, dermatomal sensory disturbances such as numbness and tingling and weakness in muscles innervated by the affected root. At diagnosis of spinal cord compression, patients typically present with leg weakness. In most cases both sensory and motor loss is seen and defects of both power and sensation occur at and below the involved level. Sphincter or bladder function loss occurs late and is associated with poor prognosis. Vertebral metastases below the L1 or L2 level may produce the cauda equina syndrome that involves bladder or bowel dysfunction (retention or incontinence), severe low back pain with motor weakness, sensory loss or pain in one or more commonly both legs, saddle anesthesia and sexual dysfunction. In a retrospective study by Hill ME et al. that involved 70 patients with spinal cord compression secondary to breast cancer, it was found that at the time to diagnosis all patients had radiological evidence of bone metastases and the most common symptoms were motor weakness (96 %), followed by pain (94 %), and sensory (79 %) or sphincter (61 %) disturbances. The majority of patients (91 %) had at least one symptom for more than a week prior to diagnosis [56].

A detailed history taking and physical and neurological examination is critical for diagnosing spinal cord compression in cancer patients. Any patient with a history of cancer and back pain should be investigated for spinal cord compression. In a prospective study involving cancer patients it was shown that there was a 30 % probability of spinal cord compression at the presence of any of the following risk factors: back pain, abnormal neurological findings at neurological examination, or detection of vertebral metastases through radiologic assessment (plain x-rays). In the case that two of the above factors were present, the likelihood of spinal cord compression was between 60 % and 70 % and in the presence of all three factors the probability was greater than 90 % [57].

MRI is very useful in the evaluation of possible malignant cord compression providing detailed information on the extent and the number of epidural

compressions [58, 59]. Patients are generally managed with either decompressive surgery or radiotherapy or a combination of the two therapeutic modalities. Surgery is usually reserved for younger patients with a good performance status, patients with a single site of cord compression and in cases of fracture dislocations and spinal instability [60]. Ambulation is the most important factor for response to therapy prior to treatment and the most important post treatment survival factor [56, 61]. In the study by Hill and co-workers 96 % of patients who were ambulant prior to therapy maintained their ability to walk post therapy and from patients who were unable to walk prior to treatment, only 45 % regained ambulation. The results suggested that that earlier diagnosis and intervention can improve the therapeutic outcome. Additionally, there was no evidence of survival benefit from surgery over radiotherapy as primary treatment [56]. Overall post therapy 20 % of patients improve neurologically, 30 % remain stable and about half of patients deteriorate. The median survival is 7 months for patients who are able to walk post treatment and 1.5 months for non ambulatory patients [62].

2.4 Metabolic Complications: Hypercalcemia of Malignancy

Hypercalcemia is one of the commonest metabolic complications seen in patients with metastatic bone disease, occurring in 3–30 % of cancer patients during the course of their disease [63]. It is most typically seen in patients with lung (squamous cell carcinoma), breast, kidney, ovarian and head and neck tumors [7, 63]. The occurrence of hypercalcemia in breast cancer patients ranges between 30 % and 40 %, but is rather uncommon in patients suffering from colorectal and prostate cancer [63]. This complication is also manifested in patients with hematological malignancies such as multiple myeloma and lymphoma. In multiple myeloma up to a third of patients develop hypercalcemia [64].

Calcium serum concentration is closely regulated by a complex homeostatic mechanism, involving organs such as bone, liver, parathyroid glands, kidneys and gastrointestinal tract. Parathyroid hormone (PTH) has a key role in the whole mechanism. When calcium serum levels are low, PTH is secreted from the parathyroid glands. PTH acts on bone by enhancing osteoclastic resorption with accompanied calcium release and on kidney by reducing urinary calcium excretion and increasing phosphorus excretion. Parathyroid hormone–related peptide (PTHrP) is secreted by a variety of tumors [65, 66] and it has been shown that its actions parallel those of PTH [63, 66]. The level of PTHrP is elevated in up to two thirds of patients with metastatic bone disease and hypercalcemia and in the vast majority of patients with humoral hypercalcemia. It was also demonstrated that impaired hepatic function in women with liver metastases from breast cancer is associated with hypercalcemia [67]. This could be explained by the fact that impaired hepatic function may result in a reduced PTHrP metabolism and consequently enhanced bone resorption. Increased calcium serum level also interferes with the action of anti-diuretic

hormone (ADH) at the distal nephrone, causing polyuria and polydipsia, a syndrome like diabetes insipitus. This results in dehydration that further exacerbates hypercalcemia [63].

Three distinct syndromes have been described in hypercalcemia of malignancy: (a) the humoral hypercalcemia of malignancy, (b) hypercalcemia associated with skeletal metastases, and (c) hypercalcemia accompanying hematological malignancies. Humoral hypercalcemia of malignancy (HHM) is manifested in patients with elevated serum calcium in the absence of skeletal metastases. The syndrome is a result of circulating PTHrP released from the tumor itself. In patients with evidence of osteolysis produced by tumor cells, metastases in bone stimulate bone resorption by the local release of PTHrP. During the process of bone resorption local factors such as the transforming growth factor alpha (TGF-a), TGF-b, epidermal growth factor and interleukin 1 are released, promoting the secretion of PTHrP from tumor cells [68, 69]. A viscous cycle is therefore formed enhancing bone resorption and calcium release. There is evidence for a humoral contribution in this syndrome, since in breast cancer patients the extent of metastatic bone disease does not correlate with the level of hypercalcemia [70]. The third syndrome is the one in which hypercalcemia is manifested in patients with hematological malignancies. Hypercalcemia is rather uncommon in patients with Hodgkins and non-Hodgkins lymphoma, but as mentioned before it occurs in about one third of multiple myeloma patients [64]. In a study with 165 patients admitted to a Hematology Department, hypercalcemia was documented in nine patients with myeloma, in five patients with high grade B-cell non-Hodgkins lymphoma and in one with myeloid neoplasia [71]. In the cases with B-cell non-Hodgkins lymphoma circulating levels of PTHrP were detected [71] and the same was true for one third of patients with elevated calcium serum level and multiple myeloma [71]. The above findings indicate that PTHrP mediated hypercalcemia is not only seen in patients with solid tumors, but also in patients with hematological malignancies.

The clinical picture of patients with hypercalcemia is in many cases nonspecific and clinicians should have a high index of suspicion. Asymptomatic patients turn out to have fatigue and malaise or signs of hypertension or renal failure. In symptomatic patients common symptoms are polyuria, polydipsia, anorexia, nausea, vomiting, constipation and bone pain. Patients may also present with abdominal pain (due to peptic ulcer or pancreatitis) or loin/ureteric pain due to urinary tract stones. Mental disturbances include confusion, depression, psychosis, alteration of the level of consciousness and in severe cases comma. In case that hypercalcemia is not corrected, renal function and mental status deteriorate and death may result from renal failure and cardiac arrhythmias. Symptoms and signs of hypercalcemia are presented in Table 2.5.

The prognosis of hypercalcemic patients is poor and treatment is effective in improving the symptomatology but not in prolonging survival [63]. Patient rehydration, bisphosphonates [72, 73], calcitonin [74], and diuretics such as frusemide [75] are important in the overall management of symptomatic hypercalcemia that is a metabolic emergency and calls for immediate patient evaluation and treatment.

Table 2.5 Clinical features and symptoms in patients with hypercalcemia

Non specific symptoms
Malaise
Fatigue
Gastrointestinal
Nausea and vomiting
Anorexia
Constipation
Abdominal pain
Mental disturbances
Confusion
Depression
Psychosis
Drowsiness
Apathy
Coma
Renal
Polyuria
Polydipsia
Signs of dehydration
Ureteric or loin pain

2.5 Symptom Clusters in Cancer Patients with Bone Metastases

Studies in cancer symptom research have mainly focused on the management and severity of individual symptoms [76]. This approach has helped advance our understanding of a particular symptom. However, symptoms seldom occur in isolation in patients with advanced cancer. It is therefore important to focus on evaluating multiple symptoms, using cross-sectional and longitudinal study designs. The term "symptom cluster" was first quoted by Dodd et al. [77] in their research with pain, fatigue, and sleep disturbances. They defined symptom clusters as three or more concurrent symptoms that are related to each other, which may or may not have the same etiology. A subsequent paper published in 2005 described symptom clusters as two or more symptoms that are related to each other, occur together, are a stable group and are relatively independent of other clusters [78]. The relationship, strength and time frame needed for these clusters to present have not been specified. Symptom clusters may have an adverse effect on patient outcomes and a synergistic effect as a predictor of patient morbidity.

Palliative radiotherapy has been well established for the treatment of symptomatic bone metastases. Although pain might have improved, patients in some clinical trials reported no significant improvement in quality of life (QOL). Failure to improve QOL significantly after palliative radiotherapy can be due to multiple bone metastases in patients. Pain relief in one irradiated site may unmask pain in other bony metastatic sites. It is important to explore whether bone pain "clusters" with other

common symptoms in advanced cancer. There is suggestion that pain, depression, and fatigue may occur in combination. Failure to recognize these symptom clusters may result in failure to improve overall QOL. One study conducted at an outpatient palliative radiotherapy clinic asked patients with bone metastases, during their initial consultation, to rate their symptom distress using the Edmonton Symptom Assessment Scale (ESAS) with an 11-point categorical scale (0–10; 0 = absence of symptom and 10 = worst possible symptom) [78, 79]. The ESAS evaluates nine symptoms: pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, sense of well-being, shortness of breath and has been successfully validated in cancer patients [79, 80]. Patients were asked to rate the item "pain" in the ESAS as bone pain at the irradiated site. All primary assessments and questionnaires were completed prior to radiation simulation and at weeks 1, 2, 4, 8, and 12 post-radiation, ESAS scores were obtained by telephone interview. Responders to radiation treatment were assigned as having complete or partial response, as defined by the International Bone Metastases Consensus Working Party [81]. Between January 1999 and January 2002, 518 patients (280 male and 238 female) with bone metastases provided complete baseline data on ESAS at the time of consultation.

Three clusters were identified and accounted for 66 % of the total variance at baseline. Cluster one included fatigue, pain, drowsiness and poor sense of well being and accounted for 44 % of the total variance. Cluster 2 included anxiety and depression and accounted for 12 % of the total variance. Cluster 3 included shortness of breath, nausea and poor appetite and accounted for 10 % of the total variance [82]. In comparing the pattern of symptom cluster dynamics in the responders, pain clustered out in weeks 8 and 12; breathlessness clustered out in week 2. Only two symptom clusters remained in weeks 2, 8, and 12. In non-responders, symptom clusters prevailed in all weeks, except for week 8 with breathlessness clustering out. Over time, symptom components of the symptom clusters changed after radiation treatment. However, some symptoms often appeared in the same cluster. Fatigue and drowsiness remained together for all weeks in both groups; anxiety and depression also followed each other. Overall, it was shown that radiotherapy did indeed influence the structure of symptom clusters in both the responders and non-responders. It appears that pain clustered with fatigue, drowsiness and poor sense of well being at baseline [82]. For the opioid consumption in responders and non-responders through weeks 1–12, there is an obvious difference between the mean morphine equivalency of opioid consumption between the two groups. Non-responders to treatment had a higher intake of analgesics than responders. Analgesic consumption in responders decreased.

As cancer patients experience a wide range of symptoms that may not have been captured by ESAS, it is important for similar, comprehensive assessment tools to be used in all symptom cluster research. A sub-analysis of patients reporting exclusively non-zero ESAS scores at baseline was undertaken from this same data set by Chen et al. in order to try and identify symptom clusters in this subgroup of patients and to compare clusters with those identified in the total population [79]. The secondary objective of this study attempted to establish whether symptom clusters in bone metastases patients varied when extracted using different statistical

methods. A data set compiled from patients with bone metastases identified a non-zero subgroup of patients who reported severity scores > 0 for all nine ESAS symptoms at baseline. Principal Component Analysis (PCA), Hierarchical Cluster Analysis (HCA) and Exploratory Factor Analysis (EFA) were performed to derive symptom clusters at baseline, 1, 2, 4, 8 and 12 weeks after radiation therapy (RT) for the non-zero subgroup. Both EFA and HCA effectively capture the essence of symptom cluster as a grouping of concurrent and related symptoms. EFA is unique in that it functions on the assumption that symptoms in a cluster share a common underlying latent factor which binds two or more symptoms together. HCA classifies and tries to put similar entities together into a cluster and attempts to separate this cluster from other clusters [83]. It was found that different symptom clusters were recognized in the non-zero subgroup compared with the total patient population, regardless of statistical method utilized. Symptom cluster results varied depending on statistical method employed for analysis. This sub-analysis did not provide a complete consensus between all three methods. Anxiety and depression were the only two ESAS symptoms to consistently occur in the same cluster across different methods over time. This study then concluded that the quantity and composition of symptom clusters varied based on whether patients with zero symptom severity scores were included at baseline as well as which statistical analysis method was employed.

A study by Hadi et al. explored how patients' worst pain clustered together with functional interference items as assessed by the Brief Pain Inventory (BPI), as well as determining whether symptom clusters change with palliative radiotherapy in responders and non-responders to radiation[84]. The BPI is a multidimensional assessment tool often used in oncology as a multiple item measure of pain, measuring both its' sensory and affective dimensions [85]. A total of 348 outpatients provided their scores of worst pain at site of radiation treatment and functional interference at baseline, 4, 8 and 12 weeks post radiation therapy. Interrelationships between symptoms were determined at all time points by using PCA on each of the worst pain scores and seven functional interference items in responders and non-responders. Changes in worst pain have shown to correlate significantly with six of seven life functions [86]. Two clusters were identified at baseline and accounted for 67 % of the total variance. Cluster 1 accounted for 55.6 % of the total variance and was comprised of general activity, walking ability, normal work, enjoyment of life and worst pain. Cluster 2 accounted for 11.4 % of the total variance and included mood, sleep and relations with others. Cronbach alpha co-efficient demonstrated good internal consistency. This study served to reaffirm the importance of achieving pain reduction as a treatment goal for palliative radiotherapy in cancer patients [87].

A reanalysis of symptom clusters comparing different statistical methods in patients with bone metastases was reported by Chen et al. [85]. The same cohort of 348 outpatients as analyzed by Hadi et al. was utilized for secondary analysis [84]. The data set compiled using the Brief Pain Inventory was analyzed using the HCA and EFA in order to identify symptom clusters at baseline, 1, 2 and 3 months following radiation treatment. These clusters were then compared to the clusters derived via PCA in the Hadi et al. paper [84]. Using PCA, HCA and EFA, the further separated subgroups of responders and non-responders to radiation therapy (RT) identified

symptom clusters as experienced by each subgroup at same time points. The three statistical methods used provided little correlation and did not provide absolute consensus at any time point in this study. There were varying patterns of symptom cluster presentation among both subgroups over time regardless of analytical method utilized. The core cluster of symptoms including worst pain, walking ability, general activity, normal work and life enjoyment often presented in the same cluster. This reanalysis concluded that the presence and constitution of symptom clusters varied depending on the statistical method employed, thus necessitating the use of a common method to help attain consistency in symptom cluster research.

In conclusion, it is important for health care professionals to take a detailed history of the commonly encountered symptoms in cancer patients with bone metastases. Various symptom assessment tools are available for use in order to enable data collection to help analyze and thus identify symptom clusters. The therapeutic importance of symptom clustering in bone metastases patients necessitates further study. Researchers should recognize the most clinically meaningful statistical findings when considering the optimal method for identifying useful symptom clusters in order to provide the best insight for symptom management for bone metastases patients [84].

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Chapter 3
Pain in Bone Metastases: Types and Mechanisms

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Abstract Cancer-induced bone pain is a common complication of bone metastases and consists of a triad of continuous pain, spontaneous pain and incident pain. It can considerably compromise social functioning, quality of life and survival. Through the use of animal models, it has been suggested that cancer-induced bone pain differs from other pain states, including inflammatory and neuropathic pain; it is increasingly considered to be a complex, mixed-mechanism pain, rather than a single neuropathic,

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visceral or inflammatory pain state. A variety of possible mechanisms by which bone metastases may cause pain have been reported. These mechanisms likely include local production of growth factors and cytokines (either tumour-induced or tumour-produced), tumour-induced osteolysis, stimulation of ion channels on nerve cell endings, and direct infiltration. However, the exact mechanism by which a bone metastasis induces pain is not completely understood. The understanding of its pathophysiology continues to evolve and further research is required into the complex basis of cancer-induced bone pain and its mechanisms.

Keywords Bone pain • Cancer • Mechanisms • Types • Pathophysiology

3.1 Introduction

The last number of years has witnessed many advances in the diagnosis and treatment of cancer, which have resulted in improved and prolonged quality of life for many cancer patients. Skeletal involvement with cancer remains a common complication, with bone metastases representing the third most common metastatic site after lung and liver [1]. Post-mortem studies have reported bone metastases to be present in up to 85 % of patients with lung, breast or prostate cancer [2, 3]. Other tumours that commonly metastasize to bone include cancers of the kidney, thyroid, endometrium, cervix, bladder and gastrointestinal tract, but these sites are reported to account for less than 20 % of patients with bone metastases [3]. Bone metastases often present as the first evidence of disseminated cancer; bone metastases are the first sign of recurrence in up to 40 % of patients with breast cancer [4].

Bone metastases are almost invariably found in the red marrow due to the high blood flow in these areas. The bones involved most frequently are therefore those with a high proportion of red marrow; more than 80 % of bone metastases are found in the axial skeleton. Earliest bones affected by metastases include the spine, pelvis and ribs, while the skull, humeri, femora, scapulae and sternum tend to be involved later. In long bones proximal regions are generally involved before distal regions. Lumbar and thoracic vertebrae are more often affected than cervical vertebrae and vertebral bodies are more commonly involved than pedicles. Metastases to bone of the hands and feet are rare and when they do occur are more frequently due to a lung primary. Bone metastases are usually widespread and multiple at the time of first clinical manifestation, with the exception of renal cell carcinoma or neuroblastoma, in which up to 10 % of patients may have a single site of bone involvement.

Bone metastases can cause considerable morbidity for patients, with complications including anaemia, increased susceptibility to infection, pathological skeletal fractures, spinal instability, compression of the spinal cord and hypercalcaemia of malignancy. The presence of bone metastases can also result in impaired mobility and decreased physical functioning, as well as psychological distress, all of which impact on the patient's overall quality of life.

The most common symptom of bone metastases is pain. Cancer-induced bone pain is frequently accompanied by radiological evidence of cancer-induced bone destruction. Bone pain often results in hospital attendance and can considerably compromise social functioning, quality of life and overall survival. Although most patients with bone metastases will ultimately die from their disease, some patients will survive for many years, often times with bone as their sole site of metastatic disease. For those with a long life expectancy following diagnosis of metastatic bone disease, effective pain control is highly important in order to maintain functioning and quality of life.

In this chapter we will review types and mechanisms of bone pain, both at a practical and at an anatomical level. Although we will touch on possible treatments for each type of pain, these are described in detail in Chap. 8.

3.2 Relationship Between Pain and Bone Destruction

Bone pain is the most common presenting symptom of metastatic bone disease and represents the most common cause of cancer-related pain [5, 6]. However, not all bone metastases are painful. Cancer-induced bone pain is reported to be present in up to 28–45 % of patients with bone metastases [7–9], but between 30 % and 50 % of patients have asymptomatic bone metastases found during tagging studies for primary tumours [10]. Pain from bone metastases frequently increases in magnitude over the course of the disease. Words such as annoying, gnawing, aching and nagging are commonly used to describe cancer-induced bone pain [11].

The relationship between bone invasion and bone pain is unclear [12]. Significant patient-to-patient variability exists in the type, severity and evolution of bone cancer pain. Patients can have multiple bone lesions without related bone pain or patients can have considerable pain without evidence of bone metastases [12]. In animal models of bone cancer, pain-related behaviour is often present before any significant bone destruction occurs [13]. There may also be distortion between the perceived location of the pain and the sites of the known bone lesions [12]. Thus the location of bone metastases and the degree of bone destruction may not necessarily correlate with the severity of the pain. Nor does the presence of bone pain correlate with the type of primary tumour and location of the tumour, with the size and number of metastases, or with the age and gender of patients [14]. Pain produced by metastatic bone lesions is often disproportionate to their size or to the degree of bone involvement. Bone pain may undergo fluctuations in intensity without apparent change in the nature or behaviour of the underlying metastases [15].

3.3 Types of Cancer-Induced Bone Pain

1. **Nociceptive Pain**
   Nociceptive pain results from direct injury to somatic structures (somatic pain) or injury to visceral structures (visceral pain). Nociceptive bone pain is caused by

stimulation of nociceptors in the endosteum by chemical mediators, including prostaglandins, leukotrienes, substance P, interleukin-1 and -6, endothelins and tumour necrosis factor A. The neural pathways involved in somatic pain are intact and the pain is typically well localized. A pathological fracture of a bone in a patient with bone metastases may also cause pain that is nociceptive in nature.

2. **Neuropathic Pain**
Neuropathic pain has been characterized as pain directly attributable to injury of a neural structure, possessing burning, stabbing, shooting or electric shock characteristics [16]. Neuropathic bone pain may result from involvement of the spinal cord, nerve roots or peripheral nerves and from direct infiltration or chemical irritation of nerves by tumours. Sensory and sympathetic neurons are present within the bone marrow, mineralized bone and periosteum and all these compartments can be affected by the presence of tumor cells, as well as by the occurrence of ischaemia and fractures. Bone metastases may also be associated with neuropathic pain mechanisms resulting from pressure on neural structures and/or maladaptive plasticity of the nervous system [17]. The neuropathic component of bone pain can also be due to pre-existing cancer-induced damage to sensory nerves such as infiltration or compression, as well as subsequent interventions such as chemotherapy (e.g. platinum compounds (cisplatin, carboplatin, oxaliplatin), taxanes (docetaxel, paclitaxel), vincristine, thalidomide and bortezomib) that may result in neuropathy. A recent prospective cross-sectional study of patients with symptomatic bone metastases showed that 17 % of patients had bone pain with distinguishable neuropathic pain features and these patients reported greater pain intensity [18]. The typical 'burning' or 'tingling' nature of the pain, the radiation of pain along a nerve distribution and the presence of sensory or motor deficits are indicators of mixed bone/neuropathic pain syndromes [19].

Typically the pain associated with spinal cord compression is neuropathic in nature. The most common primary tumours associated with this type of complication are breast and lung cancer. Pain in spinal cord compression is often localized to the area overlying the tumour, increases with activities such as straining, coughing and sneezing, and is made worse by straight leg raising. Pain often considerably pre-dates neurological changes. Radicular pain may also be present which may radiate down the legs or around the chest or upper abdomen. Depending on the level of spinal involvement, pain can be unilateral or bilateral. Metastases in the thoracic spine can often result in bilateral pain, while cervical or lumbosacral metastases frequently result in unilateral pain. While pressure on the spinal cord frequently results in pain, it can also lead to numbness, weakness, difficulty urinating and may even lead to paralysis if not addressed as an urgent matter.

Medical treatment of neuropathic pain is often not satisfactory, with pain control very difficult to achieve for a large number of patients with this condition. It has been reported in both clinical and preclinical studies that morphine is typically less efficacious in blocking neuropathic pain than in blocking inflammatory pain [20–23]. Specific medications for neuropathic pain are generally necessary (see Chap. 15).

3. **Inflammatory Pain**
   It has been suggested that inflammatory factors secreted by cancer cells are involved in the pathophysiology of cancer bone pain [24]. Inflammatory-induced changes are caused by direct tissue damage resulting from tumour growth as well as by the release of pain mediators by the cancer cells themselves. Tumour cells release pro-nociceptive compounds, including prostaglandins, nerve growth factor and endothelins, which can contribute to pain [25, 26].

4. **Muscular Pain**
   Reactive muscle cramps and spasm often occur in muscles in close proximity to painful bone lesions. Spasms of the surrounding musculature most commonly occur with bone metastases of the proximal extremities and spine and may cause pain that is poorly responsive to opioids and anti-inflammatory medications, and may require specific treatment with anti-spasmotic agents [27].

5. **Cancer Bone Pain as a Complex Pain Entity**
   For many years the question has been raised whether cancer-induced bone pain is truly a subtype of inflammatory pain or neuropathic pain or whether it represents a unique type of pain state. Bone pain is increasingly considered to be a mixed-mechanism pain, rather than a single neuropathic, visceral or inflammatory pain state. According to this model, cancer bone pain is a complex syndrome with involvement of inflammatory, neuropathic and ischaemic mechanisms.

   Animal models of malignant bone disease have enabled the effects of cancer-induced bone pain on the nervous system to be studied. It has been demonstrated that such animal models of cancer bone disease share key features with cancer-induced bone pain in humans, with progressive bone destruction accompanying progressive limping and guarding and leading to pathological fractures [28–30]. Thus, these models seem to be appropriate for the study of pain states that are analogous to human cancer-induced bone pain. Through the use of animal models, it has been suggested that cancer-induced bone pain is different from other pain states, including inflammatory and neuropathic pain. For example, specific dorsal horn neuronal responses have been shown in cancer-induced bone pain that are not present in inflammatory or neuropathic states [31].

   The complex nature of cancer bone pain suggests that the approach to its management must also be unique. The relative degree of opioid resistance in cancer-induced bone pain compared to other types of pain states highlights the difference between cancer-induced bone pain and other pain states.

3.4 Malignant Bone Pain Presentations

Cancer-induced bone pain is not considered to exist as a single entity, but rather consists of a triad of continuous pain, spontaneous pain and incident pain [32, 33]. Continuous pain, also called background pain, is present constantly, whereas spontaneous and incident pain are both subtypes of breakthrough pain, which occur episodically and sometimes unpredictably.

1. **Continuous Bone Pain**
   Continuous bone pain is described as a constant dull ache that increases in intensity as disease advances [5]. Continuous background pain is the most frequent presentation of bone pain and can be pinpointed by the patient with relative ease. This type of pain has a gradual onset over a period of weeks or months, and may come and go at first. It tends to becomes more progressive and more severe in intensity over time. Bone pain can be hard for patients to differentiate from ordinary low back pain or from arthritis. If the lesion is in weight-bearing bone, the pain may worsen on weight-bearing and these lesions may cause pain early in the course of the disease, whereas bones such as the ribs or sternum may remain asymptomatic until later in the disease, often until the development of pathological fractures. Typically this type of pain is well-localized to one or more specific bone areas. It can be dull in character and/or can have a deep sensation that burns or aches. It may also be accompanied by episodes of stabbing discomfort [19]. Continuous bone pain often increases with pressure on areas of involvement, which may account for it worsening at night when the patient is lying down. While not diagnostic of bone metastases, pain at night and pain incompletely relieved by rest are typical symptoms of bone metastases. Because of the higher prevalence of axial skeleton metastases, continuous bone pain is more likely to involve the pelvis, rib cage or lumbar, dorsal and cervical spine. Pain from bone lesions in the extremity tends to be well-defined, as opposed to lesions in the pelvis and spine which may produce vague, diffuse symptoms.

2. **Breakthrough Pain**
   Breakthrough pain is a transitory exacerbation of pain experienced by the patient who has relatively stable and adequately controlled baseline pain. Types of breakthrough pain include incident pain and spontaneous pain. In an exploratory study of cancer-induced bone pain involving cancer patients, 41 of 55 patients had breakthrough pain, with 20 of 41 patients describing breakthrough pain of rapid onset (less than 5 min) and of short duration (less than 15 min) [11]. Patients with breakthrough pain also had greater interference with quality of life, including negative impact on mood, relationships, sleep, walking, work and enjoyment of life, than those without breakthrough pain [11].

   Incident bone pain is defined as an intermittent episode of severe pain that is induced by normally non-noxious movement or mechanical loading of the tumor-bearing bone(s). Bone metastases are the most frequent cause of incident pain. Patients who experience incident pain often have mild or indeed no pain at rest. Incident-related bone pain is often repetitive and unpredictable and can occur many times during the day. Incident bone pain is difficult to treat and has been suggested to predict worse pain control [34]. Bone pain caused by cancer exacerbated by movement or posture can be more difficult to control than continuous bone pain [34, 35].

   Spontaneous bone pain (also known as idiopathic bone pain) occurs with no identifiable cause and can last longer than incident pain. It therefore represents one of the more challenging aspects of cancer pain management [27].

The clinical characteristics of cancer-induced bone pain make optimal management difficult, and a large portion of patients report poor pain control [36, 37]. Bone pain is thought to respond less well to opioid analgesics due to its temporal characteristics. Because these episodes of bone pain are relatively short lasting, the doses of opioids used to control the pain may result in troublesome adverse effects when the patient is at rest. More recently rapid-onset opioids have emerged, with fast onset and offset of action which have helped in the management of sudden-onset and short-lived movement-related pain (see Chap. 8).

3.5 Mechanisms of Cancer-Induced Bone Pain

A variety of possible mechanisms by which bone metastases may cause pain have been reported, but a limited amount of data supports these proposed mechanisms and the exact mechanism by which a bone metastasis induces pain is not completely understood. These mechanisms likely include local production of growth factors and cytokines (either tumour-induced or tumour-produced), tumour induced osteolysis, stimulation of ion channels on nerve cell endings and direct infiltration [38, 39]. Stretching of the periosteum by tumour expansion, mechanical stress of the weakened bone, nerve entrapment by the tumour or direct destruction of the bone are all possible mechanisms responsible for causing bone pain [5].

1. **Alterations in Bone Turnover**
   Bone-resorbing osteoclasts and bone-synthesising osteoblasts are responsible for the continuous restructuring and remodeling of the human skeleton. Bone is constantly being remodelled in a dynamic process where osteoblasts are responsible for bone formation and osteoclasts for its resorption. Normal bone undergoes constant resorption and new bone formation. A balance between resorption and formation maintains bone strength and structural integrity. Osteoblasts are mononucleate cells derived from fibroblasts, while osteoclasts are terminally differentiated, multi-nucleated monocyte lineage cells that resorb bone through maintaining an extracellular microenvironment of acidic pH at the osteoclast-mineralized bone interface [40]. The effects of osteoclasts and osteoblasts are normally balanced to maintain a steady state of bone density.

   When tumour cells metastasize to bone, there is a loss of mechanisms that normally regulate the balance between osteoclast and osteoblast activity, and the balance between resorption and new bone formation is altered. This may lead to an abnormal state of increased bone destruction (osteolysis), increased bone formation (osteosclerosis), or both [31].

   It has been traditional to think of bone metastases as either osteolytic or osteoblastic, with different factors being responsible for each. Increased bone destruction is characteristic of osteolytic metastases and markedly increased bone formation results in osteoblastic metastases. Osteolytic bone metastases are associated with increased osteoclast activity and formation and are highly cellular. Osteoblastic

metastases are associated with excess new bone matrix formation by osteoblasts and are relatively acellular. The predominant types of metastases are osteolytic. Purely osteolytic lesions are seen with cancers of the thyroid, uterus or gastrointestinal tract. Purely osteoblastic lesions are commonly seen in patients with prostate cancer.

This distinction between osteolytic and osteoblastic bone lesions is not absolute however; many patients with bone metastases have both osteolytic and osteoblastic lesions and individual metastatic lesions can contain osteolytic and osteoblastic elements. Increased osteoclast activity may be seen with osteoblastic lesions. Mixed lesions contain elements of osteolytic and osteoblastic metastases and are seen commonly in cancers of the lung, breast, cervix, ovary and testes. Thus, the concept that there are two distinct types of bone metastases is somewhat simplistic and there may in fact be a spectrum of bone metastases; predominantly osteoblastic metastases also have resorptive components and predominantly osteolytic metastases also have a local bone formation response, which may represent an attempt at bone repair [41]. Both osteolytic and osteoblastic bone lesions may cause pain in patients with bone metastases.

Studies have suggested that osteoclasts play an important role in cancer-induced bone loss and that they contribute to its aetiology [42–44]. Osteoclast-stimulating factors from the tumour, the tumour-associated stroma or the bone stimulate osteoclast proliferation [45–50]. Osteoclasts have been shown to be present in high numbers in animal models of bone cancer and these high numbers may correlate with cancer-induced bone pain [28, 51]. Osteoclast-mediated bone remodeling results in the production of extracellular proteins, known to be potent activators of nociceptors [52]. The acidic environment produced by osteoclasts may contribute to cancer-induced bone pain through activation of acid-sensitive nociceptors that innervate the marrow, mineralized bone and periosteum [53]. With advanced disease, bone loses mechanical strength and is subject to further osteolysis, pathological fractures, and microfractures.

2. **Nerve Injury by Tumour Invasion**
It has been suggested that nerve or nerve root injury by tumour invasion is involved in the pathophysiology of cancer-induced bone pain [24]. Sensory and sympathetic neurons are present within the bone marrow, mineralized bone, and periosteum and all of these are susceptible to injury from the presence of tumour cells, fractures and ischaemia. Sensory fibers in any of these tissues may therefore play a role in the generation and maintenance of bone pain [54]. For example, nerve root infiltration and nerve compression by osteolytic vertebrae may result in neuropathic cancer bone pain, and infiltration or compression of adjacent nerves by tumour growth can also result in pain of a neuropathic nature. Tumour cells present in bone also have the capacity to grow out from the bone and invade surrounding tissues and nerves, further contributing to bone-related pain.

3. **Stretching of Periosteum and Endosteum by Increasing Tumour Size**
Nociceptive pain may also arise as a result of stretching of the periosteum resulting from tumour infiltration of the bone. Many nerves are found in the periosteum

and other nerves enter bones surrounding blood vessels [5]. Studies have shown that the periosteum is densely innervated by both sensory and sympathetic fibres [55–57] and that it receives the greatest density of nerve fibres per unit area of all bone tissues. It has been proposed that bone pain arises predominantly, if not exclusively from the periosteum [58–60]. However, stimulation of nerve endings in the endosteum also results in the release of chemical agents from the destroyed bone tissue, such as prostaglandins, bradykinin, substance P and histamine. It has been suggested that the main mechanism of bone pain from small metastases is from this stimulation of nerve endings in the endosteum by chemical agents from the destroyed bone tissue [12].

4. **Microfractures and Pathological Fractures**
Bones involved with cancer are weakened and thus are at increased risk of fracturing. Microfractures can occur in the bony trabeculae at the site of the metastases resulting in bone distortion. Microfractures cause pain that result from the destruction of bone, reducing its weight bearing capabilities. In the appendicular skeleton, instability due to the presence of metastases results in symptoms with use of the extremity or with weight bearing. A pathological fracture can result when loads are applied that are greater than the support provided by the normal bony trabeculae. Fractures can occur with a fall or injury, but can also occur during everyday activities, resulting in sudden severe pain. Pathologic fractures have been reported at some time in approximately 8–30 % of patients with bone metastases [61, 62].

Fractures are more likely to occur with osteolytic metastases and can occur in ribs and vertebrae as well as in long bones. Long bone fractures occur in 10–20 % of patients [27]. The femur and humerus are the bones most commonly fractured due to metastases. A long bone fracture or an epidural extension of tumour into the spine causes the most disability.

Bone metastases of the axial skeleton develop a gradual weakening of the trabeculae and loss of architecture which can result in mechanical pain and/or pain at rest. Tumour growth may also cause weakness of the vertebrae, with eventual collapse of the bone resulting in sudden pain in the middle of the back. Painful vertebral compression fractures, pathologic or osteoporotic, are a source of considerable morbidity in cancer patients. Most fractures occur in the thoracolumbar region and adjacent-level fractures occur in approximately 18 % of patients [63].

As the development of a fracture can have detrimental effects on quality of life, as well as on survival, efforts have been made to predict sites of fracture. Various characteristics have been suggested as important criteria for determining a patient's risk of fracture, with certain cancer types associated with an increased risk. Only few cancer types, however, have been an object of detailed study of fracture risk. Patients with multiple myeloma have been shown to have the highest fracture incidence, followed by breast, prostate, and lung cancer [64]. Much research has focused on prostate cancer, where a decreased bone mineral density and an increased risk of fractures, mainly linked to the use of anti-androgen

therapy, has been demonstrated [65]. Patients with breast cancer have a relatively long survival, thus these patients are more likely to develop pathological fractures. Women with low bone mineral density also have an increased risk of breast cancer [66], and may therefore have an increased risk of fractures. Aromatase inhibitors have been shown to be associated with a significantly higher risk of fractures than tamoxifen due to the lowering of estradiol levels, whereas tamoxifen has partial estrogen agonistic properties [67]. Bone fractures also represent a frequent complication of thyroid cancer and renal cell cancer [68–70]. Renal cell metastases to bone can be unusually expansile and destructive, which creates an increased risk of pathological fracture.

Other implicated characteristics for increased risk of fracture include: duration of lesions, (the risk of pathologic fracture appears to increase with the duration of metastatic disease [71], size of the lesion, location of the lesion (cortical involvement in the subtrochanteric region of the femur increases the risk), type of treatment, and osteolytic versus osteoblastic lesions. Breast cancer metastases that are purely osteolytic are more likely to fracture than those that are osteoblastic or mixed osteolytic and osteoblastic. Osteoblastic lesions in high-risk areas such as the proximal femur have a high rate of fracture however.

Because fractures are associated with increased risk of death in patients with malignant bone disease, prevention of fractures is an important goal of therapy.

5. **Activation of Acid-Sensing Nociceptors by Tumour-induced Acidosis**
As inflammatory cells invade tumour stroma, they release proteins that generate local acidosis. Areas of ischaemic necrosis and osteoclasts contribute to further lowering pH. The large amount of apoptosis that occurs in the tumour environment may also contribute to the acidotic environment.

Pain receptors expressing acid-sensing ion channels are sensitized and activated by this decrease in pH. The low pH causes the acid-sensing ion channels on nerve cell endings to be stimulated, resulting in activation of nociceptors. This activation of acid-sensing receptors by tumour-induced acidosis in bone metastases and tumour-induced release of proteins and acidosis may be particularly important in the generation of cancer-induced bone pain [24, 72]. Inhibiting acid-sensing ion channels may therefore lead to a reduction in cancer-induced bone pain.

6. **Nociceptor Sensitization**
It is also reported that malignant bone pain may have distinct additional mechanisms that contribute to pain, including CNS excitation and disinhibition and nociceptor sensitization (increased responsiveness to noxious or non-noxious stimuli), which may underlie more persistent, mechanically evoked pain. This sensitization could originate in the periphery (peripheral sensitization) or in central structures (central sensitization).

Central sensitization is responsible for tactile allodynia (pain in response to light touching of the skin) and for the severe burning pain such as that seen from mere blowing on the skin in patients with nerve damage. Central sensitization is also responsible for the spread of pain beyond an area of tissue damage resulting in tenderness in adjacent non-damaged tissue. It can also occur following orthopaedic surgery which may contribute to pain on movement or touch [73].

3.6 Conclusion

Cancer-induced bone pain can considerably impact on the quality of life, functional status and survival of patients with metastatic cancer. Cancer-induced bone pain is a complex pain state, arising via activation and destruction of the primary afferents within bones. The understanding of its pathophysiology continues to evolve and in the last decade much progress has been made. Notwithstanding, further research is required into the complex basis of cancer-induced bone pain and its involved mechanisms. This will hopefully enable expansion of the therapeutic options available for the treatment of this challenging pain.

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Part II
Investigations of Bone Metastases

Chapter 4
Radiological Evaluations: Radiography, CT, MRI

Petros Polyviou, Demos Michaelides, Dimitrios Vomvas, Panteleimon Kountourakis, Vassilios Vassiliou, and Dimitrios Andreopoulos

Abstract The role of imaging is crucial in detecting and differentiating bone lesions and has a vital role in monitoring response to treatment and providing guidance for interventional procedures. Bone scintigraphy is a very sensitive method and remains the basic screening examination. Plain radiography is a supplementary method for assessing symptomatic sites and confirming suspicious findings revealed in scintigraphy. The role of conventional radiography (CR) is still important in multiple myeloma evaluation and is the best method for delineating the nature of a bone lesion.

Computed tomography (CT), due to its high temporal and spatial resolution, is more sensitive than CR in detecting bone metastases. Because of its wide use and availability for staging and follow up of oncologic patients this method is of particular importance for the evaluation of skeletal disease. MR imaging is considered as the most sensitive and effective imaging modality in detecting and characterising bone metastases but the cost and the low availability are major drawbacks.

Keywords Bone metastases • Conventional radiography • Computed tomography • MR imaging • Therapy monitoring • Imaging guidance

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4.1 Introduction

Bone metastases are the most common cause of a destructive skeletal lesion and a major cause of morbidity. Moreover they may deteriorate the quality of life of oncologic patients. Although the overall incidence of bone metastases is not known, over one-half of patients who die of cancer in the United States each year are thought to have bone involvement [1]. Breast, prostate, lung and kidney carcinomas exhibit a predilection for metastases to bone. About 70 % of patients with advanced breast or prostate cancer will develop skeletal metastases [2]. Other malignancies that can give rise to skeletal metastases are gastrointestinal carcinomas and bone sarcomas.

Although bone metastatic disease may be the hallmark of advanced malignancy, for some patients disease may remain confined to the skeleton, with progressive worsening of the quality of life and eventually death, being entirely as a result of skeletal complications [2]. Moreover, with the increased efficacy of antineoplastic treatments patients survive longer. This contributes to the rise in incidence of symptomatic skeletal disease making the definitive treatment of skeletal metastases a very important task [3]. Such treatment modalities include external beam radiotherapy, chemotherapy, systemic therapies and surgical interventions.

Direct complications of bone metastases are severe pain, pathological fractures, epidural spinal cord compression and life-threatening hypercalcemia [4]. As these manifestations may be the first presentation of malignant disease, skeletal metastases may be confused with other diseases. The incidence of bone metastases from an unknown primary source at presentation may be as high as 30 % [3]. The key clinical issues that must be addressed are whether the symptoms are due to a metastasis, the differential diagnosis, the mechanical risk of the integrity of the skeleton, the safest location and image guidance for a biopsy, the localization of the primary disease and eventually the response of the metastases to therapy. The role of imaging in addressing these issues is crucial [5]. Several imaging techniques may be employed for detecting and evaluating bone metastases, each having drawbacks and advantages.

4.2 Mechanisms of Metastatic Spread

A metastatic malignancy spreads to the bones mainly via three routes:

- Haematogenous
- Direct invasion
- Lymphatic

The Batson's paravertebral venous plexus appears to be an important pathway for metastatic implants to the axial skeleton and proximal long bones. This plexus is longitudinal and valveless and extends from the sacrum to the skull. The venous flow from the breast, lung, prostate, kidney, and the thyroid drains into this vertebral

vein plexus resulting in a predilection for metastases to the axial skeleton [6]. Remote deposits may develop from cancer cells which gain access to the arterial system [5]. Another reason for the preferential involvement of the axial skeleton is the presence of red marrow which is highly vascular.

Direct invasion is less frequently observed and it may result from a direct infiltration by the primary tumor. The most prevalent example is invasion of the chest wall by a lung cancer. Lymphogenous spread to bone is uncommon but secondary invasion from involved lymph nodes is not rare, especially in the spine. The left side of the spinal column is more often affected due to the imbalance of lymph channels between the left and right sides.

4.3 Pathophysiology

Micrometastases usually result from the haematogenous dissemination of cancer cells that lodge in the medullary cavity. Tumor cells may produce or express various adhesive molecules, which bind to the corresponding receptors on the stromal cells of the marrow and bone matrix [7]. This explains the preferential localization and growth of tumor cells in bone. The involvement of both the tumor cell properties and the bone microenvironment is supported by the "seed and soil hypothesis" [8].

Not all such micrometastases though are viable or result in clinically significant metastases. The tumor cells must evade immunologic destruction by the host and be able to survive and grow in the new metastatic site. Their ability to stimulate neoangiogenesis has also been implicated in this process.

4.4 Types of Metastases

Skeletal metastases are classified in three groups based on their radiologic appearance: lytic, mixed and sclerotic. The balance between osteoclastic and osteoblastic activity in a bone metastasis determines whether a lesion is classified as either osteolytic or osteoblastic. This distinction is not absolute since many patients have both osteolytic and osteoblastic metastases, while individual metastatic lesions can contain both osteolytic and osteoblastic components and are considered as mixed lesions. In all types of lesions there is a dysregulation of the normal bone remodeling process.

The imaging characteristics of each type of metastases can be used for the differential diagnosis of the primary tumor, although there is little practical value in predicting the primary tumor from imaging alone, since histological examination is mandatory for an accurate diagnosis. However the knowledge of the underling pathophysiology of each type of metastasis can be useful in understanding the imaging changes after treatment.

4.5 Imaging Methods

All imaging methods can be used to detect or delineate bone metastases. In order of effectiveness for the detection of skeletal lesions these are as follows [5]:

- Magnetic resonance imaging (MRI)
- Bone scintigraphy (nuclear medicine, NM)
- Positron emission tomography with computed tomography (PET-CT)
- Positron emission tomography (PET)
- Computed tomography (CT)
- Conventional radiography (CR)
- Ultrasound (US)

In order of their value in defining the nature of a known lesion they are [5]:

- MR imaging
- PET-CT
- CT
- CR
- PET
- NM
- US

The initial identification of bone metastases occurs through the use of bone scintigraphy, which has a high sensitivity for recognizing any type of lesion within bone. The radionuclide bone scan using technetium Tc-99 m is a sensitive (approximately 90 %) but a nonspecific imaging modality that provides a map of high bone turnover [9]. PET and PET-CT are newer alternative nuclear scanning methods that use biologic tracers to reveal uptake in metabolically active tissue. The advantage of these methods is their ability to detect occult lesions that other imaging modalities are unable to identify [10]. MR imaging has surpassed all other imaging modalities because of its high spatial and contrast resolution, its high specificity and sensitivity, the fact that it does not entail radiation exposure and does not involve in most cases the use of paramagnetic contrast [11].

While both MRI and modern nuclear methods are technologically advanced imaging techniques, they are expensive to operate, more difficult to interpret and not widely available. In routine clinical practice, plain x-ray, bone scintigraphy, and a CT scan are the most affordable and accessible methods for the evaluation of bone metastases. In this chapter we will analyze the role of CR, CT and MR in the detection and evaluation of skeletal metastases.

4.5.1 Conventional Radiography

As it was mentioned before bone metastases can be lytic, osteosclerotic or mixed. CR is the most suitable imaging method for delineating the nature of a bone lesion. The margins and the transitional zone around a lytic bone are very important

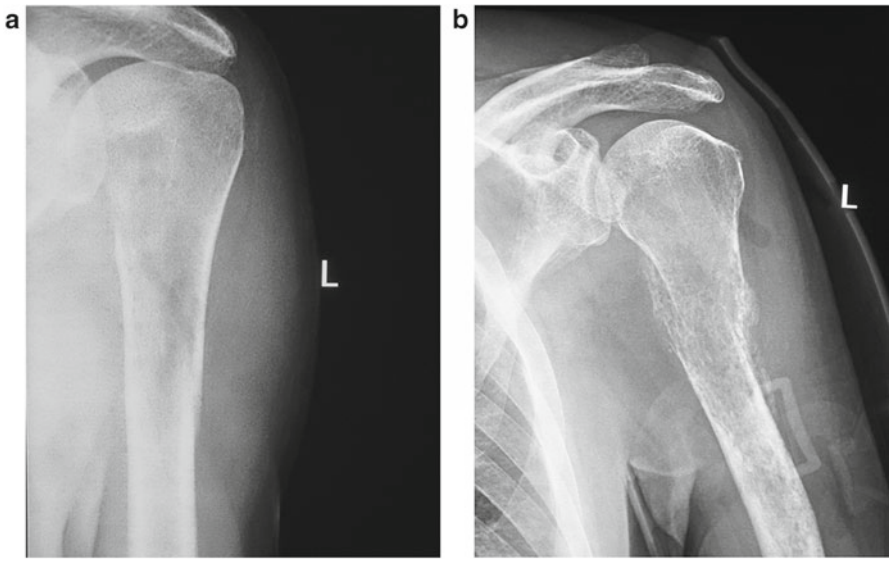

Fig. 4.1 CR: Fracture of the upper shaft of the left humerus because of underlying lytic metastasis from a neuroendocrine tumor (**a**). Complete destruction of the bone because of diffuse metastatic infiltration and pathological fracture (**b**)

features that may characterize the lesion as aggressive or benign. Permeative or moth-eaten destructive lesions with ill-defined margins and large transitional zones between abnormal and normal bone are suggestive of an aggressive disease (Fig. 4.1). It is important to differentiate such lesions from infection. Well circumscribed or geographic lesions with sclerotic margins and short transitional zones are more indicative findings of a benign process. On the other hand osteosclerotic lesions may be nodular or diffuse and they typically lack the spiculated appearance of a bone island [12].

Although CR is considered to be an essential method for the detection of metastatic bone disease, it is relatively insensitive and can not be used as a screening method for asymptomatic patients. Up to 30–50 % of the trabecular bone may need to be destroyed or a lesion must be greater than 1.5 cm before any radiographic change becomes evident [13]. Sensitivity depends partly on location. For instance, metastases to dense cortical bone are easier to detect than those involving trabecular (medullary) bone [14]. This is especially true for the spine where CR cannot rule out metastatic disease. Sacral metastases are also usually missed due to overlying bowel gas. According to a study, skilled x-ray radiologists miss approximately 30 % of instances that depict evidence of disease and are likely to over-interpret up to 2 % of films that are negative for disease [15]. Previous knowledge of the clinical presentation of disease and the clinical history of the patient may increase the specificity of the method and strengthen the consensus [15]. Careful interpretation of plain films is essential, especially when clinical symptoms do not correlate with image findings.

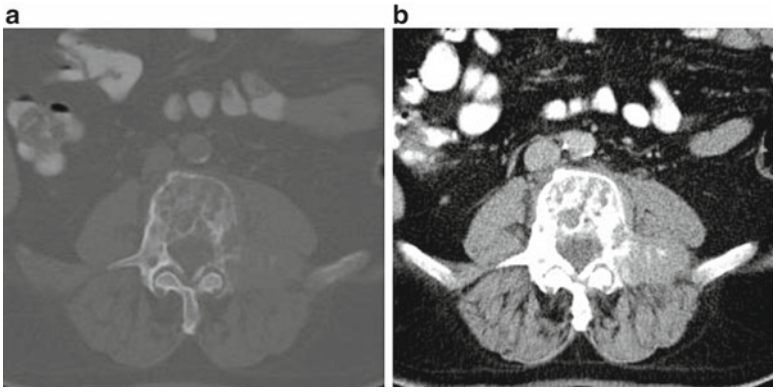

Fig. 4.2 CT presenting destructive lytic lesion of L5 due to a metastasis from prostatic cancer (**a**) accompanied by soft tissue mass enhancing after IV contrast administration (**b**)

CR is commonly used to evaluate symptomatic sites and to confirm metastatic deposits evident on bone scintigraphy. Correlative radiographs should always be performed for equivocal or suspicious scan findings to exclude proliferative changes and articular erosions from inflammatory arthritis that may produce confusion with metastatic disease [16].

Also CR may be used to assess the risk for pathologic fracture, which is high when 50 % or more of the cortex is destroyed or the lesion is larger than 3 cm. However, CT seems to be more accurate for this task. Finally the radiographic survey remains valuable for the staging of multiple myeloma due to the poor sensitivity of radioisotope scanning in this condition. However studies utilising CT skeletal surveys for multiple myeloma staging instead of CR have been published.

4.5.2 Computed Tomography

CT is widely used in oncologic patients for localizing the primary tumor, to aid the initial staging and assessment for metastatic bone disease. The images should be reviewed in bone and soft tissue windows during staging and follow up investigations when suspicion for bone metastatic disease is raised.

Due to its high spatial and temporal resolution, CT is more sensitive than CR for the detection of bone metastases and is often used to delineate equivocal lytic areas seen on CR. Bone metastases are very unlikely if CT is normal. According to some studies CT shows good correlation with NM for the detection of bone metastases and they question the need for bone scintigraphy if CT of thorax, abdomen and pelvis is performed [17, 18].

CT can also readily demonstrate the extent and pattern of bone destruction and the presence of an accompanying soft tissue mass, especially in complex anatomic areas such as the spine and pelvis (Fig. 4.2). Similarly, CT may successfully assess paravertebral or intraspinal extensions, transarticular tumor spread and soft tissue

involvement with infiltration of neurovascular structures [19]. This information is particularly important prior to interventional therapies.

In CT images destructive bone lesions appear as grey voids in white ossified areas of bone. Actually, CT can detect bone marrow infiltration even before bone destruction has occurred, since its presence causes an increase in attenuation due to fat replacement by more than 20 HU [20]. Sclerotic deposits appear as whiter areas of bone with sharply defined margins, while many lesions exhibit a mixed pattern. More subtle osteoblastic lesions appear as ill defined areas of increased bone density, with a loss of normal trabecular pattern.

The use of intravenous iodinated contrast media may enhance the margins of tumors and the vascularity of associated soft tissue lesions. Additionally, CT is especially useful in determining the nature of vertebral fractures (osteoporotic vs pathological) and as compared to CR it can assess more effectively the risk for pathologic fractures.

Although CT is not generally used for screening the entire skeleton, the introduction of multidetector CT (MDCT) allows the use of low dose protocols for whole body scanning and may replace conventional skeletal survey for the staging of multiple myeloma and for the evaluation of the spine. The use of MDCT and multiplanar and 3D reconstructions can contribute to the evaluation of the stability of skeletal metastases and aid in surgical and radiotherapy planning [17, 21].

Last but not least another application of CT is to provide precise anatomic localization which is necessary for high diagnostic accuracy in several fusion techniques like SPECT or PET/CT that also depict metabolic tumor activity.

4.5.3 Magnetic Resonance Imaging

MRI plays a pivotal role in the detection, characterization and post treatment follow up of bony metastases. It has a high sensitivity and specificity in detecting and characterizing skeletal lesions. It is the only modality that images directly bone marrow and hence allows early detection. It also demonstrates local spread of bone metastases and accurately depicts any extension into the spinal canal.

With the appropriate use of MRI sequences and knowledge of physiological bone marrow components and their variation, MRI can reach a very high specificity. The bone marrow is made largely of fat and water hence sequences that demonstrate the difference between them is used to detect infiltrating disease. The prime sequence used is the T1W, which demonstrates bone marrow fat and can detect replacement of normal fatty bone marrow signal by low signal metastases. Hematopoietic bone marrow contains both fat and water and has a signal intensity in-between that of fat and normal muscle. Infiltrating lesions with signal intensity lower than that of muscle and discs are abnormal and are likely to be malignant.

Due to the high signal of fatty marrow on T2W sequences, and similar signal intensity of some bone metastases, the latter may be missed. Fat saturation can be a helpful tool in such cases suppressing background fatty bone marrow and increasing the conspicuity of lesions. Fat saturation however is subject to field inhomogeneities and may even suppress signal from water and obscure pathological conditions.

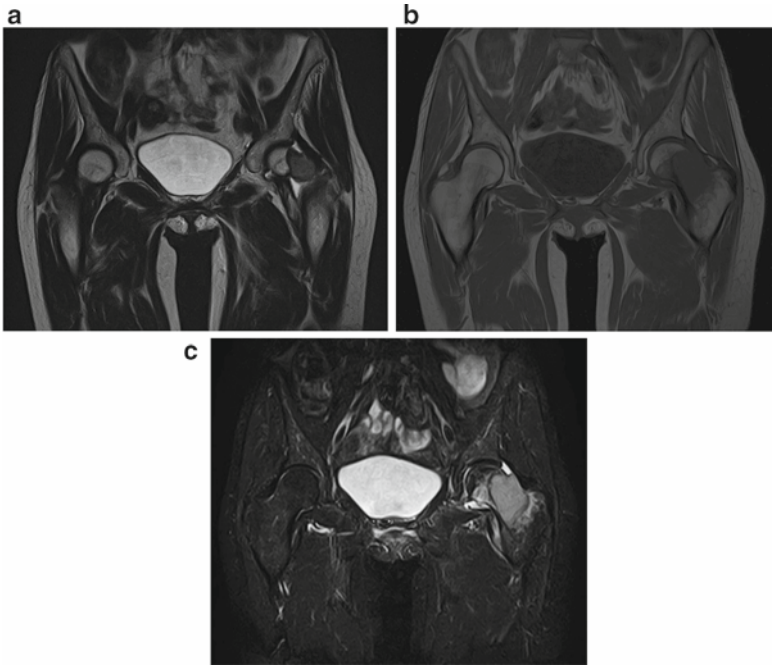

Fig. 4.3 Coronal T2W/FSE (**a**), T1W/FSE (**b**) and STIR (**c**) demonstrate a left femoral neck metastasis

STIR sequence is less affected by field inhomogeneity and is very sensitive in detecting bone marrow abnormalities. However, it is less specific as it tends to suppress anything that has a T1 relaxation time similar to that of fat (Fig. 4.3).

Gradient echo chemical shift imaging makes use of the signal cancelling effect between fat and water protons on opposed phase imaging to demonstrate fatty bone marrow replacement. This type of imaging results in a low signal of normal bone marrow and a high signal in pathologic sites. Several studies have suggested the use of this sequence as an additional tool to detect malignant lesions by assessing the degree of signal loss, the latter being greatest in benign lesions [18, 22]. The same technique can be used in distinguishing between benign or malignant vertebral compression fractures [23].

Diffusion weighted imaging exploits its ability to detect alterations in water mobility and to evaluate diffusion capacity, which when quantified, can be used for tissue characterization. Contrast enhanced sequences after the injection of intravenous Gadolinium chelates would accentuate bone marrow abnormalities. No uptake of contrast would be evidenced in the absence of infiltrating bone marrow disease. MRI also has the ability to indirectly assess for trabecular lysis on Gradient echo sequences. Immobile protons inside intact trabeculae would lead to loss of MRI signal from adjacent bone marrow due to local T2* artifacts. This loss of signal is reduced with trabecular lysis as there are less susceptibility artifacts.

Bony metastases may have a variety of appearances on MRI depending on whether they are osteoblastic, osteolytic or mixed. Lytic metastases are iso- to mildly hypointense to muscle on T1W sequences, mildly hyperintense on T2W FSE images and hyperintense on T2W FSE FS or STIR images. They demonstrate heterogeneous enhancement after iv contrast. Sclerotic metastases exhibit reduced signal intensity on T1W and T2W sequences and may demonstrate a rim of hyperintensity on fat saturation sequences. Mixed lesions demonstrate a combination of the above with T1W signal intensity ranging from iso intense to markedly reduced. Flow voids have been described in osseous metastases from renal cell carcinoma [24]. Such metastases may involve an extraosseous extension.

Differentiating bone metastases from normal heterogeneity of bone marrow can sometimes be difficult. Nevertheless, areas of red bone marrow tend to have a signal intensity lower than fat and higher than muscle, whereas bone metastases are either iso or hypointense to muscle. Red marrow areas have ill-defined feathery margins and are asymmetrical, whereas bone metastases are well defined, rounded lesions. Red bone marrow spares the epiphyses unless there is already advanced reconversion. Moreover, red bone marrow has a low signal on fat saturated T2 sequences and fails to demonstrate significant enhancement on post iv contrast sequences [25, 26].

Furthermore the bull's eye sign of central hyperintensity within an osseous lesion is a negative discriminator for metastasis whereas the halo sign of peripheral hyperintensity around an osseous lesion is a positive discriminator for bone metastases [27].

Similar diagnostic dilemmas can arise when trying to differentiate between osteoporotic and metastatic vertebral compression fractures. Metastatic compression fractures are more likely to demonstrate abnormal signal intensity and spread into the pedicles at the time of the fracture as compared to osteoporotic compression fractures [28–32]. Spared bone marrow signal within the vertebral body is highly suggestive of osteoporotic collapse [31, 33–35] as is the presence of a linear horizontal hypointense band [32]. Metastatic compression fractures are more likely to demonstrate a convex posterior border (Fig. 4.4) [28, 32, 36]. On the other hand retropulsion of a posterior fragment is more likely in osteoporotic compression fractures [28, 32]. The presence of multiple compression fractures is more suggestive of osteoporosis, whereas the presence of further spinal metastases would point towards a metastatic compression fracture [32].

There is discrepancy in literature between studies regarding the T2W signal intensity and post intravenous contrast enhancement in osteoporotic and metastatic compression fractures. More specifically, some studies suggest a high or inhomogeneous T2W signal intensity and contrast enhancement in metastatic compression fractures [28] and other studies report no difference between the two aetiologies [32].

An epidural mass or focal paraspinal mass is also more frequently encountered in metastatic compression fractures. DWI has also been shown to have a high accuracy in differentiating between metastatic and benign compression fractures. With the exception of sclerotic metastases or partly treated metastases, compression

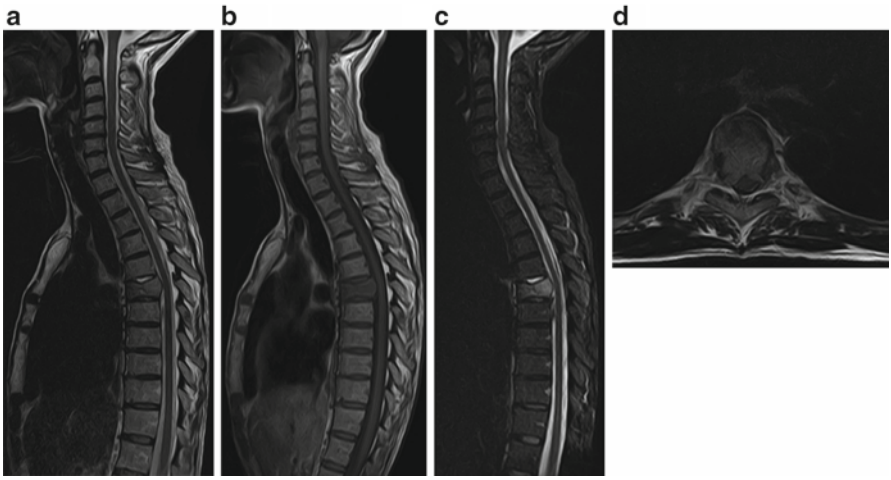

Fig. 4.4 Sagittal T2W/FSE (**a**), T1W/FSE (**b**), STIR (**c**), axial T2W/FSE (**d**). There is a metastatic compression fracture of T6 vertebra with posterior bulging of the vertebral cortex. The axial T2W image shows extension into the spinal canal

fractures due to metastatic disease are hyperintense on DWI, whereas benign fractures are hypointense relative to normal bone marrow [37–39]. ADC values can also be measured for quantification [40].

MRI can detect metastatic lesions before changes in bone metabolism make the lesions detectable on bone scintigraphy [39, 41, 42]. MRI has been shown on multiple studies to be more sensitive than bone scintigraphy is detecting bone metastases [41, 43–45]. Whole body bone screening is more easily carried out with bone scintigraphy and is also more cost effective. However it has been shown that whole-body MRI can be an alternative. It involves the use of STIR and T1W sequences and takes less than an hour to complete [46]. In addition MRI can be used for problem solving when the combination of bone scintigraphy and plain radiography does not establish a diagnosis [47–50].

FDG-PET scanning is an alternative way of early detection of malignant bone-marrow infiltration. It depicts skeletal regions with an increased metabolic activity that is a result of the presence of malignant cells. It has limited spatial resolution and additional cross-sectional imaging such as MRI or CT is required to localize an area of high uptake. Like in MRI there is the issue of local availability and cost effectiveness [51–53].

4.6 Differential Diagnosis

One of the key issues when imaging a solitary or multiple bone lesions is determining the nature of the lesions. Although in a patient with a known primary malignant disease the probability that biopsy of a new suspicious bone lesion will show the lesion to

be other than metastasis from the primary tumor is low (2 %), other benign diseases should be ruled out [54]. The possible diagnoses are mainly the following [5]:

- Focal marrow lesions
- Infiltrations
- Trauma
- Infections
- Multiple benign lesions

4.6.1 Focal Marrow Lesions

Radiotherapy damage with areas of bone necrosis and repair may be evident for years and may appear as disease progression. The localization of the abnormalities in the radiotherapy field, the mixed lytic and sclerotic pattern and the fatty replacement of bone marrow readily seen on MRI are signs of radiotherapy damage, while soft tissue involvement with presence of a mass is suggestive of recurrent disease. Acute radiation effects within the radiation field may be seen on MRI as bone and soft tissue edema persisting for several months after treatment and should not be mistaken for metastatic disease.

Other common benign findings are hemangiomas. On MRI they typically appear as high signal intensity lesions on fat specific sequences and with a low signal intensity on water specific sequences. They also exhibit internal striae of low intensity in all sequences and normally don't cause any diagnostic problem. Atypical cases though may contain water and hence high signal on water sequences. However the absence of bone destruction and the dot like calcified areas seen on CT ultimately reveal the true diagnosis.

4.6.2 Infiltrations

Residual or reactivation of red marrow causing geographic or patchy bone involvement with fluid containing tissue in spine may mimic metastatic disease. Also marrow replacement by rare infiltrative disorders such as macroglobulinemia, lysosome storage diseases, Gaucher's disease or myelofibrosis may also cause diagnostic problems. However, the absence of bone destruction on CT in these cases is characteristic and helps for the differential diagnosis.

4.6.3 Trauma

Traumatic fractures appear as lucent lines breaching usually the bone cortex with associated soft tissue and bone marrow edema. Fractures through a deposit cause

confusion. The presence of a hole that is larger than expected and enlarges instead of regressing after several weeks or unusual fracture directions or the presence of a soft tissue mass are useful signs. In some cases biopsy may be indicated.

4.6.4 Infections

Osteomyelytic lesions are usually solitary and in contrast to metastases tend to be near the joints or disc spaces involving both sides. Rare indolent infections like tuberculosis or fungal infections, may mimic tumor, while miliary disease usually in immunosuppressed patients may be difficult to distinguish from metastatic disease. Metastases are usually uniform in contrast to infection which tends to be more variable with heterogeneous pattern. However histological examination or culture may be necessary for diagnosis.

4.6.5 Benign Lesions

Multiple benign lesions like osteomas, granulomatosis, lymphangiomatosis, osteopoikilosis and sclerosing osteitis may cause confusion with metastases. In such cases conventional radiographs and CT may be helpful. If there is any doubt, imaging should be repeated in several weeks.

4.7 Imaging Guidance for Interventional Procedures

Another potential role for imaging is the guidance of biopsy to obtain histological confirmation. Lytic or blastic bone lesions and/or soft tissue masses in patients with a history of known malignancy are the most frequent reason for biopsy [55]. An image guided biopsy is also indicated whenever the pathologic diagnosis would alter the management of an oncologic patient, since systemic therapy varies with tumor types [56].

Planning is a crucial step in the procedure and demands careful review of available imaging. Discussing the route of biopsy with a surgeon in case of a solitary lesion that may be excised is mandatory. Seeding of tumor along the needle tract is a possibility and therefore it is important to use a route that will be excised surgically. However this remains an important issue in only a minority of cases because usually surgical treatment is not indicated in metastatic bone disease. The type of specimen needed should be agreed in advance with the pathologist as the appropriate needle and technique should be utilized.

In planning a bone biopsy the safest site and route avoiding important structures should always be sought, aiming at the most superficial and largest lesion. Necrotic areas, usually located within the centre of a tumor, should be avoided. Fracture sites should also be avoided because the repair process may mimic mitotic activity and resume false positive results. Lytic areas of a mixed lytic and sclerotic lesion should be sampled first and soft tissue masses that occur adjacent to bone lesions should also undergo biopsy. If a mass is calcified or ossified, sampling the least mineralized portion often shows the highest atypia. More than one biopsy may be required if multiple lesions have different imaging characteristics [57] and more samples from the same lesion may be needed if the lesion is large. The enhancing regions of a soft-tissue mass as seen on contrast-enhanced CT should be sampled, as should the center and periphery of a lesion.

Clotting function defects or thrombocytopenia must be recognized and corrected before the procedure and the patient should be warned for any possible complication (hematoma, pain, damage to adjacent structures, allergy and infection). A signed consent should be obtained in all cases. Usually biopsies are undertaken under local anesthesia but some patients may require neuroleptic anesthesia or even full general anesthesia. Anesthetizing the periosteum and the adjacent soft tissues is very helpful for minimizing patient motion due to pain.

The specimens should be as large as possible for more accurate results. Fine needle aspiration (FNA) sampling is adequate for differentiating a metastasis from benign lesions, but a core needle biopsy (CNB) is required for cell type characterization. Bone cutting needles or drilling devices are often required to penetrate bone. All specimens should be sent for both histological examination and culture in order to exclude infection.

The diagnostic accuracy of percutaneous biopsy of vertebral body lesions using a variety of approaches with fluoroscopy or CT guidance is 88–100 % [55]. Fine-needle aspiration biopsy of vertebral lesions has a similar, but consistently lower success rate when compared to core biopsy [56]. The reported positive predictive value of combined needle aspiration and core biopsy is 82 % and the negative predictive value 100 % [58].

The preferred method for guidance of the biopsy will depend on the location of the lesion. The chosen technique should readily depict structures that should be avoided during the procedure. Fluoroscopy was the first method used for imaging guidance in 1949, and is still one of the most widely employed [59]. Real time visualization of the needle, low cost and short time procedures are the main advantages, but the inability to show the surrounding soft tissue structures is a major disadvantage.

CT guidance is precise and is the standard procedure in many institutions. The visualization of soft tissues helps to avoid important structures, yet allows access to central lesions. The high radiation dose, the long procedures in time and the limitation of the axial plane are the main drawbacks. CT fluoroscopy (CTF) combines the advantages of conventional fluoroscopy with near realtime visualization by acquiring six images per second. However the high radiation dose exposure is a major concern.

The open architectures of modern MR scanners and the development of MRI-compatible instruments, has allowed MRI to become a new modality for image guidance [54, 60]. The real time monitoring of the needle track, the multiplannar capability, the increased soft tissue contrast and the absence of ionizing radiation are the main advantages. However, the high cost and the limited availability don't allow wide use of this method.

The precision and safety provided by imaging guidance have also opened up new therapeutic and palliative interventional procedures like radiofrequency ablation (RFA), cementoplasty, cryotherapy and coblation.

4.8 Vertebral Fractures

Vertebral body metastases may present with pain or neurologic deficits. Usually they are detected during screening examinations in patients with known malignancies but may be also revealed after imaging carried out to evaluate local symptoms. Osteoporosis and metastases may bring about vertebral fractures, with osteoporosis being the commonest cause. The diagnostic distinction between the two is therefore crucial.

Helpful signs that indicate osteoporotic fractures are the different aged lesions, evidence of healing with time, the sparing of pedicles, and the absence of expansion or a soft tissue mass. On the contrary the location of the fracture in the upper thoracic spine, or the presence of angular or irregular deformities at the vertebral endplates should raise the suspicion for a metastasis.

In MRI recovery of bone marrow a normal fatty signal is noted in osteoporotic lesions. On the other hand edema and haemorrhage from an acute fracture may mimic a metastatic lesion.

Most osteoporotic fractures will heal in time while metastatic disease progresses. Therefore a wait and rescan policy may be preferential in difficult cases. Otherwise biopsy may be applied to reach a definite diagnosis.

4.9 Imaging Monitoring of Tumor Response to Treatment

Radiological imaging is essential for monitoring the therapeutic response of patients with bone metastases. Imaging modalities that can be used to assess the response of bone lesions to treatment include CR, NM, CT and MRI (Figs. 4.5 and 4.6). The establishment of appropriate objective criteria would allow an oncologist to evaluate the therapeutic outcome of patients in a timely manner and help in taking appropriate and correct treatment decisions. More over the use of uniform criteria in clinical trials evaluating the therapeutic outcome of such patients would allow comparisons between different studies employing different treatment strategies.

Three sets of criteria for evaluating the therapeutic outcome have been proposed. The criteria of the International Union against Cancer (UICC) and the world Health

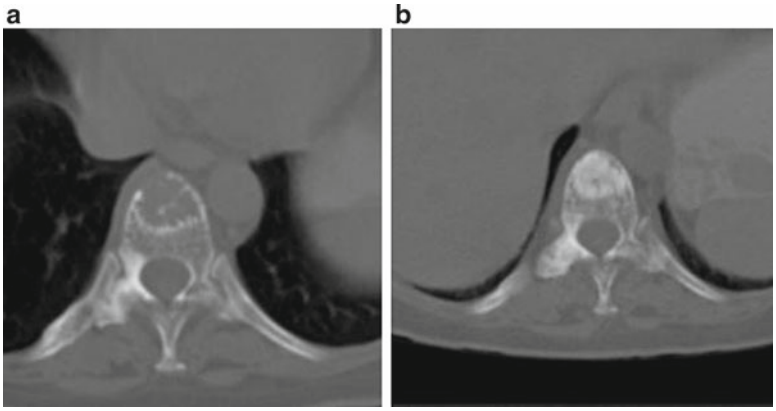

Fig. 4.5 CT of thoracic spine presenting lytic metastasis from breast cancer (**a**). Osteosclerosis of the lesion after chemotherapy (**b**)

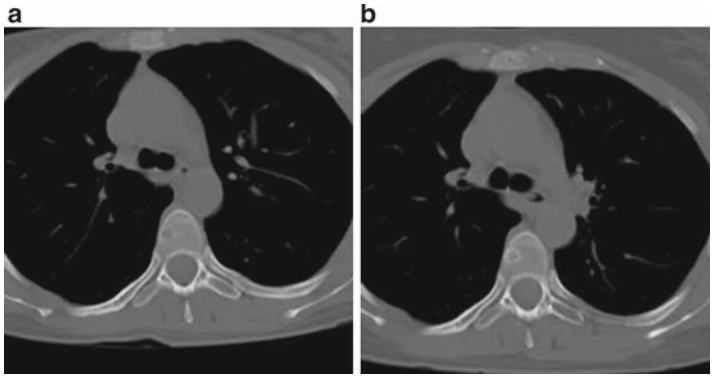

Fig. 4.6 CT of thoracic spine showing a small lytic lesion due to breast cancer metastasis (**a**) presenting rim sclerosis after response to chemotherapy (**b**)

Organization (WHO) criteria were proposed three decades ago and take into account radiography (UICC) or radiography and skeletal scintigraphy (WHO). Newer criteria were proposed by MD Anderson (MDA) and take into account apart for radiography and scintigraphy, CT and MRI [61, 62]. These criteria are presented in detail in Chap. 21.

4.10 Summary

Prostate, breast, lung, kidney and GI are the most frequent tumors associated with bone metastases, usually spreading hematogenously via venous plexi. Metastases can be osteoblastic, lytic or mixed and may be present long before they produce

symptoms or can be detected by any imaging method. The role of CR is limited to investigation of symptomatic sites or to confirm NM findings, as almost 90 % of the trabecular bone must destroyed before the lesions are revealed by plain films. MDCT and whole body MR imaging are more effective in detecting metastatic bone disease. Finally imaging can be employed to guide interventional procedures and monitor therapeutic response to treatment.

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Chapter 5
Nuclear Medicine Imaging Modalities: Bone Scintigraphy, PET-CT, SPECT-CT

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Abstract Nuclear medicine allows imaging of (patho) physiological processes within the body and contributes in the diagnosis and treatment of specific diseases. In patients with bone metastases, nuclear medicine not only plays an important role in the diagnosis, but may also be used for therapeutic purposes. For several decades, bone scintigraphy has been used and nowadays is still the nuclear medicine imaging method of choice for diagnosing bone metastases in many malignant diseases. Its sensitivity (>90 %) is still superior to any other available imaging method. However, the specificity is rather low and interpretation of scans needs to be carefully evaluated by expert nuclear medicine physicians together with other biological, anatomical and clinical information.

In the last two decades, nuclear medicine rapidly evolved. New radiopharmaceuticals (SPECT and PET) were produced, specific for a certain cancer type. Recent development in soft- and hard-ware led to the introduction of hybrid camera systems (SPECT-CT and PET-CT), combining (patho)physiology and anatomy together, leading to better diagnostic results and many advantages, also for the patient.

In this chapter the basic principles of nuclear medicine, the different camera systems, and the technique and procedure of the bone scintigraphy will be explained.

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An overview is given of the available radiopharmaceuticals (SPECT and PET) to detect bone metastases in different cancer types. The role of nuclear medicine in patients with prostate cancer, breast cancer, lung cancer, and some other cancer types will be discussed more extensively.

Keywords Nuclear medicine • Bone metastases • SPECT • PET • Radiopharmaceuticals • SPECT/CT • PET/CT • Diagnosis

5.1 Introduction

In the study of bone metastases, nuclear medicine not only plays an important role in diagnosis, but also in therapy. This chapter focuses on the role of nuclear medicine in diagnosing bone metastases.

Bone imaging was one of the first applications of nuclear medicine in humans and still is one of the hallmarks of this discipline. The sensitivity of this nuclear medicine technique in diagnosing bone metastases is remarkably high, exceeding 90 %. On the other hand, the specificity is rather low, although the specificity rates have improved since the introduction of hybrid cameras that make it possible to combine (patho) physiological and anatomical information together. Interpretation of scans needs to be carefully evaluated by expert physicians in combination with other biological and clinical information or by other imaging modalities.

In this chapter we will explain the basics of nuclear medicine and the working mechanisms of the different imaging techniques. We will then give an overview of the available radiopharmaceuticals that are used for diagnosing bone metastases, followed by some special imaging characteristics in the most common malignancies that metastasize to the bone.

5.2 Basics of Nuclear Medicine

5.2.1 Radiopharmaceuticals and Isotopes

In the field of nuclear medicine, radiopharmaceuticals are used to image (patho) physiological processes in the body. A radiopharmaceutical is a synthesized compound consisting of a radioactive isotope and a pharmaceutical. Isotopes are nuclides with the same number of protons in their nucleus and are therefore nuclides of the same element. Most nuclei that are present in nature are stable. However, some are not stable and want to transform themselves to form stable configurations. These nuclides are called radionuclides or radioactive isotopes. Transformation to their stable state is achieved by emission of either particles or energy from the nuclei. Radionuclides may emit gamma-rays (which can be imaged on a gamma camera), beta-rays (which are used for therapy purposes), or both. Some

radionuclides are positron emitters (positively charged electrons) and may be used for positron emission tomography (PET) imaging. The transformation process, occurring spontaneous and at random, is also called radioactive decay. The rate at which the atoms decay is measured in disintegrations per second, also called Becquerel (Bq), the radiation unit. One disintegration per second is equal to 1 Bq. Each radionuclide has its uniquely defined decay constant, also called the physical half-life. This is the time required for half of the amount of radionuclide to decay. This half-life is important in imaging purposes, since it determines the time intervals between which imaging has to take place.

The biodistribution and targeting characteristics of the radiopharmaceutical is determined by the drug to which the radionuclide is attached. The presence of the radionuclide may not alter these drug characteristics. The drug part of the radiopharmaceutical can be almost every target that is characteristic of a disease or a target that is present on a particular cell (drug, antibody, enzyme, receptor, etc.). For example, in bone scan imaging, the ligand hydroxymethylene-diphosphonate (HDP) is the drug part that is preferentially taken up by osteoblasts. Consequently, by chemically attaching HDP to the radionuclide ^{99m}Technetium (^{99m}Tc), the radiopharmaceutical is transported to the bone for imaging purposes.

Radiopharmaceuticals are usually administered intravenously. Therefore, the patient is the source of the radioactivity, in contrast with radiology where the imaging devices emit X-rays or gamma-rays through the patient. The detection of gamma-rays (photons) emitted from the patient and transforming it into an image is the main principle of the camera systems used in nuclear medicine (the gamma-camera and the PET-camera).

5.2.2 Gamma-Camera

A decaying radionuclide emits photons in all directions. Different radionuclides produce different characteristic photons of a specific energy. ^{99m}Tc for instance predominantly emits photons with an energy of 140 keV, whereas radioactive iodine (^{131}I) emits predominantly 364 keV energy photons. A gamma-camera consists of one, two, or three heads with a detector that registers the impact of these photons. Each detector consists of a collimator, a scintillation crystal, a light guide, photomultiplier tubes, and a positioning and energy discrimination system.

A collimator is made of parallel strips of lead with multiple holes. The holes guide the individual photons towards the scintillation crystal. Photons that do not travel in the right direction are absorbed in the septa between the holes. Different types of collimators are available, depending on the energy level of the emitted photons. In the scintillation crystal the photons are absorbed and converted into a small flash of light. Brighter flash of light means a higher energy of the photon. This light reaches the photomultiplier tubes (PMTs), where it interacts with photocathodes and transforms into a photoelectron. This signal is amplified by electrodes or dynodes at increasing voltages, and eventually all the signals are combined in a

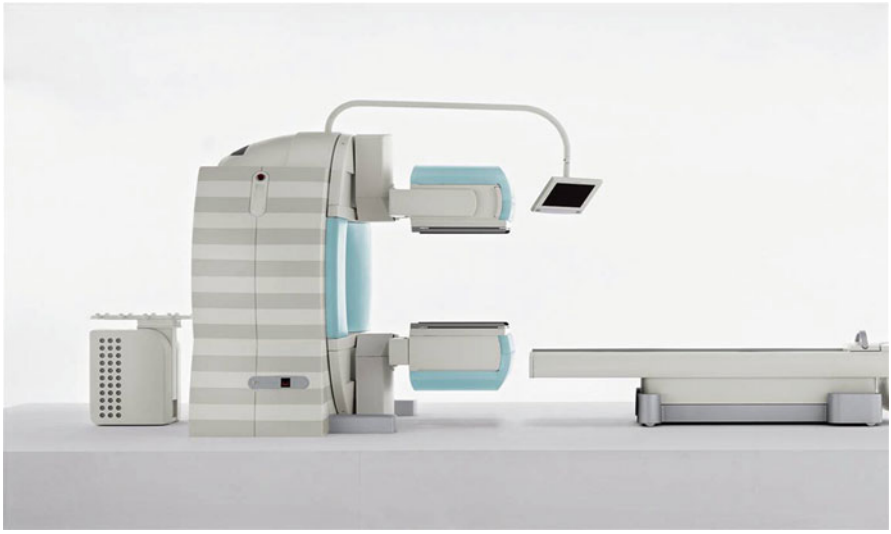

Fig. 5.1 SPECT-CT camera (Symbia T, Siemens Medical Systems)

position system, which gives each signal from the individual PMTs different weights to derive the position information of the photons in x- and y-direction. Only photons falling within a determined photopeak region are accepted. This described technique forms the basis of conventional planar nuclear medicine images.

5.2.3 SPECT(-CT)

The image contrast of conventional planar imaging is rather low due to overlying structures that may interfere with the region of interest. This limitation can be overcome by acquiring images from different angles (64–128°) in a circular manner around a patients and subsequently reconstruct a 3D-image. This technique is called Single Photon Emission Computed Tomography (SPECT). These collected imaged can be reconstructed into different slices and visualized in transverse, sagittal and coronal views. The resolution of this technique is around 8 mm.

Development in soft- and hardware led to the implementation of hybrid systems, combining SPECT with multi-detector computed tomography (CT). An example of a SPECT-CT camera is shown in Fig. 5.1. SPECT and CT are performed in an immediate sequential setting, without changing the position of patients. This allows us to correlate the (patho) physiological information with anatomical information, leading to better specificity rates and better diagnostic accuracy. Acquiring SPECT images takes approximately 20 min per part of the body (head and neck, thorax, abdomen etc.)

Fig. 5.2 PET-CT camera (mCT Biography 64, Siemens Medical Systems)

5.2.4 PET (-CT)

Positron Emission Tomography (PET) is another imaging tool to visualize various processes in the body. For this technique, radionuclides are used that emit a positively charged particle (a positron) to become stable. At the end of its kinetic energy (or at the end of its range, maximum 2,8 mm) the positron reacts with an electron. The masses of the positron and electron are transformed into energy ($E = mc^2$) forming two photons that are emitted with the same energy (511 keV) in exactly opposite directions. This process is called annihilation. This phenomenon is registered by a PET camera by using a ring detector around a patients, thereby registering the photons by opposite detectors and within a certain time window, to consider these two as one pair from the same annihilation process. New developments in software lead to a correction method for the time a photon needs to travel from its origin to the detector. This correction, called Time-of-Flight (TOF) has advantages for spatial resolution. The resolution of this technique is approximately 4 mm.

Nowadays, PET cameras are always combined with CT (PET-CT, see Fig. 5.2) with the same advantages as SPECT-CT. Moreover, costs are reduced (one imaging modality) and the one-stop-shop principle (one scan on one department instead of two scans on two departments) reduces waiting time for the patient. In contrast to SPECT-CT, where only a part of the body can be imaged, a patient can be imaged completely by moving in the PET-CT camera. A PET-CT scan of the body (head to mid-thigh) is nowadays performed in approximately 20 min.

5.2.5 *Radiation Issues*

The use of radioactive materials means that not only the tumor endures radiation, but also healthy organs and tissues. Furthermore, persons nearby should be protected from the radiation exposure. To put this in perspective: the annual radiation burden from background radiation by natural radiation sources in general is around 2–2.5 mSv. The radiation burden of a bone scan (including SPECT) using a radiopharmaceutical with an administered activity of 500 MBq is 2.3 mSv. For ^{18}F-fluorodeoxyglucose (^{18}F-FDG), the most often used PET radiopharmaceutical, the radiation burden is around 7.6 mSv (using 400 MBq). The radiation dose of a low dose CT is approximately 1.5 mSv. However, in contrast to the natural background radiation that is continuously present in our environment, the activity rate from diagnostically injected amount of a radiopharmaceutical decreases exponentially over time. The radiation burden for people nearby is calculated at a distance of 1 m and overall exposure is marginal compared to the natural background radiation. Another consideration when referring to the radiation exposure is the age of a person. The added risk decreases with increasing age. Consequently, young children are most susceptible to damage due to radiation exposure.

5.3 Bone Metastases from the Nuclear Medicine Point of View

Several diagnostic modalities are available for the detection of metastatic bone lesions. These include plain X-rays, CT scan and Magnetic Resonance Imaging (MRI). All these techniques, described elsewhere, are based on the anatomical characteristics of bone metastases and do not provide any information concerning the (patho) physiology or metabolic activity of evaluated lesions. Therefore, nuclear imaging modalities are valuable, not only in diagnosing bone metastases, but also in the differential diagnosis between metastases and other bone lesions or pathology. By applying specific radiopharmaceuticals, specific for a specific type of tumor, different biophysical and biochemical characteristics of bone metastases are depicted, helping physicians to establish an accurate diagnosis. In the following subchapters, the characteristics of different SPECT and PET radiopharmaceuticals are described and their role in detecting bone metastases is discussed.

5.4 Bone Scintigraphy

Bone scintigraphy is widely available and is a well established modality within nuclear medicine. It is one of the oldest techniques within nuclear medicine imaging with a clinical experience of almost 50 years. It still remains the

cornerstone of modern nuclear medicine imaging in the evaluation of bone metastases. Its sensitivity is high (>90 %); however, its specificity is rather limited.

5.4.1 ^{99m}Tc-Diphosphonates

The most commonly used radiopharmaceutical for the detection of bone metastases is ^{99m}Tc labelled with diphosphonates. Different forms exist, such as ^{99m}Tc-hydroxymethylenediphosphonate (^{99m}Tc-HDP), ^{99m}Tc-methyldiphosphonate (^{99m}Tc-MDP), and ^{99m}Tc-dicarboxypropane diphosphonate (^{99m}Tc-DPD) with slightly different kinetic qualities, all three being incorporated in the bone (hydroxyapatite deposition) by the activity of osteoblasts. The differences between these three diphosphonates are marginal, and all three can be used for bone scintigraphy, each of them showing high lesion-to-normal bone ratio. The factors that control accumulation of phosphonates in bone are the blood flow and the extraction efficiency, which in turn depends on capillary permeability, acid–base balance, parathyroid hormone levels, etc. Overall, about 50 % of the injected radiopharmaceutical accumulates in the skeletal system. The maximum bone accumulation takes place 1 h after injection and remains practically constant for up to 72 h.

5.4.2 Imaging Techniques and the Three Phases

Bone scintigraphy images the distribution in the skeletal system and can be performed in several ways:

- Limited bone scintigraphy or spot views (planar images of a preselected part of the body)
- Whole body bone scintigraphy (planar images of the entire skeleton in both anterior and posterior view)
- Single Photon Emission Computed Tomography (SPECT) combined with CT of a preselected part of the body
- Three phase bone scintigraphy (flow, bloodpool, and late planar images)

In oncology, the standard recommended technique is whole body scintigraphy, complemented by SPECT (CT) imaging if necessary. However, for best accuracy in single lesions and best differential diagnosis between benign and malignant lesions, a three phase bone scintigraphy may be the best choice. The first phase (or flow phase) is sort of an angiogram, performed dynamically for 2 min directly after administration, over the part of interest. In this phase, the radiopharmaceutical is delivered to the surface of the bone. Increased bone uptake is seen in areas with high blood flow. The second phase (also called blood pool phase) is a soft tissue phase, performed directly after the first phase (2–5 min after injection). The third phase

(or static/planar phase) represents the situation in which the radiopharmaceutical has been absorbed into the hydroxyapatite matrix of the bone and is usually performed 3 h after administration. A three phase bone scintigraphy characterizes the vascularization of a process as well as its metabolic activity and may help distinguishing bone metastases from infectious processes, recent fractures and primary bone neoplasms.

5.4.3 Role of Bone Scan in Diagnosing Bone Metastases

The sensitivity of bone scintigraphy is determined by the level of osteoblastic activity. This means that in case of osteoblastic metastases a bone scan will reveal highly intense uptake in the metastases. In case of osteolytic metastases, normal bone tissue surrounding metastatic lesions will normally respond with compensatory osteoblastic activity, which will also lead to highly intense uptake of the radiopharmaceutical. Only in case of slowly growing osteolytic metastases there can be absence of an osteoblastic reaction that would render the metastases undetectable through bone scanning. The incidence of lytic, blastic, and mixed type of bone metastases is different in various tumor types. Bone metastases of bladder, kidney, and thyroid cancer and lesions of multiple myeloma are invariably lytic. Cold spots on the bone scan, i.e. focal absence of activity, is typically observed in patients with multiple myeloma with large osteolytic lesions. Blastic lesions are frequently seen in prostate and breast cancer, and occasionally in lung, stomach, pancreas, and cervix carcinomas [1].

The radiopharmaceutical is excreted by the kidneys and the bladder and these organs are normally visualized on a bone scan. However, in some cases there is extremely high uptake in the bones and absence of activity in kidneys and bladder. This is called a superscan, suggestive for metastatic disease in the entire skeleton. Three examples of a bone scan, made to visualize or exclude bone metastases, are shown in Fig. 5.3.

The major limitation of the interpretation of bone scans is the low specificity. It may be difficult to distinguish bone metastases from degenerative changes, inflammatory processes, traumata, mechanical stress, Paget's disease, fibrous dysplasia or benign or malignant primary bone tumours [2].

A recent meta-analysis of the role of bone scintigraphy in the diagnosis of bone metastases from various malignancies showed a pooled sensitivity of 86 % and a specificity of 81 % [3]. A meta-analysis only in breast cancer showed a pooled sensitivity of 87 % and a specificity of 88 % [4]; in lung cancer a pooled sensitivity of 86 % and specificity of 88 % was reported [5]. Even-Sapir et al. reported that for the detection of bone metastases in patients with high-risk prostate cancer bone scintigraphy had a low sensitivity of 70 %, a specificity of 57 % and a positive and negative predictive value of 64 % and 55 % respectively. However, by using SPECT, the sensitivity was improved to 92 %, the specificity to 82 %, and the positive and negative predictive values reached 86 % and 90 % respectively [6]. Combining SPECT with CT may offer even better results.

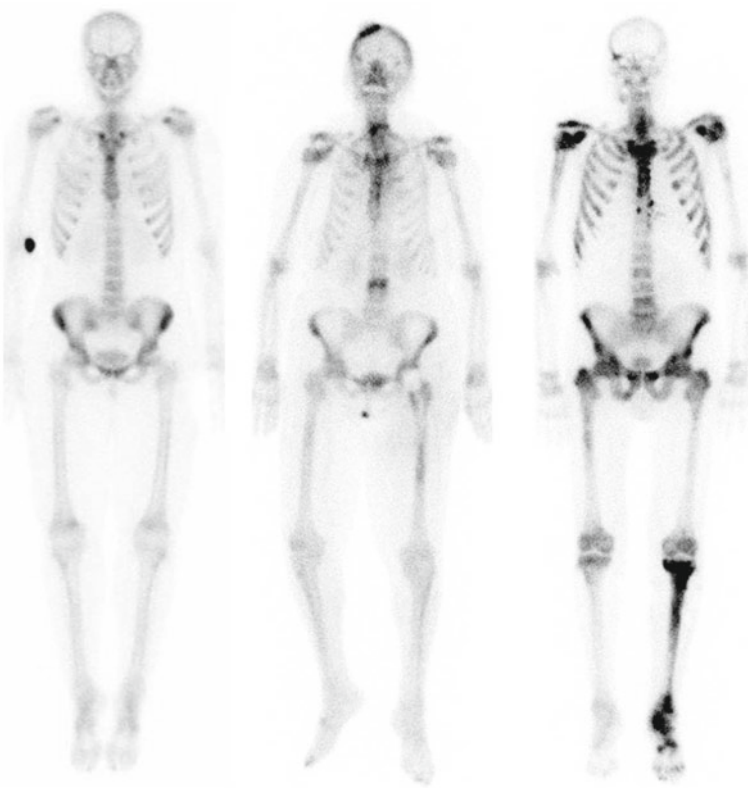

Fig. 5.3 Three examples of a bone scan. *Left*: normal bone scan (administration artifact at the elbow on the *right side*). *Middle*: metastasis on the skull and in a lumbar vertebra. *Right*: multiple metastases, no visualization of the kidneys, so called "superscan"

5.5 Other SPECT Radiopharmaceuticals

The following SPECT radiopharmaceuticals are unspecific for bone metastases. They are specific for certain tumor types, depicting also bone disease if present. Because of their non-specificity to bone, it may be difficult to localize exactly the location or to distinguish metastatic bone lesions from localization in surrounding soft tissues. Therefore, SPECT-CT should be performed in these cases.

5.5.1 ^{123}Iodine and ^{131}Iodine

^{123}Iodine (^{123}I) and ^{131}Iodine (^{131}I) accumulate in the thyroid where it is built into thyroid hormone and stored for later secretion. Because of this characteristic it can be used to identify well-differentiated (papillary and follicular) thyroid tumours and

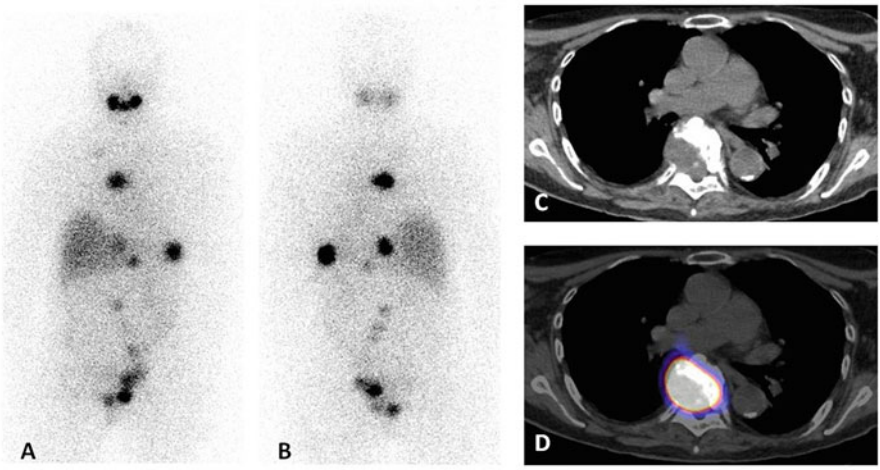

Fig. 5.4 ^{131}I post therapy scan of a patient with follicular thyroid carcinoma. Planar images (**a**) anterior view, (**b**) posterior view): bone metastases in the vertebral column and in costa 11 on the *left side*. (**c**) CT image with destruction of Th6. (**d**) Fusion SPECT/CT image with high uptake of ^{131}I in Th6

their metastases. ^{123}I is a gamma-emitter with a half life of 13 h and can be used for diagnostic reasons before treatment with high dose ^{131}I. The latter emits beta-rays for therapeutic purposes and gamma-rays which makes imaging possible. The half-life of ^{131}I is 8 days. Theoretically a high treatment dose provides a better sensitivity as compared to the low diagnostic dose of ^{123}I, but several researchers found no differences between the diagnostic accuracy of ^{123}I pre-treatment scanning with low dose and ^{131}I post-treatment scanning with high dose [7, 8].

For the initial diagnostic work-up for nodule investigation or thyroid cancer, ^{123}I or ^{131}I scanning has no role anymore, since ultrasound and fine needle aspiration (FNA) biopsy are standard diagnostic procedures. Similarly, the follow-up of recurrent disease is done by following thyroglobulin levels instead of $^{123/131}$I scanning. However, in some cases diagnostic scanning with $^{123/131}$I is worthful, especially when searching for metastases. Both isotopes may also be used before ablation therapy, to reveal the amount of thyroid remnant after surgery or to see if there are metastases. Furthermore, after treatment with ^{131}I because of differentiated thyroid cancer, a post-treatment scan (7–10 days after therapy) is always performed (Fig. 5.4).

Even though these radiopharmaceuticals are highly specific for thyroid tumours, scintigraphy is associated with a poor signal-to-noise ratio. Upon the physiological accumulation in the salivary glands, liver, spleen, intestines, kidneys and bladder, little to no accumulation is seen in structural tissues which makes if often difficult to identify the exact localization of (bone) metastases. SPECT-CT should therefore be performed to exactly localize metastatic (bone) disease in patients with thyroid tumours.

5.5.2 ^{123}I- and ^{131}I-MIBG

Metaiodobenzylguanidine (MIBG) is a noradrenalin analogue which accumulates in neurosecretory granules of adrenergic tissue. This makes it suitable for imaging neuroendocrine tumours, such as phaeochromocytomas, carcinoid, and paragangliomas. In children, it may also be used for the diagnosis and staging of neuroblastoma. ^{123}I-MIBG is only used for diagnostic purposes, whereas ^{131}I-MIBG (since ^{131}I is a beta- and gamma-emitter) may be used for both diagnosis and therapy. The advantage of $^{123/131}$MIBG is its high specificity for tissue characterization and reported sensitivities and specificities are high. In detecting phaeochromocytomas and neuroblastoma, the diagnostic accuracy of MIBG scintigraphy is superior to other imaging modalities [9]. For the detection of other neuroendocrine tumours, sensitivity is lower, and other imaging modalities may be preferred. The specificity for neuroblastoma is mentioned to be 84 %. However, since other neuroendocrine tumours in childhood are rare, a positive MIBG scan is nearly diagnostic for a neuroblastoma [10].

As described earlier, the imaging characteristics of $^{123/131}$I are poor, not showing accumulation in structural tissues, rendering the exact localization of metastases difficult. Fusion of the MIBG scintigraphy (SPECT) with a morphological imaging modality (CT) improved the diagnostic value [11] with the main advantage being the identification of normal distribution of the radiolabelled MIBG in organs such as intestines and renal system, leading to a reduction of false positive results. Also, better differentiation of bone metastases from a local recurrence of a phaeochromocytoma, was possible.

The use of MIBG scintigraphy purely to diagnose bone metastasis is still doubtful. The paper by Zuetenhorst et al. directly compared MIBG scintigraphy with the bone scan in carcinoid tumours with bone metastases. The bone scan outperformed MIBG scintigraphy, showing multiple bone lesions in all patients, whereas MIBG scintigraphy only identified lesions in 22 % [12].

5.5.3 Radiolabelled Somatostatin Analogues

Neuroendocrine tumours frequently express a high density of somatostatin receptors, which is exploited by nuclear medicine imaging techniques using somatostatin analogues. These analogues have been developed since somatostatin itself has a short plasma half life (approximately 3 min). For most somatostatin analogues, internalization of the ^{111}In-octreotide complex with residualization of the ^{111}In label (gamma-emitter, half-life 2.8 days) is the most likely mechanism accounting for the good scintigraphic tumor-to-background ratio observed 24 h after injection [13]. Based on the high receptor expression, somatostatin receptor scintigraphy (SRS) provides important information on tumour localization and metastases of many neuroendocrine tumours. Best results are published in paragangliomas and neuroendocrine gastrointestinal tumours (87 % and 88 % sensitivity) [9]. Of course,

functional mapping by using SPECT/CT was reported as leading to higher diagnostic accuracy [14]. However, SRS failed to detect a large proportion (50 %) of metastatic bone lesions that were detected by bone scintigraphy [12]. More recently other radiolabelled somatostatin analogues have been successfully used, such as ^{99m}Tc-EDDA-HYNIC-TOC and ^{99m}Tc-Depreotide.

5.6 PET Radiopharmaceuticals

PET has two major advantages in comparison to SPECT. First of all, the better spatial resolution (4 mm compared to 8 mm), allows the investigators to see smaller structures. Secondly, PET offers the possibility of absolute quantification, leading to an improved sensitivity of the follow-up of metastatic lesions. PET imaging allows us to diagnose and monitor not only the number and size of pathological lesions, but also the amount of uptake per lesion. This uptake intensity is calculated by using the Standardized Uptake Value (SUV). It represents the tissue activity within a region of interest corrected for the injected activity and for patient's weight or lean body mass [15]. This quality makes PET imaging useful to monitor response to therapy and/or disease progression [2].

5.6.1 ^{18}F-Fluoride

^{18}F-fluoride is a positron emitter specific for bones since it images any form of calcification. The radiopharmaceutical itself was already used in the 1950s for bone scintigraphy, using an old general-purpose rectilinear scanner for imaging purposes. It was abandoned due to the fast introduction of ^{99m}Tc, the development of diphosphonates, and the introduction of the gamma-camera. The "normal" bone scan (labelled diphosphonates) became the gold standard in nuclear bone imaging. Since the introduction of high resolution PET cameras in the early 1990s, ^{18}F-fluoride is reintroduced into nuclear medicine imaging.

Fluoride ions enter the extracellular fluid of bone by diffusion through capillaries, leading to a slow exchange with hydroxyapatite crystals and the formation of fluoroapatite [2]. The faster blood clearance of ^{18}F-fluoride and the twofold higher uptake in developing bone cells of fluoride, makes it possible to image earlier (1 h after injection), and leads to better ratios between uptake in bone with faster turn-over and normal bone [16].

The characteristics of ^{18}F-fluoride are in general identical to the diphosphonate complexes. Both radiopharmaceuticals are normally symmetrically distributed throughout the entire skeleton. ^{18}F-fluoride deposition favours the axial (spine and pelvis) over the appendicular (shoulder girdles and limbs) skeleton and is greater for joints than for shafts of long bones [17]. The route of excretion is through the urinary tract. In accordance with the ^{99m}Tc-diphosphonate bone scan, the degree of uptake does not differentiate benign from malign. However, the pattern may be

suggestive for a specific diagnosis. Still, physiological uptake may be more variable in ^{18}F-fluoride due to higher resolution of the PET/CT camera.

Limitations of this technique are the high costs (five times higher compared to the bone scan with diphosphonates) and the non-possibility to perform flow and blood pool imaging. A study performed by Even-Sapir et al., reported a sensitivity for bone metastases of 100 %, a specificity of 62 %, a positive predictive value of 74 %, and a negative predictive value of 100 %. By applying CT to the PET scan all afore mentioned parameters were improved to 100 % [6].

At the moment, the classical bone scan with diphosphonates is the gold standard for the detection of bone metastases. However, ^{18}F-fluoride PET is at least as sensitive and specific and should be considered for the individual patient although most bone metastases can also be detected with ^{18}F-FDG.

5.6.2 ^{18}F-FDG

The glucose analogue ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is used extensively in various malignant and infectious diseases, and is also a useful radiopharmaceutical for bone imaging. Processes with high glucose turnover show a high uptake of FDG, because of its intracellular accumulation. FDG enters the cell by using several glucose transporters (mainly GLUT-1 and GLUT-3) that are located on cellular membranes. After phosphorylation of normal glucose by hexokinase, glucose-6 phosphate is formed and further metabolized by glycolysis. On the contrary, FDG is phosphorylated to FDG-6-phosphate, which cannot be glycosylated and is therefore retained in the cell. Malignant cells have an increased glucose turn-over, which is related to a higher density of GLUT-1 and GLUT-3 transporters on the cell membrane and to a higher concentration of hexokinase. This leads to a favourable signal-to-noise ratio which has made ^{18}F-FDG an extensively used radiopharmaceuticals for all kind of malignancies.

The high glucose metabolism is related to growth, which makes ^{18}F-FDG especially useful for aggressive, fast growing, less differentiated tumours and their (bone) metastases, such as lung cancer, melanoma, lymphoma, breast cancer, sarcomas etc. Less FDG-avid tumours are the slow growing, well-differentiated tumour types, such as prostate carcinoma, neuroendocrine tumours, and well-differentiated thyroid cancer. However, every form of these well-differentiated tumours may turn into FDG-avid tumours once they dedifferentiate.

Before undergoing a ^{18}F-FDG PET scan, patients have to fast 4–6 h before the administration of the radiopharmaceutical. This fasting period stimulates the uptake of FDG into the organs of interest. In a ^{18}F-FDG scan made directly after eating, all the FDG accumulates in the muscles, thereby hindering correct image interpretation. The blood glucose level should be <10 mmol/L to increase sensitivity. Physiological uptake is seen in the brain and in the left ventricle of the heart, and sometimes in the intestines. Excretion is by the urinary tract. To avoid uptake in muscles, patients have to lay quiet and are not allowed to talk during the waiting time, which is 1 h after injection.

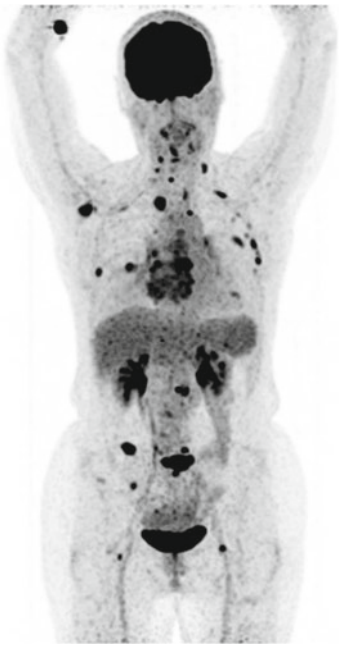

Fig. 5.5 ^{18}F-FDG PET of a patient with metastasized breast cancer showing multiple lesions in the bone and in mediastinal lymph nodes. Physiological uptake is seen in the brain, excretion via kidneys and bladder

As with bone scans, specificity is the limiting factor of ^{18}F-FDG, since a variety of processes may show a high glucose metabolism. In the bone, such processes may include infections, loosening of prosthesis, benign bone tumours etc. The advantage of ^{18}F-FDG PET over bone scintigraphy is that is also provides information on soft-tissue metastases (combined with CT). Secondly, by calculating SUV, better differentiation is possible between malignant and benign diseases. An example of an ^{18}F-FDG PET/CT is shown in Fig. 5.5.

5.6.3 ^{18}F-FLT

The nucleoside analogue 3-deoxy-3-[^{18}F]fluorothymidine (^{18}F-FLT) is used to image tumour cell proliferation. The uptake of FLT relies on the thymidine kinase 1 (TK1) enzymatic activity and thus on DNA synthesis. ^{18}F-FLT PET is mainly used to diagnose bone marrow diseases [18]. For imaging bone metastases, FLT is outperformed by ^{18}F-FDG [19].

5.6.4 ^{11}C-Choline

Since FDG is not taken up in huge amounts in slow growing well-differentiated tumours, it is not the radiopharmaceutical of choice in diagnosing and staging prostate cancer. Instead of ^{18}F-FDG, ^{11}C-Choline is used in the imaging of nodal

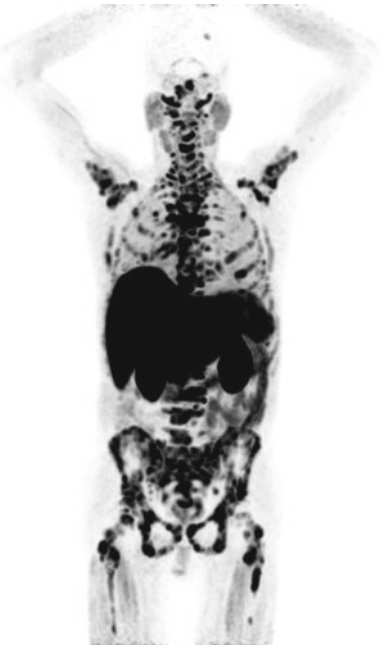

Fig. 5.6 ^{11}C-Choline PET scan of a patient with prostate carcinoma showing multiple bone metastases and probably bone marrow invasion

metastases from prostate cancer as well as in the imaging of metastatic bone disease (Fig. 5.6). It was found that in malignancies there is a high intracellular trapping of phosphatidylcholine (PC) together with an up regulation of choline kinase, an enzyme that is responsible for the synthesis of PC. Consequently, by labelling choline with ^{11}C, it enables imaging of PC trapped in malignant cells.

Another reason for the superiority of ^{11}C-Choline over ^{18}F-FDG in imaging prostate cancer is the low urinary clearance and therefore its low concentration in the bladder. The use of ^{18}F-FDG is associated with higher urinary clearance and a high bladder activity that obscures the imaging of the prostate. However, imaging with ^{11}C-Choline has also limitations. Benign prostatic hypertrophy also gives a high choline activity. Discrimination between benign and malignant lesions is not possible, also not by using SUV calculations. For patients with biochemical recurrence after initial treatment of the primary tumour, ^{11}C-Choline is an accurate technique, identifying more abnormalities suspect for recurrent disease or metastases than ^{18}F-FDG [20].

Currently, Choline is also labelled with ^{18}F and used for imaging purposes. Results in sensitivity and specificity are similar. However, ^{18}F is excreted by the urinary tract, so bladder emptying or placement of a catheter is necessary to visualize the prostate region.

In summary, ^{11}C-Choline PET (-CT) is not an appropriate imaging technique for accurate T-staging of prostate cancer prior to radiotherapy. However, it holds great potential as a single step diagnostic procedure of lymph nodes and skeleton, which could also facilitate radiotherapy treatment planning [21].

5.6.5 ^{11}C-Methionine

Cellular proliferation is associated with protein synthesis. Since amino acids are the natural building blocks of proteins, avid uptake of these precursors is a normal feature of rapidly proliferating cells. Amino acid transport and protein synthesis are increased in most types of tumours compared to normal healthy tissue. The most frequently used radiolabelled amino acid is 1-[methyl-^{11}C]-methionine (^{11}C-Methionine), primarily reflecting the trans-membrane transport by the sodium-independent L-transporter into cells [22]. ^{11}C-Methionine is mainly used to image brain tumours and metastases; however it also has a place in imaging prostate cancer and metastases. For diagnosing the primary tumour, ^{11}C-Methionine was found equal to ^{18}F-FDG [23]. In a study involving only a small group of patients it was reported that both sensitivity and specificity for imaging metastases was 70 % (both higher than ^{18}F-FDG) [20]. This was also noticed in another study reporting ^{11}C-Methionine was more effective than ^{18}F-FDG for detecting bone metastases (69.8 % of metastatic bone lesions found with ^{11}C-Methionine, vs 48.3 % with ^{18}F-FDG). The authors assumed that the increased sensitivity of ^{11}C-Methionine may be the result of differences in tumour metabolism between patients, or a time-dependent metabolic cascade in metastatic prostate cancer, with initial uptake of ^{11}C-Methionine in dormant sites followed by increased uptake of ^{18}F-FDG during progression of the disease [24].

5.6.6 ^{18}F-DOPA

The metabolic pathways by which neuroendocrine tumours synthesize peptides and the intracellular processes which are essential to sustain production of these peptides are ideal candidates for the development of radiopharmaceuticals specific for neuroendocrine tumours [9]. The most important one, in the catecholamine pathway, is 6-[^{18}F]-L-3,4-di-hydroxyphenylalanine (^{18}F-DOPA). Premedication with the decarboxylase inhibitor carbidopa is used to reduce the urinary extraction, resulting in lower renal and bladder activity and a higher availability of DOPA for neuroendocrine tumour cells. ^{18}F-DOPA PET yields a very high sensitivity in the detection of carcinoid tumours, paragangliomas and phaeochromocytomas (higher than MIBG scintigraphy and SRS). With the application of ^{18}F-DOPA for all metastatic lesions, including bone lesions, sensitivities ranging between 65 % and 100 % and specificities between 75 % and 100 % are reported [25]. In cases of dedifferentiation of the tumour and its metastases the intensity of the lesions by using ^{18}F-DOPA may decrease, whereas the intensity increases when ^{18}F-FDG is used.

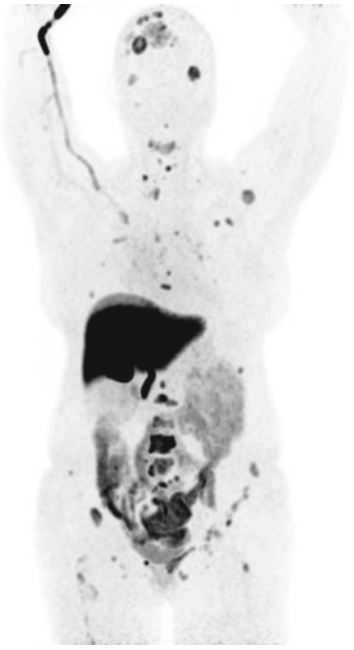

Fig. 5.7 ^{18}F-FES PET scan of a patient with breast cancer showing multiple bone metastases. Physiological uptake in the liver, excretion via gallbladder, bile ducts and intestines

5.6.7 ^{18}F-FES

Approximately 75 % of breast tumours express the oestrogen receptor (ER) at diagnosis. Knowledge of the ER status of a patient has important consequences for treatment decision making, since patients with ER-positive tumours are likely to respond to antihormonal therapy. During metastatic disease, evaluation of ER status is also important to determine changes in receptor expression. Discordant ER expression between primary tumour and metastatic lesions occur in 18–55 % of patients. PET scanning with 16α-[^{18}F]-fluoro-17-β-estradiol (^{18}F-FES) provides a unique method to noninvasively obtain molecular information about ER expression (Fig. 5.7). Several studies have shown that ^{18}F-FES-PET can reliably detect ER-positive tumour lesions and correlation with immunohistochemical scoring was well. Low ^{18}F-FES uptake was a strong predictor for failure of antihormonal therapy. ^{18}F-FES-PET may be used in breast cancer to give up-to-date information about the ER expression in known metastases. Furthermore, it may be used as valuable additional diagnostic tool when standard work-up is inconclusive [26].

5.6.8 ^{18}F-FDHT

^{18}F-fluoro-5α-dihydrotestosterone (^{18}F-FDHT) is a labelled analogue of the major ligand for the androgen receptor (AR), dihydrotestosterone. The androgen receptor is over expressed in 90 % of primary prostate tumours and plays a major role in tumor growth. ^{18}F-FDHT could be used in the same diagnostic questions as in ^{18}F-FES, i.e. to see if there are metastases, to solve diagnostic dilemmas and give up-to-date information about the AR expression in known metastases. At this moment, only a few studies with ^{18}F-FDHT PET are available, but this radiopharmaceutical seems very useful in deciphering the role of AR in resistant and progressive metastatic disease and in assessment of treatment [27].

5.6.9 ^{68}Ga Labelled Somatostatin Analogues

^{68}Gallium (^{68}Ga) is a generator-produced radionuclide that can be chelated with DOTA to form a stable complex with somatostatin analogues. Several variants have been tested and compared to other imaging modalities, e.g. [^{68}Ga-DOTA^{0}, Tyr^{3}] octreotide (^{68}Ga-DOTATOC) and [^{68}Ga-DOTA,1-nal^{3}]octreotide (^{68}Ga-DOTANOC), all sharing excellent image quality with better spatial resolution compared with the imaging of SPECT analogues. Some authors state that PET/CT with ^{68}Ga-labelled somatostatin analogues will become the image modality to be used for SRS in the future [28]. These peptides could also be labelled with ^{177}Lutetium (^{177}Lu) or ^{90}Yttrium (^{90}Y) for therapy. A recent paper showed that bone metastases of neuroendocrine tumors have a good prognosis if well diagnosed and treated [29].

5.7 Nuclear Medicine Characteristics in Prostate Cancer

Prostate cancer cells metastasize mainly through the haematogenous route, and despite dissemination to multiple organs, growth preferentially occurs in the bone and particularly in the red marrow of the axial skeleton. The vertebral column is the most common site for prostate cancer cells to metastasize. Other common sites are the pelvis, ribs, and—to a lesser extent—the skull and extremities.

Prostate cancer cells release prostate specific antigen (PSA), a serine protease that cleaves the parathyroid hormone-related peptide that is responsible for tumour-induced bone resorption. PSA may also activate osteoblastic growth factor release in the bone microenvironment during the process of bone metastases formation. Increased bone turn-over is also caused by bone-derived factors such as bone morphogenetic proteins (BMPs). Moreover, there is a focal imbalance between osteoblastic and osteoclastic activity. All this may lead to a vicious cycle which results in the development of osteoblastic metastases [30].

For nearly 40 years, bone scintigraphy with ^{99m}Tc labelled diphosphonates has been the 'reference standard' to detect skeletal metastases, due to its availability and low cost.

Not all patients with prostate cancer should undergo a bone scan. Routine use of a bone scan is omitted when the serum PSA level is <10 ng/mL, and may also be not necessary for those with PSA levels between 10 and 20 ng/mL, when they have T1 disease and Gleason scores of 6 or lower [31]. Almost all patients with a PSA >100 ng/mL have a widespread skeletal involvement. Bone scintigraphy should also be performed when levels of alkaline phosphatase (ALP) are >90U/L [32]. In summary, bone scintigraphy should be performed in patients with high-risk cancer, elevated serum ALP levels, bone pain, or equivocal bone lesions on other imaging modalities. Serial scans are often used to assess the extent of bone involvement and the effectiveness of therapy.

PET radiopharmaceuticals may also be of value in detecting bone metastases in patients with prostate cancer. The most commonly used one, ^{18}F-FDG, has been shown to be challenging in the imaging of prostate cancer. The glucose utilization in well-differentiated prostate cancer is often too low to visualize the metastases. Moreover, the uptake in the primary tumour is difficult to visualize, due to its proximity to the bladder that shows intense accumulation of FDG. The slow rates of prostatic tumour growth are associated with low rates of glycolysis and therefore a low tumour uptake, which is also evident in metastatic bone disease [33]. ^{18}F-FDG-PET was shown to be less specific than planar bone scintigraphy in prostatic bone metastases. Prostate cancer is the "classic" malignancy with false-negative results on ^{18}F-FDG-PET [34].

Other PET radiopharmaceuticals that are used for the assessment of patients with bone metastases from prostate cancer are ^{11}C- or ^{18}F-labelled choline, ^{18}F-fluoride, and ^{18}F-FDHT. ^{18}F-fluoride was reported to be highly sensitive in detecting bone metastases [35, 36] and has been shown to be more sensitive and specific than the bone scan in detecting bone metastases [6]. Increased cell proliferation in tumours and up regulation of choline kinase in cancer cells are suggested as two possible mechanisms for increased choline uptake in prostatic cancer cells. ^{18}F-Choline may be superior for early detection of metastatic bone disease (especially for bone marrow involvement) [2]. This statement should, however, be collaborated by other studies. In patients with negative suspicious sclerotic lesions (after ^{18}F-Choline PET), a second bone-seeking agent such as ^{18}F-fluoride is recommended [37]. ^{18}F-FDHT may be used when current knowledge of androgen receptor (AR) expression is necessary, or to solve diagnostic dilemmas that conventional imaging techniques or imaging techniques with unspecific radiopharmaceuticals cannot solve.

5.8 Nuclear Medicine Characteristics in Breast Cancer

Metastases in bone occur often in patients with breast cancer: In 26–50 % of patients bone is the first site of metastasis [38]. A high percentage of patients (30–85 %) with metastatic breast cancer will develop bone metastases during the course of the disease [39]. In most cases of metastatic bone lesions from breast cancer, mixed

forms (both osteolytic and osteoblastic) are present. Breast cancer preferentially metastasizes to vertebrae and the pelvis, followed by ribs, skull and femur [40].

The detection rate of metastatic bone disease by using bone scintigraphy is 0.82 % in patients with stage I disease, 2.55 % in stage II, 16.75 % in stage III, and 40.52 % in stage IV [41, 42]. On the basis of these results routine screening with a bone scan in early stage breast cancer (stage I and II) is not recommended. The assessment of the response of bone metastases to therapy by solely following the changes in the intensity of bone scans is also not recommended [43]. For this purpose other imaging modalities (CT or MRI) may be better suitable.

In a meta-analysis, the value of bone scintigraphy and ^{18}F-FDG-PET was evaluated in detecting bone metastases in patients with breast cancer. ^{18}F-FDG-PET was found to have a higher specificity than a bone scan and proved to be superior to bone scintigraphy when used as a confirmatory imaging modality [44]. In another study it was reported that the morphologic appearance of the metastases influences their detection. Patients who had lytic or mixed type metastases had a higher number of lesions identified by using ^{18}F-FDG, whereas in patients with sclerotic lesions the bone scan found a larger number of metastases [2].

As in prostate cancer, ^{18}F-fluoride PET has the potential to replace the bone scan for routine patient assessment of breast cancer. When up-to-date knowledge of the estrogen receptor (ER) status is necessary or to solve diagnostic dilemmas that other imaging techniques cannot solve, ^{18}F-FES could be the radiopharmaceutical of choice.

5.9 Nuclear Medicine Characteristics in Lung Cancer

The role of bone scintigraphy in patients with lung cancer has changed over the course of time. Advances in other imaging techniques (especially ^{18}F-FDG PET/CT) have resulted in an improved accuracy of staging newly diagnosed lung malignancies. In the past, bone scintigraphy was commonly used as a routine staging technique for non small cell lung cancer (NSCLC) patients. Since the routine availability of PET/CT imaging, evidence of metastatic disease is often first identified in lymph nodes (hilar or mediastinal) or in distant organs (liver, adrenal glands), thereby obviating the need for bone scintigraphy. Furthermore, ^{18}F-FDG PET/CT is also able to locate bone metastases with high sensitivity.

A study in 100 patients with NSCLS compared ^{18}F-FDG-PET with conventional imaging modalities for staging. Ninety of the one hundred patients also underwent bone scintigraphy. In total, 12 patients were diagnosed with metastatic bone disease. ^{18}F-FDG-PET identified bone metastases in 11 patients (92 %), only missing a bone metastasis located in the distal femur in 1 patient. That part of the body was not assessed during the study. The bone scan revealed metastatic bone lesions in only 6 (50 %) patients. The authors stated that the use of bone scintigraphy for staging NSCLC patients can be replaced by ^{18}F-FDG-PET [45]. Nowadays, ^{18}F-FDG-PET/CT is indeed routinely used for staging lung cancer patients. There is no need any more for the bone scan in these patients.

5.10 Nuclear Medicine Characteristics in Other Solid Tumours

Various radiopharmaceuticals are available to stage neuroendocrine tumours, $^{123/131}$I-MIBG and somatostatin analogues for SPECT, ^{18}F-FDG and ^{18}F-DOPA for PET. The choice between all these options remains difficult. In carcinoid, reported sensitivities for ^{18}F-DOPA-PET are high, ranging from 65 % to 100 % and this technique seems to be an excellent staging method. To localize tumours causing catecholamine excess (most often caused by phaeochromocytomas), ^{18}F-DOPA PET was found superior to ^{123}I-MIBG scintigraphy and CT/MRI [46]. ^{18}F-FDG PET may be useful when tumours are dedifferentiated. Using ^{18}F-DOPA of ^{18}F-FDG is also dependent on the differentiation grade of the tumour. In patients with more aggressive and fast growing tumours, ^{18}F-FDG performs better than ^{18}F-DOPA and vice versa.

In well-differentiated thyroid cancer, ^{131}I is still the radiopharmaceutical of choice, since it is possible to diagnose and predict therapeutic outcome. However, sometimes thyroglobulin levels are rising without any iodine uptake on the post therapy scan. Then ^{18}F-FDG PET or ^{99m}Tc-HDP may be useful, to search for dedifferentiated metastases. In medullary thyroid carcinoma, ^{18}F-DOPA PET imaging has been reported to perform equal or better than the reference imaging techniques. In this cancer type, there is a suspicion that one may have to rely on the calcitonin doubling-time to select the optimal PET radiopharmaceutical for the individual patient. Again, in more aggressive tumours (rapidly elevating calcitonin) ^{18}F-FDG may perform better, in slow growing types ^{18}F-DOPA is the radiopharmaceutical of choice.

Another cancer type is hepatocellular carcinoma (HCC), one of the most common cancers worldwide. Normally these patients are preoperatively staged by bone scintigraphy and CT of the chest in search for metastases. A recent study, however, showed that only a very minor percentage of patients (2 %) had positive findings on the bone scan. Recurrence rate and disease-free and overall survival showed no significant differences between patients with and without preoperative baseline bone scintigraphy. In conclusion, the authors state that there is no justification for routine preoperative bone scintigraphy to detect asymptomatic skeletal metastases in patients with resectable HCC [47].

5.11 Conclusions

Many radiopharmaceuticals are available and helpful for the diagnosis of bone metastases. Bone scintigraphy is still the nuclear medicine imaging method of choice in many malignancies and has been used for many years with good results. However, new emerging radiopharmaceuticals (SPECT and PET) are developed, specific for a certain type of cancer, and may also be used and may even—in some cancer types—replace bone scintigraphy. In general, PET radiopharmaceuticals are

better to use than SPECT radiopharmaceuticals, since PET offers better spatial resolution and quantification is possible. Clinician and nuclear medicine physician have to work together, to use the best radiopharmaceutical for the individual patient leading to the best diagnostic accuracy.

The recent developments in soft- and hard-ware led to the introduction of hybrid camera systems, combining SPECT and PET with CT. All reports in literature point out that taking the (patho) physiology and anatomy together is essential for the field of nuclear medicine. Reported sensitivities, specificities, and diagnostic accuracies with the use of these new camera systems are better than before. For the patient it also has advantages: imaging can be performed earlier, is faster, and the patient only has to come once. Furthermore, the integrated reports of the radiologist and nuclear medicine physician should make it easier for the clinician to understand what is found.

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Chapter 6
Bone Biomarkers in Research and Clinical Practice

Janet E. Brown, Liang Zeng, and Caroline Wilson

Abstract Biomarkers as tools for aiding diagnosis, for identifying patients at risk, for monitoring response to therapy and for use as surrogate end points in clinical trials are increasingly being used across a range of medical specialties. Bone biomarkers (often simply called bone markers) are assuming increasing importance in the management and understanding of conditions which involve disturbance of bone metabolism, such as osteoporosis and metastatic bone disease and can reflect underlying changes in pathology or response to treatment, well in advance of such changes being detectable by imaging methods. Improvements in the understanding of the mechanisms underlying both normal bone metabolism and metastatic bone disease have led to a variety of potential bone biomarkers. Some have already demonstrated their utility in clinical studies, though more validation is needed before their routine use in clinical practice. In this chapter, we review the bone biomarkers associated with bone turnover and consider the evidence from clinical studies for their potential in the future management of patients with metastatic bone disease.

Keywords Bone metastases • Bisphosphonates • Bone markers • Radiotherapy

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6.1 Introduction: Why Bone Biomarkers?

Biochemical markers (biomarkers) are increasingly being used in the management of patients across a wide range of medical specialties. A biomarker is an objective measurement that acts as an indicator of normal biological processes or pathological processes or pharmacological response to therapeutic intervention. Biomarkers are valuable tools for aiding diagnosis, for identifying groups of patients at risk, for monitoring response to treatment and for use as surrogate end points in development of new therapies. Ideally, a biomarker should be capable of rapid and simple quantitative measurement in easily obtained biological fluids such as blood or urine. As such, they can often give valuable information on the change of disease status (for example in indicating response to therapy), before such changes become clinically evident.

Biomarkers are often proteins or peptides and their practical value is increased when they can be routinely and accurately measured in biological fluids. Whilst biomarkers are often discovered empirically, the confidence that such a biomarker will prove to be clinically useful is increased if it is biologically plausible, i.e. if there is a logical, scientific rationale that it should be increased (or reduced) in the relevant disease state.

Bone biomarkers (often simply called bone markers) are assuming increasing importance in the management and understanding of conditions which involve disturbance of normal bone metabolism, such as osteoporosis and metastatic bone disease. Pathological changes in bone are often slow to become apparent symptomatically or to become evident by imaging, for example on plain X-ray, but there is growing evidence, considered in this chapter with respect to bone metastases, that bone marker changes reflect underlying changes in pathology or response to treatment, well in advance of such changes being detectable by imaging methods. Thus, bone marker measurements are complementary to imaging methods and therefore can potentially be used to influence therapeutic and other patient management decisions at an early stage. However, the most appropriate applications of bone markers are still being evaluated and further validation through prospective studies are required before they become fully established in routine clinical practice.

In this chapter we consider the bone biomarkers which are most developed in terms of clinical utility, their applications in different aspects of metastatic bone disease and their potential in future patient management.

6.2 Bone Turnover and Effects of Bone Metastases

During adult life, normal bone undergoes a continuous remodeling process of resorption of old bone by osteoclasts and new bone formation by osteoblasts. Up to 25 % of cancellous bone is remodeled annually, compared to only 3 % of cortical bone [1]. The process occurs in discrete packets throughout the skeletal system, known as bone remodeling units [2]. Within these units, the remodeling sequence begins with bone resorption via activation of osteoclasts, which resorb bone by the production of proteolytic enzymes and hydrogen ions [2]. This process takes

place over about 10 days [3] and is followed by bone formation to repair the defect. The whole remodeling process is normally under tight control, responding to a wide variety of local and systemic factors, as well as mechanical loading [4–6]. This results in a fine balance between bone formation and bone resorption, so that the total amount of bone remains approximately constant [2].

The normal processes of bone resorption and formation result in shedding of proteins, protein fragments and mineral components directly involved in bone structure or metabolism into the blood and urine and this represents a rich source of potential bone markers for the processes of bone turnover. Such biomarkers are often classified according to whether they are produced from the bone resorption process (resorption markers) or the bone formation process (formation markers) [6, 7].

Metastatic tumour development in bone is thought to follow the occupation of the bone erythropoietic stem cell niche by cancer stem cells and results from complex interactions between tumour cells and the bone microenvironment [8, 9]. Tumour-derived factors attract and stimulate osteoclasts, increasing bone turnover and releasing bone-derived growth factors and cytokines which facilitate cancer cell proliferation in a vicious cycle of tumour growth and bone destruction [9, 10]. The acute changes in bone turnover associated with metastatic bone disease might be expected to be reflected in bone turnover markers and, as will be seen from the sections below, this turns out to be the case. Indeed, bone biomarkers may provide an excellent quantitative tool in the management of metastatic bone disease.

6.3 Biomarkers of Bone Formation

6.3.1 Collagen Biosynthesis

Under the control of osteoblasts, collagen biosynthesis is a complex process and includes several post-translational modifications. Osteoblasts first secrete type I procollagen, a protein rich in the hydroxylated amino acids hydroxyproline and hydroxylysine and formed by combination of two α1 and one α2 polypeptide chains [11]. Conversion of procollagen into native collagen requires cleavage of both the N-terminal and C-terminal regions. Intermolecular crosslinks are then formed rendering the protein insoluble and the collagen fibrils are formed by precise spatial alignment of the collagen chains. These processes give rise to several molecules which can be used as markers of bone formation. The characteristics of the main bone formation markers are shown in Table 6.1.

6.3.2 Propeptides of Type I Procollagen

During the conversion of procollagen into native collagen through the action of specific proteases, both the N-terminal fragment, known as Type I procollagen N-terminal propeptide (P1NP) and the C-terminal fragment, known as Type I procollagen

Table 6.1 Biomarkers of bone formation and bone resorption

Biomarker	Abbreviation	Function
Type I procollagen N-terminal propeptide	PINP	Bone formation
Type I procollagen C-terminal propeptide	PICP	Bone formation
Bone alkaline phosphatase	BALP	Bone formation
Osteocalcin	Osteocalcin	Bone formation
Calcium	Ca^{2+}	Bone resorption
Hydroxyproline	Hydroxyproline	Bone resorption
N-terminal cross-linked telopeptide of Type I collagen	NTX	Bone resorption
C-terminal cross-linked telopeptide of Type I collagen	CTX	Bone resorption
Pyridinoline cross links of type I collagen and	PYD	Bone resorption
Deoxypyridinoline cross links of type I collagen	DPD	Bone resorption
Bone sialoprotein	BSP	Bone resorption
Osteoprotogerin	OPG	Bone resorption
Tartrate-resistant acid phosphatase serum type 3b	TRACP5b	Bone resorption

C-terminal propeptide (P1CP) are released into the circulation and can therefore be used as serum bone formation markers for collagen formation. Molecular characterization of both P1CP and P1NP has been carried out and reviewed by Brandt et al. [12]. Care is needed in analysis because of different molecular forms but analysis may be carried out by electroimmunoassays, ELISA techniques and radioimmunoassay [12]. P1NP is increasingly thought to be useful as a bone formation marker because, not only does it appear to accurately reflect changes in bone metabolism, but also because it appears to be a stable molecule and is less sensitive to diurnal variation and dietary intake than some other markers [12, 13]. More studies are now using P1NP as a formation marker, for example the studies by Brasso et al. [14] and Jung et al. [15], discussed in Sect. 6.6, which showed that high levels of serum P1NP were associated with poor outcome in prostate cancer, with multivariate Cox analyses showing that P1NP was an independent predictor of survival. A similar study by Jung et al. [15] showed that prostate cancer patients with bone metastases who had high P1NP levels had significantly shorter survivals than patients with low P1NP levels. Further studies in breast cancer [16] and prostate cancer [17] have also recently been reported (see Sect. 6.6).

6.3.3 Bone Alkaline Phosphatase (BALP)

Osteoblasts are rich in a particular isozyme of alkaline phosphatase (BALP), which has been used for many years as a serum bone formation marker. In early studies, it was difficult or impossible to distinguish alkaline phosphatase activity arising from bone from that arising from liver and other organs. However, more recently, immunoassay methods relying on monoclonal antibodies specific for the bone isozyme have been developed and have improved both the sensitivity and

the specificity of the assay [18]. The release of the enzyme into the circulation from osteoblasts corresponds predominantly to the matrix maturation phase of bone formation and therefore reports on an intermediate phase of osteoblast activity compared with P1NP and P1CP, which report on the earlier phase of osteoblast proliferation.

Elevated BALP levels occur in Paget's disease, renal rickets, osteomalacia, celiac disease and in bone cancers [7]. BALP levels are also often increased in metastatic bone disease and may be correlated with bone resorption. This is because increased bone formation may occur as a response to accelerated bone resorption caused by bone metastases.

The use of BALP in clinical studies in bone metastases is illustrated in the later sections of this chapter.

6.3.4 Osteocalcin

Osteocalcin is a small protein synthesized by mature osteoblasts and serum osteocalcin is considered a marker of the late phase of bone formation [19, 20]. Although the protein binds strongly to bone mineral, small levels appear in serum and may be measured by radioimmunoassay or ELISA techniques, though there are multiple isoforms and different assays detect different forms [21].

It has advantages in that it is bone-specific, it correlates with changes in bone turnover and assays are widely commercially available. However, it is subject to diurnal variation, has poor sample stability and there is wide variation in assays using different kits [19].

6.4 Biomarkers of Bone Resorption

Under the action of osteoclasts, bone resorption involves the breakdown of collagen and other components of the skeleton and it is from these breakdown products that most established or 'conventional' bone resorption markers are derived. Many such products released into the blood and the urine have been investigated for marker utility. A list of the bone resorption markers which have been most studied is included in Table 6.1.

6.4.1 Early Biomarkers of Bone Resorption

Urinary calcium excretion, expressed relative to urinary creatinine, has been widely used as an indicator of bone resorption for more than 25 years [22, 23]. Provided that measurements are made on early morning urine samples after overnight fasting,

urinary calcium can be a convenient and reproducible marker for quantifying calcium excretion [24] and for monitoring response to treatment [22, 25]. However, relating urinary calcium excretion to the specific events occurring in bone turnover is more complex because it reflects net turnover (i.e. the difference between formation and resorption) and is also influenced by dietary factors as well as the levels of parathyroid hormone and parathyroid hormone-related protein [26]. Other studies have shown that calcium excretion was not elevated in patients with metastatic bone disease relative to controls [27], nor did calcium excretion levels correlate with response to bisphosphonate treatment [28].

Since hydroxyproline is an amino acid which is found in collagen, but in few other proteins, its metabolic levels are dominated by collagen breakdown. However, it is not a specific bone marker, since around 50 % of human collagen is extraskeletal [29]. Most collagen is metabolized through the liver, but there is sufficient renal clearance (around 15 %) to enable useful urinary measurements [29, 30]. Urinary excretion of hydroxyproline is also strongly influenced by diet, age, and soft tissue destruction of tumor. Additionally, there is a circadian rhythm, with a peak between midnight and 8am [29]. Although urinary hydroxyproline is a useful indicator of accelerated collagen breakdown in metastatic bone disease, it is not particularly useful or reliable for documenting disease progression or response to therapy [30].

6.4.2 Collagen Breakdown

After initial work on calcium and hydroxyproline, it became clear that there was a need for additional biomarkers which more specifically reflected bone resorption. Much attention in the last decade has been focused on the potential of more bone-specific collagen breakdown products in this context. Type I collagen is helical except for regions at the N-terminus and C-terminus, which are known as N-telopeptide and C-telopeptide. Within these regions, side chains of three hydroxylysine or lysine residues from three different collagen molecules combine to form a pyridinium ring such that the three collagen chains become cross-linked, stabilising the collagen structure [11]. Pyridinoline crosslinks (PYD) result from the post-translational combination of three hydroxylysine residues, whereas deoxypyridinoline crosslinks (DPD) result from the post-translational combination of two hydroxylysine residues with one lysine residue [31]. PYD crosslinks are found in collagen in bone, cartilage and other connective tissues, whilst DPD is almost exclusive to bone [32].

Following collagen breakdown with the enzyme cathepsin K, the crosslinks are found in both peptide bound (N-terminal cross-linked telopeptide of Type I collagen, NTX and C-terminal cross-linked telopeptide of Type I collagen CTX) forms and free (PYD and DPD) forms where breakdown is more complete. All of these have been evaluated as potential bone biomarkers in metastatic bone disease and are considered below.

6.4.3 N-Telopeptide (NTX) and C-Telopeptide (CTX)

Although these peptides may be formed from collagen-containing tissues other than bone, the peptides derived from osteoclast action may occur in different forms from those derived from other tissues [7]. In the case of NTX for example, the bone-derived peptide is a so-called alpha-2 isoform, whereas that derived from non-skeletal tissue is a different isoform, designated alpha-1 [33]. CTX can exist in either alpha or beta isoforms, with the beta isoforms predominating in the peptides derived from bone [7].

Assay of NTX and CTX is now straightforward and reproducible, using ELISA assays. Commercial assay kits are readily available but, currently, routine measurements are generally only available in specialist centres which have sufficient throughput to run the assays as a service to other centres. This often therefore involves freezing and storing of samples for bulking up and later assay. Because of the growing potential of bone marker measurement on directing patient therapy, there is some interest in developing point of care devices for NTX and CTX assay, so that sample assay and patient management decisions can be made at the same outpatient visit. A hand held point of care device has been described by Hannon et al. [34] which is able to measure NTX on a spot of urine in the outpatient setting. A similar point of care device has been described for assay of CTX in urine, which uses a dipstick approach [35] with a second dipstick assay which measures creatinine for urine volume correction. Although not currently available, it can confidently be predicted that such devices could be quickly developed commercially, if bone marker measurements become part of routine clinical practice.

For NTX the monoclonal antibody for the assay is against the alpha-2 isoform and was originally derived against urinary collagen cross links from a patient with Paget's disease [11]. Although NTX can be measured in serum, this is rarely used, preference being given to measurement in urine, with standardisation relative to creatinine. However, there is a marked diurnal variation in NTX release through the kidneys and assays should be carried out on the second morning voided urine sample.

For CTX, the monoclonal antibody used in the assay is against the beta isoform. Both serum and urinary CTX can be measured using an assay called Crosslaps. This does not measure cross links directly, but measures an octapeptide sequence of the CTX region of the alpha-1 chain [36]. Serum is generally preferred because of better precision throughout the concentration range.

There is an additional C-telopeptide assay in serum which recognises a different domain in the C-telopeptide region to the CTX assay, lying between the two alpha-1 chains. This bone collagen product, known as 1CTP is probably derived from non-osteoclast mediated bone resorption, utilising matrix metalloproteinases derived from the underlying pathological process, rather than the cathepsin-K mediated pathway associated with physiological bone resorption. 1CTP appears to be not sufficiently sensitive for use in osteoporosis, but it may have potential value in metastatic bone disease [37]. Some studies have shown increased levels of 1CTP in metastatic bone

disease, for example in lung cancer patients [38] and in multiple myeloma [39, 40], although relatively little use has so far been made of this marker. This may be due, in part, to problems with the current antibody-linked assay, where it has been shown that, whilst metalloproteinase-induced collagen breakdown leaves the antigenic site of 1CTP unchanged, cathepsin-K cleaves collagen at the antigenic site [41].

There has recently been increased interest in the use of the CTX alpha/beta ratio as a marker of the degree of collagen maturation and therefore of bone age [42]. Although this has the potential to be of value as a bone marker, it does not appear to have yet received any extensive attention in the bone metastasis field.

6.4.4 Pyridinoline Cross Links (PYD) and Deoxypyridinoline Cross Links (DPD)

These molecules are released in an approximately 3:1 ratio during bone resorption and are excreted via the kidneys [1]. Bone accounts for the majority of release of these markers both because bone is their major reservoir, but also because bone has a higher turnover rate than most connective tissues [7]. Nevertheless, soft tissues may make a significant contribution to total urinary PYD especially and, because they may be less specific than the telopeptide markers, results must be interpreted with care. In a study of the metabolic effects of pamidronate in patients with metastatic bone disease, DPD was been found to be a more sensitive indicator of bone resorption that PYD [28]. A number of ELISA systems are now available for the measurement of PYD and DPD [43–45].

6.4.5 Bone Sialoprotein (BSP)

Bone sialoprotein is a non-collagenous protein of the bone extracellular matrix and is one of the most abundant proteins in bone. BSP is also secreted by non-skeletal cells and has been classified as a member of the integrin-binding SIBLING family, which also contains osteopontin and several other proteins expressed in the skeleton [46].

The assay for bone sialoprotein is not currently widely available, but is based on immunoassay, including a competitive ELISA assay [46]. However it has been shown that BSP (and OPN) binds to complement factor H in serum and the complex needs to be disrupted, before accurate BSP assay is possible [46].

In conditions such as osteoporosis, bone sialoprotein appears to be a sensitive biomarker of bone turnover [6] probably mainly relating to bone resorption. Elevated levels of BSP have been reported in patients with multiple myeloma [47], while multivariate Cox proportional hazards regression showed that BSP was an independent prognostic factor for survival in prostate cancer patients with bone metastases [15].

In one especially interesting study in 388 patients with primary breast cancer without metastasis at baseline, increased levels of BSP (above 24 ng/ml) appeared to correlate with the subsequent development of bone metastases in breast cancer patients [48]. This has been followed up by more recent work in which tissue BSP was shown to be predictive of bone metastases in resectable non-small cell lung cancer in a retrospective case study. These observations merit further study, but suggest that BSP levels may have a role in the prediction of which cancer patients will develop bone metastases.

6.4.6 The RANK/RANK-L System and Osteoprotogerin

Osteoclasts control bone resorption and the biology of this process and the factors controlling the production of osteoclasts have been intensively investigated. These studies have revealed the importance of receptor activator of nuclear factor-κB (RANK) and its ligand (RANK-L) in osteoclastogenesis [49, 50]. Osteoprotogerin (OPG) is a decoy receptor cytokine, which binds to RANKL and is a powerful inhibitor of the RANKL/RANK interaction, thereby preventing the simulation of osteoclastogenesis [50].

Experimental studies have shown that OPG halted further bone damage and diminished the skeletal pain associated with tumour-induced bone destruction [51]. Such studies have led to new therapeutic strategies and the development of novel anti-resorptive drugs either through synthetic analogues of OPG or through the production of monoclonal antibodies to RANK-L, which exists in both membrane-bound and soluble forms [52]. Such a drug (XGEVA or denosumab) is now in advanced Phase outine clinical practice.

These findings suggested that OPG and RANK-L might be useful biomarkers for osteoclastogenesis and therefore for bone resorption. Immunoassays have been developed for OPG and for both isoforms of RANK-L. In multiple myeloma [13], the RANK-L: OPG ratio was found to be an independent prognostic factor for survival. However, in other studies to date in both post-menopausal osteoporosis and in metastatic bone disease, results have been variable and the utility of these proteins as bone resorption biomarkers remains uncertain [53, 54].

6.4.7 Tartrate-Resistant Acid Phosphatase Serum Type 5b (TRACP5b)

This is an inactive, metalloprotein, pro-enzyme associated with osteoclasts, requiring proteolytic cleavage via cathepsin κ or L before the active enzyme form can be secreted into the circulation when the osteoclasts attach to the bone surface. A second isoform of the enzyme (TRACP5a) is secreted into serum by macrophages. Circulating TRACP5b activity is derived exclusively from osteoclasts and the

activity of active enzyme in the circulation therefore reflects recently released enzyme as a result of bone resorption [7]. Immunoassays have been developed for the measurement of this enzyme [55].

Many recent studies have evaluated this resorption marker in both osteoporosis and metastatic bone disease. Halleen et al. [56] showed that the marker was significantly elevated in patients with osteoporosis and changes in TRACP5b (but not TRACP5a) correlated well with changes in other resorption markers and also correlated negatively with change in bone mineral density. In metastatic bone disease, whilst several recent studies have found positive correlations between TRACP5b levels and occurrence of bone metastases, especially in breast cancer [57, 58] and prostate cancer [59–61], other studies have found no difference in TRACP5b levels between renal cancer patients with bone metastases and controls [62]. In metastatic bone disease, further investigation of TRACP5b is needed to establish its role as a resorption marker.

6.4.8 Sclerostin

Osteocytes are former osteoblasts which become embedded in the mineralised bone matrix and there is growing evidence of the role of these cells in bone remodeling through modulation of both osteoblastic and osteoclastic activity [63]. Sclerostin is produced by osteocytes and there is now strong evidence of the importance of sclerostin in negative regulation of bone formation, primarily through its effects in inhibiting the canonical Wnt signalling pathway [63]. However, recent studies suggest that sclerostin also positively regulates bone resorption by enhancing osteoclast formation via the RANK-L system. The recent study by Yavropoulou et al. [63] clearly demonstrated that circulating sclerostin levels were significantly increased in patients with increased bone turnover, irrespective of the cause of the increased turnover. Serum sclerostin levels were also significantly correlated with P1NP ($p < 0.001$) in this study which included 88 patients with Paget's disease, 20 patients with bone metastases consequent to prostate cancer and 237 healthy individuals. Although there are currently few studies of sclerostin in patients with metastatic bone disease, it is clearly a potential biomarker and a recent study in myeloma showed that patients with active myeloma have elevated sclerostin which correlated with advanced disease features, including severe bone disease [64]. Sclerostin is also a target for therapy [65] as has been recently demonstrated by use of monoclonal antibodies against sclerostin in a biological model [66].

6.5 Correlation of Bone Biomarker Levels and Presence of Metastatic Bone Disease

Can bone biomarkers be used for diagnosis of metastatic bone disease? Certainly, many studies have now shown a positive relationship between levels of various bone markers and the presence of metastatic bone disease. Early studies showed that both

urinary calcium [22, 25] and hydroxyproline [25, 67] may be elevated in patients with metastatic bone disease. Urinary calcium may be derived from many sources and has been shown to be unsuitable as an indicator of bone metastases, particularly in patients receiving concomitant bisphosphonates [26, 28]. Similarly, as well as skeletal breakdown, diet and soft tissue destruction by tumour influence hydroxyproline levels, which are therefore not well correlated with presence of metastatic bone disease, with progression or with response to therapy.

More recently, attention has been focused on the more specific markers of bone turnover. Many studies over the last 15 years have shown elevated bone markers in patients with bone metastases, compared to cancer patients without bone metastases and to healthy subjects [7, 68–75]. In one example, using radiographic and bone scan findings, 127 cancer patients were divided into three groups. Group A contained 83 patients with no bone metastases, Group B contained 22 patients with one or two bone metastases and Group C contained 22 patients with three or greater. In both groups with bone involvement PYD, NTX and CTX were significantly increased indicating a high level of specificity and sensitivity of these markers [76, 77]. Another study compared breast cancer patients with bone metastases with healthy pre-menopausal women. The percentage of elevated values for the cancer group were 47 % for urinary calcium, 74 % for hydroxyproline, 83 % for CTX and 100 % for each of the collagen crosslinks PYD and DPD. BALP, but not urinary calcium, correlated significantly with the other four bone markers [78]. Other examples are considered in further sections of this chapter.

Whilst bone metastases are primarily osteosclerotic in prostate cancer, nevertheless increased bone resorption also occurs with a corresponding increase in resorption markers. For example, one study of 39 prostate cancer patients with metastatic bone disease showed an approximate doubling in urinary CTX compared with healthy age-matched men [72]. In the same study, no increases in bone resorption markers were observed in prostate cancer patients without bone metastases (n = 9) or in patients with benign prostatic hyperplasia (n = 9). Formation markers, including BALP, P1NP and P1CP have also been shown to be correlated with bone metastases in patients with prostate cancer [79, 80]. Serum P1NP levels were compared between patients with benign prostatic hypertrophy (n = 32), prostate cancer without bone metastasis (n = 38) and patients with confirmed bone metastasis (n = 30). P1NP levels were significantly higher in patients with bone involvement (median 194.7 ng/ml) than patients without bone metastasis (median 38 ng/ml) or BPH (median 42.2 ng/ml). In the same study, P1NP demonstrated the highest combined sensitivity (86.7 %) and specificity (78 %) for identifying bone metastasis compared to PSA and alkaline phosphatase [17].

Osteoblastic metastases and a response to healing [20] induce the highest levels of BALP, corresponding to new bone formation, whilst increased levels of serum osteocalcin are primarily associated with bone metastases resulting from breast and prostate cancer [25]. Osteocalcin levels [25] and bone specific alkaline phosphatase levels [81] have both been shown to be significantly raised in patients with metastatic bone disease from breast cancer compared with normal controls. In such patients, levels of these two formation markers are significantly higher in those with

blastic rather than lytic metastases [32]. Neither of these markers appears to be useful for early detection of bone metastases. However, a recent study by [16, 82] in breast cancer concluded that P1NP is a useful tool for estimating the extent of bone involvement and for the detection of bone metastases, though it cannot replace conventional methods.

As well as correlating with the presence of bone metastases, it would be useful if markers could give an indication of the extent of bone disease. There is evidence from several studies that a range of markers including PYD, DPD and bone specific alkaline phosphatase (BALP) correlated with the number of skeletal areas involved [83, 84].

With a choice of both formation and resorption markers, how do investigators choose the most appropriate marker for their studies? Lipton et al. [85] have attempted to determine which marker best correlated with skeletal metastases and concluded that NTX was the most predictive for the presence of bone metastases, but this may depend upon the cancer type and other factors. It should be emphasised that bone markers are not specific for malignant disease and can be elevated in a number of benign bone diseases. Currently, however, bone biomarkers are not used routinely for diagnosis of bone metastases and there is still a need for skeletal imaging to diagnose bone metastases with certainty.

6.6 Role of Bone Biomarkers in Predicting Disease Recurrence Following Adjuvant Treatment

Adjuvant trials have focused on the utility of bone marker levels for predicting the development of metastasis in both skeletal and extraskeletal sites.

In the breast cancer setting, Lipton et al. demonstrated that baseline (pre-adjuvant treatment) CTX levels correlated with relapse (n = 621). A high serum beta-CTX, in patients receiving tamoxifen +/− octreotide, predicted a shorter skeletal relapse-free survival (p = 0.02), but did not correlate with extraskeletal relapse, indicating that a high bone turnover in early breast cancer promotes a favourable environment for survival of disseminated tumour cells in the bone, see Fig. 6.1 [86]. This was further supported by data from an adjuvant clodronate trial, which demonstrated that a fall in P1NP of >20 %, at 1 year compared to baseline, significantly decreased the risk of development of bone metastasis, indicating that reducing bone turnover correlates with a decreased survival of tumour cells in the bone microenvironment [87].

AZURE is a large adjuvant breast cancer trial evaluating addition of zoledronic acid to standard therapy (n = 3360). Baseline serum P1NP and CTX, measured in >860 patients, did not significantly predict either prognosis or response to zoledronic acid. Interestingly vitamin D was demonstrated as a potential marker of risk of recurrence. Vitamin D levels classified as ‘sufficient’ (>30 ng/ml) at baseline, predicted lower risk for bone relapse (HR 0.11; CI 0.02–0.76 p = 0.0257) compared to all other patients with insufficient or deficient levels [88].

Several studies have supported the potential utility of vitamin D as a predictive marker for recurrence in breast cancer. A study of 512 patients diagnosed with early

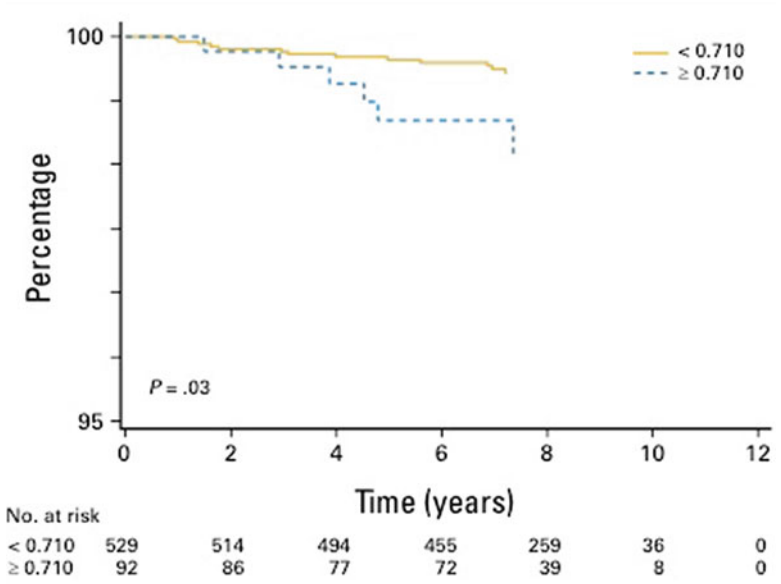

Fig. 6.1 Cox survivor plot demonstrating pretreatment serum beta C-terminal telopeptide (**β**-CTx) predicts for bone-only relapse in the MA.14 trial (National Cancer Institute of Canada). Univariate hazard ratio 2.8 (95 % CI 1.05–7.48 p = 0.03) (Figure reproduced with permission from Lipton A et al. JCO 2011:20:3605–10)

breast cancer demonstrated insufficient vitamin D levels (<50 nmol/L) correlated with an increased risk of recurrence (HR 1.94; CI 1.16–3.25) and death (HR 1.73; CI 1.05–2.86) compared to those with sufficient levels. [89]. Further evidence comes from a large study of 1,800 early breast cancer patients, correlating serum vitamin D at diagnosis to tumour characteristics and clinical outcomes. A sufficient vitamin D at diagnosis (>30 ng/ml) significantly improved overall survival (p = 0.0101) and time from breast cancer diagnosis to breast cancer related death, especially in postmenopausal women (p = 0.0192) [90].

6.7 The Role of Bone Biomarkers in Predicting Skeletal Complications and Survival

The severe bone pain and other skeletal complications (skeletal related events, SRE) associated with metastatic bone disease are often the most significant factors limiting quality of life in these patients. Details of these complications (which include hypercalcaemia, bone pain requiring radiotherapy, pathological fracture and spinal cord or nerve root compression) and their treatment are given in other chapters of this book. Identification of patients with bone metastases who are at high risk of

developing SREs may be valuable in patient management, especially in decisions as to when to apply therapeutic interventions such as bisphosphonates and other bone specific therapies.

A study by Lipton et al. [91] investigated the fracture rate in 21 cancer patients with bone metastases who received intravenous pamidronate and whose baseline uNTX levels were above the normal range. In the 12 patients who normalised uNTX on the bisphosphonates only five (42 %) developed fractures, whereas in the nine patients who failed to normalise, eight patients (89 %) developed fractures. Although this small study fell just short of statistical significance, it illustrated the link between marker levels and SREs and pointed to the importance of normalisation of markers as a therapeutic goal. Ali et al. [92] investigated serum NTX levels in 250 post-menopausal metastatic breast patients with bone-only metastases. Twenty-four percent of patients had elevated serum NTX levels and median survival time was significantly shorter in patients with elevated baseline serum NTX (663 days) compared with patients with low baseline NTX (941 days, $p < 0.001$). A similar relationship between urinary NTX (uNTX) and overall survival was demonstrated in castrate resistant prostate cancer patients (CRPC) receiving zoledronic acid. 94 patients receiving zoledronic acid for at least 2 months were evaluated for uNTX. In multivariate analysis elevated uNTX was an independent prognostic factor for overall survival (HR 2.2; CI 1.2–4.0). Median OS was only 12 months in patients with uNTX >20 nmol/mM compared to 25 months in patients with uNTX <20 nmol/mM. [93].

The prognostic potential of bone markers in multiple myeloma was highlighted by Abildgaard et al. [94], who showed that elevated pre-treatment values of serum 1CTP and uNTX were predictive of early progression of bone disease during standard chemotherapy.

The first study to examine the possible correlation between the rate of bone resorption, as measured by a bone marker, and the frequency of skeletal complications across a range of SREs in metastatic bone disease was carried out in 121 patients, mainly with breast and prostate cancer [95]. Data were available for 121 patients over the first 3 month period of monitoring (0–3 months) and for 95 patients over the second 3 month period of monitoring (4–6 months). The results showed that patients with uNTX values ≥100 nmol/mmol creatinine were almost 20 times more likely to experience a SRE/death during the following 3 month period, than those patients whose uNTX value at the beginning of the 3 month period was <100 nmol/mmol creatinine ($p < 0.001$ for both 0–3 month and 4–6 month periods). In a multivariate logistic regression model, uNTX was highly predictive for SREs/death.

This initial work has been developed and expanded in very large retrospective analyses of bone markers and skeletal complications/survival from the randomised Phase 3 trials of zoledronic acid in patients with bone metastases from a variety of primary cancer types. In patients with bone metastases from prostate cancer (N = 203), lung cancer or other solid tumours (other than breast (N = 238), in the placebo arm of these studies, elevated bone marker levels correlated with negative clinical outcomes [74]. High uNTX levels (≥100 nmol/mmol creatinine) were

Table 6.2 Relative risk of death and skeletal complications for patients with high NTX compared with patients with low NTX

	Prostate cancer		Non small cell lung cancer and other solid tumours (excluding breast)	
Clinical outcome	Relative risk	p	Relative risk	P
Death on study	4.6	p<0.001	2.7	p<0.001
Occurrence of SREs	3.25	P<0.001	1.79	P=0.010

Data refer to the placebo arm of the phase III zoledronic acid trials [74]

associated with a 4.6 fold increased rate of death on study in patients with prostate cancer and a 2.7 fold increased risk of death on study in patients with non small cell lung cancer and other solid tumours, compared with patients in these groups with low uNTX levels (<100 nmol/mmol creatinine), with p< 0.001 in both cases. The relative risk of SREs was 3.25 times higher (p < 0.001) and 1.79 times higher (p=0.010) for patients with high uNTX in the prostate and non small cell lung cancer and other solid tumour groups respectively, compared with the corresponding patients with low uNTX (see Table 6.2). The above analysis refers to updated marker values, though baseline marker values were also significantly predictive.

In a combined analysis of 1,824 bisphosphonate-treated patients with metastatic bone disease (breast, prostate, non small cell lung, myeloma, other), an exploratory analysis grouped patients by baseline levels of uNTX as low (<50 nmol/mmol creatinine, moderate (50–99 nmol/mmol creatinine) and high (≥100 nmol/mmol creatinine) and by baseline levels of BALP as low (<146 U/L) or high (≥146 U/L) [75]. Patients with high and moderate uNTX levels had twofold increases in risk of skeletal complications and disease progression compared with those with low uNTX levels (p<0.001 in all cases) and high uNTX levels in each solid tumour category were associated with a four to sixfold increased risk of death on study (p < 0.001 in all cases). Although BALP levels also showed some correlation with risk of negative clinical outcomes, it was not a strong prognostic indicator. Further analyses of the zoledronic acid trials data have shown a strong positive association between zoledronic acid treatment and survival in patients with high baseline levels of uNTX. For example, in non small cell lung cancer, the reduction of risk of death was 35 % (p=0.024) [96].

A further study of 117 CRPC patients receiving zoledronic acid measured serum P1NP, NTX and 1CTP at baseline pre-bisphosphonate, and at 1 yearly intervals up to 5 years, correlating levels of these bone markers to SREs. At all time points, all three markers were found to be higher in those experiencing SREs compared to those without. NTX remained a significant predictor of SREs after multivariate analysis [97].

In multiple myeloma, a phase III randomised study comparing zoledronic acid to pamidronate, demonstrated high NTX was a significant prognostic marker for both first SRE and death (p ≤ 0.02 for both) [98].

In these prognostic studies, NTX has been shown to be the most consistently reliable bone marker, but other markers have also been studied in a range of tumour

types including CTX, osteocalcin, BALP, lactate dehydrogenase (LDH), BSP, P1NP and parathyroid hormone (PTH).

In a trial of 2 mg monthly IV ibandronate versus placebo in patients with multiple myeloma, Menssen et al. [99] found that the occurrence of SREs per patient year and the time to first SRE were not significantly different between the two groups. However, ibandronate patients with strongly suppressed bone markers (CTX and osteocalcin) developed significantly less bone morbidity. This is a relatively low dose of ibandronate compared with that used in breast cancer.

The utility of BALP and LDH as predictors of SREs was demonstrated in 444 zoledronic acid treated breast cancer patients with bone metastases. BALP was a prognostic marker for both number and timing of first SRE. Multivariate analysis demonstrated elevated baseline BALP and LDH as significant prognostic markers for first SRE [100]. Further validation of these factors in a separate cohort of clinically similar patients (n = 435) confirmed the utility of serum LDH in predicting survival, with increasing levels correlating to increased risk of death [101]. However baseline bone markers were not significantly correlated with survival.

BALP has demonstrated reliability in predicting SRE-free survival and overall survival in prostate cancer patients receiving zoledronic acid. Thirty patients with bone metastases receiving zoldronic acid had 1CTP, BALP and PSA measured at the start of treatment and at four weekly intervals afterwards. Patients who demonstrated an increase in 1CTP and BALP at 3 months had a shorter SRE-free survival compared to those who experienced a decrease ($p = 0.004$). Overall survival was significantly longer in patients who demonstrated a fall in BALP at 6 months ($p = 0.035$) and 1CTP at 1 and 3 months ($p = 0.013$ and 0.027 respectively) [102].

In multiple myeloma patients, Woitge et al. [47] showed that BSP could be a useful marker for survival, demonstrating that survival was increased in patients with normal BSP levels compared to patients with elevated BSP levels ($p < 0.001$).

P1NP is also proving interesting in the prognostic setting. Brasso et al. [14] showed that, in 153 metastatic prostate cancer patients, serum P1NP was associated with poor outcome, with multivariate Cox analyses showing that P1NP was an independent predictor of survival. Interestingly P1NP was elevated (compared to healthy male controls) in 87 % patients compared to elevated BALP in 55 % and elevated CTX-I in 33 %. A study by Jung et al. [15] showed that prostate cancer patients with bone metastases who had high P1NP levels, had significantly shorter survivals than patients with low P1NP levels. In the same study, elevated levels of OPG, BALP, BSP, NTX and CTX also correlated with shorter survival.

Parathyroid hormone (PTH) was identified as a potential prognostic marker in prostate cancer. In a study of 643 prostate cancer patients with bone metastasis, elevated baseline PTH, prior to initiation of zoledronic acid, was negatively associated with overall survival (HR; 1.448: 95 % CI 1.045–2.006. $p < 0.03$), suggesting secondary hyperparathyroidism predicts a poor outcome in zoledronic acid treated bone metastatic prostate patients [103].

A wealth of data on the role of several bone markers, in prevention of SRE's, has been gained from bisphosphonate trials, and these data have been supported by phase II and III trials of the RANK-ligand inhibitor denosumab. In a phase II trial

of denosumab in patients (n = 111) with breast, prostate and other solid tumours, with elevated urine uNTX despite IV bisphosphonates, a reduction in SREs was demonstrated with denosumab. This was associated with a greater proportion of patients on denosumab achieving uNTX levels of < 50 nmol/L compared to those continuing on bisphosphonates (71 % vs 29 % respectively p <0.001) [104]. A similar phase II study in breast cancer (n = 255) supported these data with an SRE rate in the denosumab group of 9 % vs 16 % in patients on bisphosphonates. The denosumab group demonstrated a higher proportion of patients experiencing a fall in uNTX of >65 % compared to bisphosphonate (74 % vs 63 %) [105]. The reduction in SREs with denosumab has been further demonstrated in large Phase III RCTs of denosumab vs placebo [68], and denosumab vs zoledronic acid [106, 107]. Although SREs were the primary endpoints in these trials, the benefit of reduced SREs on denosumab was mirrored by a significantly greater fall in uNTX and BALP for denosumab compared to placebo by Smith et al. (−68 % denosumab vs +1 % placebo for uNTX, and −49 % denosumab vs −7 % placebo for BALP) [68] and for denosumab compared to zoledronic acid by Henry et al. (−76 % denosumab vs −65 % zoledronic acid for uNTx, and −37 % denosumab vs −29 % zoledronic acid for BALP) [107].

6.8 Role of Bone Biomarkers in Monitoring and Directing Bisphosphonate Therapy

Objective assessment of response in bone metastases from breast cancer takes up to 6 months using radiological techniques and bone markers have been studied with the aim of providing an earlier indication of response. There is currently major interest in using bone markers as fast and convenient surrogate end points for clinical efficacy (primarily reduction in skeletal complications). Whilst it is now well accepted that bone-targeted systemic therapy, particularly the use of the bisphosphonates, can substantially reduce morbidity of skeletal metastases, the optimisation and timing of these therapies remains to be established. Bone markers potentially offer a powerful and relatively simple tool to assist the clinician in developing the most appropriate treatment strategies. Moreover, there is the prospect that it may be possible to use bone markers to tailor treatment to the individual patient.

There are many studies which show rapid and substantial decrease in bone marker levels following initiation of bisphosphonates therapy, with initial decreases of up to 60–70 % in uNTX and CTX being demonstrated and maintained [108, 109]. However, a key question in using bone markers in patient management is whether targeting therapy to achieve reduction of marker values into the normal range is associated with clinical benefit. Early, relatively small studies have suggested that this is the case for pain [110] and fracture rate [92], but the zoledronic acid trial data have allowed retrospective assessment of this question very recently in much larger patient groups. In breast cancer, analyses suggested that early normalisation of elevated baseline uNTX while receiving zoledronic acid is associated

with longer event-free and overall survival times than in patients with persistently elevated NTX levels [111]. In all tumours studied (breast cancer, prostate cancer, non small cell lung cancer and other solid tumours, the analyses suggested that breaking the cycle of bone destruction and tumour growth in bone with bisphosphonates can produce profound benefits [112]. Normalisation of elevated baseline uNTX within 3 months was associated with significant improvements in survival compared with persistent NTX elevation and zoledronic acid normalized NTX in the majority of patients, so normalisation would seem a reasonable and achievable therapeutic target. Trials using this approach are considered below. However, normalisation did not appear to represent a particular threshold and NTX reductions were associated with benefit, regardless of whether normal NTX levels were reached.

Whilst it is clear that bisphosphonates can reduce the levels of bone markers, as well as producing clinical benefit, caution is needed in over-generalising the correlation between bone marker levels and clinical advantage. This has recently been illustrated by Coleman et al. [7] in the analyses from the large zoledronic acid trials, where zoledronic acid was more effective than pamidronate in reducing SREs in breast cancer patients and this was mirrored by reductions in uNTX, but no differences were observed in changes in BALP. Such data suggest that correlations between bone markers and clinical benefit may depend upon both the marker and the tumour type and that establishment and wider acceptance of bone markers as surrogates for skeletal complications will require more specific trials such as the SWOG study, a prospective trial which is currently under way (expected completion in 2015) to compare clinical efficacy of oral ibandronate with zoledronic acid, where a comparison across SRE endpoints is the primary objective [7, 113].

The dependence of bone marker levels on circadian rhythm has been studied by Generali et al. [114] who showed that the circadian rhythm of biomarkers of bone resorption is synchronized in breast cancer patients with lytic bone metastases, independently of tumour load. An interesting question in terms of bisphosphonate therapy is whether its effectiveness can be altered by matching the dosing to the circadian rhythm. Recent work in breast cancer patients with bone metastases has shown that administration of zoledronic acid at two opposite phases of the circadian cycle causes similar changes in bone turnover marker levels, with no difference in effect on uNTX and CTX ($p < 0.001$) [115]. There do not appear to have been any studies assessing the differential effects of night versus day administration on skeletal complications.

Since bone marker levels are reduced by bisphosphonates, the possibility arises of using bone marker measurements to direct the dosing and scheduling of therapy, effectively tailoring the therapy to the individual patient. In practical terms, the minimum dosing intensity would be used which would bring the marker level into a target range. The feasibility of this approach was demonstrated by a study of clodronate in patients with advanced prostate and breast cancer, metastatic to bone [116, 117]. Patients were initially given the standard 1,600 mg daily oral clodronate dose, which was escalated at 6 weekly intervals, through 2,400 mg, 3,200 mg and 1,500 mg intravenously until uNTX levels fell below 67 nmol/mmol creatinine. Patients whose uNTX still did not normalise were given zoledronic acid infusion.

An incremental proportion of patients normalised at each stage of escalation, although 24 weeks to reach the maximum dose was felt to be too long. These studies were followed up with further investigations in breast cancer patients, which showed that patients with either progressive bone metastases or SREs while on clodronate or pamidronate can have relevant palliative benefits with a switch to zoledronic acid [118] or oral ibandronate [119] reflected by improvement in pain control and bone turnover markers [120].

The BISMARK trial randomized breast cancer bone metastases patients to receive either zoledronic 4 mg every 3–4 weeks (standard schedule), or zoledronic acid 4 mg on a marker-directed schedule based on changes of uNTX from baseline. The primary endpoint was the frequency and timing of SREs. 289 patients were recruited, and the median number of zoledronic acid cycles in the standard arm was twice that in the marker directed arm. The number of SREs experienced was higher in the marker directed arm compared to the standard arm (38 % vs 32 % respectively). Multivariate analysis adjusting for minimization factors and baseline uNTX, demonstrated a hazard ratio of 1.14 (marker directed vs standard, CI; 0.98–2.02 $p = 0.12$) suggesting the marker directed therapy may be sub-optimal compared to the standard therapy. uNTX levels also remained higher at all time points in the marker directed group compared to standard [121].

The marker directed approach continues to be assessed in ongoing trials, including OPTIMIZE-2 ($n = 650$), comparing monthly versus quarterly ZOL in breast cancer induced bone metastases in patients who have already received intravenous bisphosphonates, and Z-MARK ($n = 120$) following a comparable schedule in multiple myeloma. Results from these trials will provide further evidence to guide bisphosphonate treatment schedules.

6.9 Effect of Radiotherapy for Bone Metastases on Markers of Osteoclast Activity

Radionuclides have been employed in the treatment of bone metastases. Papatheofanis [122] measured serum P1CP concentrations as a semi-quantitative index of bone turnover in patients with bone metastatic prostate cancer before and following palliative 89Sr chloride therapy. Two groups of ten patients each were studied: one group received irradiation, whereas the other group received 89Sr chloride therapy. The concentration of serum P1CP rose from 649 ± 279 ng/ml before treatment with external beam radiotherapy to 927 ± 157 ng/ml 4 months after therapy ($p < 0.05$). However, the results demonstrated a fourfold decrease ($p < 0.001$) in serum P1CP in clinical responders to 89Sr chloride therapy versus baseline, 4 months after the completion of treatment. The clinical non-responders demonstrated no significant change in P1CP concentrations during that interval. These data demonstrate that serum P1CP concentration correlates with clinical response to 89Sr chloride therapy and may also be extremely useful in predicting a therapeutic response to such intervention.

Papatheofanis [123] also investigated the production of urinary PYD and DPD in prostate cancer patients with bone metastases who were and were not treated with 89Sr-chloride therapy. Patients were monitored for PYD and DPD production for a 6-month interval. The urinary production of these compounds remained unchanged for 6 months after 89Sr-chloride therapy for symptomatic osseous metastases. However, the patients who were not treated with 89Sr-chloride therapy exhibited a twofold increase in PYD and a fourfold increase in DPD above controls during the interval. The author concluded that PYD and DPD are sensitive and specific bone resorption markers which demonstrate a slowing of bone resorption after palliative 89Sr-chloride therapy in patients with bone metastases.

Papatheofanis also studied whether 89Sr-chloride decreased the production of cell adhesion molecules (E-selectins) that participate in the metastatic process [124]. Sera were collected from 25 men with metastatic prostate carcinoma who received 89Sr-chloride palliative therapy and from five patients who received two courses of radionuclide therapy. A 2.8-fold decrease in serum E-selectin concentration occurred within 2 months of radionuclide therapy ($P < 0.0001$). At 10 months, however, the concentration increased to a mean (± SD) of 151.2 ± 51.3 ng/ml, surpassing the baseline concentration. This pattern coincided with symptomatic improvement and subsequent health status deterioration. For patients who received two courses of radionuclide therapy, a second fall in serum E-selectin concentration followed the second radionuclide treatment. The author concluded that a significant decrease in serum E-selectin concentration was observed after systemic radionuclide therapy. This finding suggests that expression of cell adhesion molecules, an important determinant of metastatic progression, may be inhibited by 89Sr-chloride.

The utility of uNTX and P1NP in predicting response to the radionucleotide (186) Re-HEDP was evaluated in 36 prostate cancer patients with painful bone metastases. Using a novel ratio of uNTX: P1NP, a pretreatment ratio of ≥1.2 significantly predicted for a better symptomatic response and longer duration of response (RR = 3.04, p = 0.036). A fall in uNTX of >20 % from pre- to post-treatment, also significantly predicted for longer duration of response. Bone markers may therefore have a role in selecting which patients would benefit the most from palliative treatment with the radionucleotide (186) Re-HEDP [125].

Further research is needed in the assessment of the utility of bone markers in selection of patients for radionucleotide therapy, but data so far suggests that high pre-treatment bone turnover markers may predict for response to therapy [126].

External beam palliative radiotherapy is well established for the treatment of symptomatic bone metastases [127]. The exact mechanism of its action is still uncertain, although tumor cell kill may be an important reason. However, the absence of a dose-response relation, rapid responses, and poor correlation of efficacy with radiosensitivity suggest that an effect on host mechanisms of pain could also be important. Markers of bone remodeling have been shown to be suppressed by anti-resorptive therapy, and the response of these bone markers has been applied to monitoring therapy for bone metastases.

In the UK Bone Pain Radiotherapy Trial [128], 22 patients were entered into a supplementary study to establish the effects of local radiotherapy for metastatic

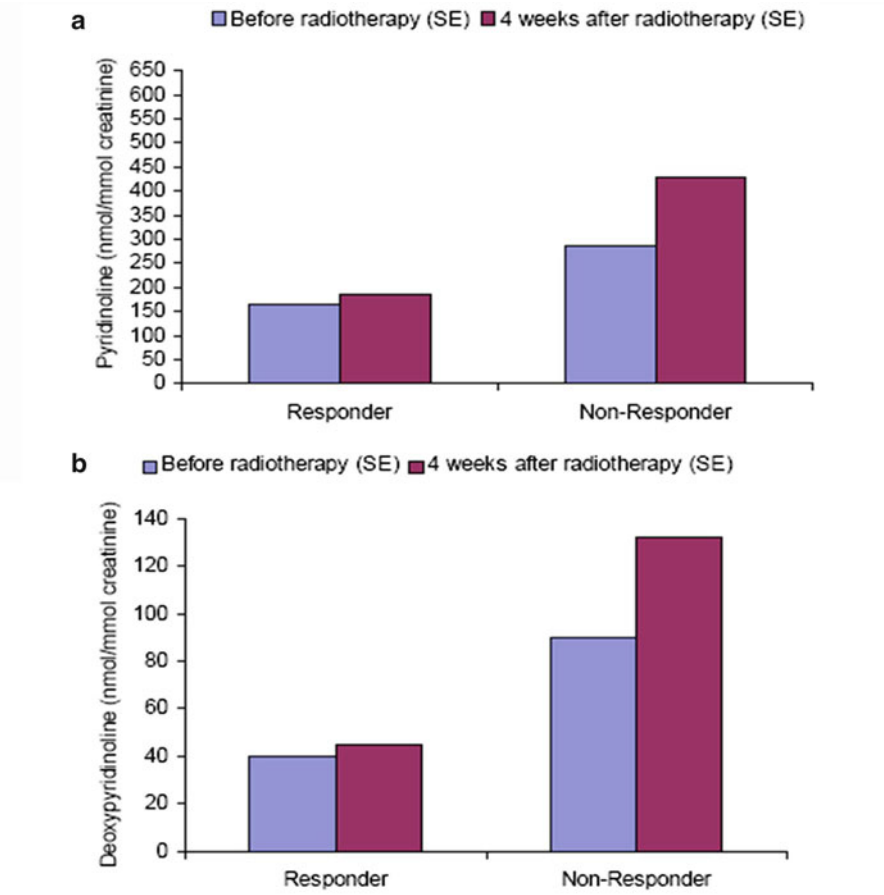

Fig. 6.2 Effect of radiotherapy on urinary markers of osteoclast activity related to pain response (**a**) pyridinoline; (**b**) deoxypridinoline

bone pain on markers of osteoclast activity, particularly the PYD and DPD, the latter being specific for bone turnover [129, 130]. Urine samples were collected before and 1 month after radiotherapy. Patients were treated with either a single 8 Gy or 20 Gy in five daily fractions. Pain response was scored with validated pain charts completed by patients.

Urinary pyridinium concentrations were compared with pain response (Fig. 6.2). In the non-responding patients, baseline concentrations of both PYD and DPD were higher than responders, and rose further after treatment, whereas in responders, the mean values remained unchanged. This resulted in significant differences between responders and non-responders for both indices after treatment ($p=0.027$). The authors conclude that radiotherapy-mediated inhibition of bone resorption, and thus

osteoclastic activity, could be a predictor for pain response. They also propose either that tumor cell killing reduces the production of osteoclast activating factors, or that there is a direct effect upon osteoclasts within the radiation volume, distant from tumor shrinkage. Their study supports the results from randomized trials that high dose radiotherapy is not necessary for pain relief, and that single low-doses of treatment are more than adequate for most patients. However, their study is limited by a small sample size.

Three additional studies have investigated markers and their levels after palliative radiotherapy. Topkan and Karaoglu [131] assessed the response of urine calcium (Ca^{2+}) and deoxypyridinoline (DPD) for prediction of response to palliative radiotherapy for metastatic bone disease. A total of 42 patients with breast or lung primary cancers were enrolled and received 30 Gy in ten fractions. Ca^{2+} and DPD were measured before radiotherapy, and 6 and 12 weeks after. There was significant correlation at baseline between pre-irradiation Ca^{2+} ($r = 0.6$, $p < 0.001$) and DPD ($r = 0.8$, $p < 0.001$) to the extent of bone metastases, confirming that these were appropriate markers. In patients without disease progression outside the treated sites, there was significant decrease in Ca^{2+} and DPD ($p < 0.001$). In those with bone disease progression, Ca^{2+} and DPD significantly increased ($p = 0.006$ and $p = 0.009$, respectively). The authors concluded that both markers were able to predict progression of bone metastases in cancer patients. Unfortunately, the measurements of biomarkers stratifying by pain response to radiotherapy were not analyzed.

Mose et al. [132] analyzed TRACP5b as a marker after irradiation for bone metastases. A total of 48 breast cancer patients with bone metastases were analyzed at the beginning and end of radiotherapy, and at 6 and 12 weeks post-treatment. Patients with $< = 3$ bone metastases had significantly lower levels of TRACP5b than those with >3 bone metastases ($p = 0.01$). In patients who did not have bone metastases progression in non-irradiated regions, there was a significant decrease in TRACP5b whereas those that did progress remained stable.

Pain flare is a common side effect of palliative radiotherapy for bone metastases. De Angelis et al. [133] analyzed urinary cytokines/chemokines as markers of pain flare in these patients and found that EGF, fractalkine, GRO, IL-8, IP-10, MCP-1, MDC, sIL-2Ra and TGF-alpha levels increased after radiation in patients who had a pain flare; PDGF-AA decreased while IL-4 and VEGF were stable. These preliminary results are promising and it is hoped that additional data be gathered during the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) SC.23 trial which investigates pain flare after palliative radiotherapy for bone metastases. It should also be mentioned that recently, the NCIC CTG SC.20 trial, investigating optimal re-irradiation dose for painful bone metastases closed. This trial also collected urine with the hopes of assessing markers associated with response to radiotherapy.

6.10 Current and Future Directions

Bone biomarkers have played and continue to play a key role in the research and development of new bone specific therapies including bisphosphonates and, more recently, RANK-L inhibitors and other agents such as cathepsin-K. All agents

which have proved to be useful in bone specific therapy have demonstrated a reduction in bone resorption markers and this currently has become a requisite for development of new agents for clinical success. For example, the novel, fully human monoclonal antibody specific to RANK-L, denosumab, has been investigated in multiple trials for the prevention and treatment of bone metastases, as previously discussed, and has now gained approval by the FDA and EMEA for use in solid tumours in both America and Europe. A recent cost-effectiveness analysis of denosumab vs zoledronic acid across solid tumour types with bone metastasis, demonstrated acceptable cost per QALY gained for denosumab vs zoledronic acid in CRPC, breast and non small cell lung cancer [134].

With this exciting phase of development which is likely to result in approval of several new bone specific agents for routine therapy, bone markers may also have an important role in directing choice of therapy or, indeed, switch from one agent to another at different stages of a patient's illness, as demonstrated in the Phase II trial of denosumab in bone metastatic solid tumour patients with high uNTX despite prior IV bisphosphonate treatment [104]. These data suggest that a switch of agent could add benefit to patients with particularly aggressive metastatic bone disease.

Most work with bone biomarkers in cancer relates to existing bone metastases and therapies to reduce skeletal complications and, although there is some work suggesting that increases in bone resorption markers may represent an early indication of impending macroscopic bone metastases which are not yet detectable using imaging techniques [76, 84, 135], there are currently no biomarkers which are able to predict individual risk of developing metastatic bone disease. Such markers are urgently needed since it will be important on cost and safety grounds to direct adjuvant anti-metastatic therapy to those patients who are most likely to benefit. This is especially topical, since recent studies [136] [137] have highlighted the likely adjuvant use of zoledronic acid and other agents in preventing bone metastases. For such studies, newer, more sensitive technologies such as proteomics present exciting opportunities in novel biomarker discovery. Matrix metalloproteinases, cathepsin K and other proteases derived from both the invading cancer cells and the bone microenvironment play key roles in the metastatic process suggesting a rich source of protein fragments for proteomic studies. However, at present, proteomic approaches remain relatively unexploited in bone metastasis. The relatively sparse existing body of proteomic knowledge regarding bone cancer and the potential for the future has been reviewed by Suva and colleagues [138]. Several research groups are now focusing in this area.

In conclusion, although the development of bone metastases is generally regarded as indicating that curative management is no longer feasible, developments in bone specific therapies and the parallel development of accurate and meaningful bone biomarker measurements have improved clinical care for these patients. New bone specific therapies may be expected to continue to emerge, complementing and enhancing the bisphosphonates. In parallel, novel bone markers such as BSP, TRACP5b, RANK-L, OPG and sclerostin still require further study and verification in particular tumour types and their usefulness remains to be determined. In practice, however, full validation and exploitation of biomarkers requires extensive prospective clinical trials and this is likely to limit the number of bone biomarkers which will enter routine clinical practice.

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Chapter 7
The Application of 'Omics' Techniques for Cancers That Metastasise to Bone: From Biological Mechanism to Biomarkers

Steven L. Wood and Janet E. Brown

Abstract The study of the mechanisms underlying the spread of cancer to sites of bone metastasis have benefitted greatly from recent advances in the high-throughput analysis of biomolecules using modern "omic" techniques. Omic-based profiling can provide both qualitative and quantitative data about the expression of key biomolecules within body fluids, tissues and sub-cellular compartments within both healthy and disease states. Individual omic platforms which analyse DNA-sequences (genomics), mRNA (transcriptomics), proteins (proteomics) and metabolites (metabolomics) have provided key information relating to the biological alterations which occur as a result of cancer spread to bone. Application of omic-techniques to both patient derived samples and animal models of bone metastasis have identified molecules which could serve as diagnostic and prognostic biomarkers of disease development. Biomarkers identified by omic techniques also offer the potential to assist in making cancer treatment decisions. Biomarkers identified by omic techniques require extensive validation in large patient cohorts and across multiple institutions before their adoption within clinical practice. The large number of potential biomarkers which have already been identified within pre-clinical omic-based studies in the field of bone metastatic cancer provides considerable promise for the future of both cancer detection and treatment.

Keywords Multiple myeloma • Prostate cancer • Breast cancer • Biomarker • Proteomics • Genomics • Metabolomics

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Abbreviations

APRIL	A proliferation inducing ligand
BAFF	B-cell activating factor
BCa	Breast cancer
cDNA	Complementary DNA
miRNA	Micro-RNA
MM	Multiple myeloma
mRNA	Messenger RNA
MS	Mass spectrometry
NMR	Nuclear magnetic resonance
PCa	Prostate cancer
TF	Transcription factor

7.1 Introduction: The Promise of "Omics" in Bone Metastasis

Bone metastasis occurs in greater than 70 % of patients with advanced breast and prostate cancer and multiple myeloma. The consequent skeletal complications, which include pathological fracture, bone pain, spinal cord compression and hypercalcaemia represent a major cause of morbidity and loss of quality of life [1, 2]. Prediction of patients at high risk of developing bone metastases as well as early diagnosis would enable more timely and effective interventions aimed at prevention or treatment of bone metastases. Markers of cancer development and metastatic spread have historically been discovered by immunological profiling of tissues and body fluids (for instance the elucidation of serum prostate specific antigen-PSA [3]). Scientific developments such as the sequencing of the complete human genome (complete sequence published in 2003), combined with high speed computing and other technological developments within analytical chemistry have ushered in the era of large scale qualitative and quantitative analysis of biomolecules ("omics"-technologies). These high-throughput platforms for biomolecular analysis offer exciting prospects of discovering new and improved markers for cancer metastasis to bone, as well as the identification of pivotal molecules within cancer development and spread which may serves as future drug targets.

7.2 Molecular Profiling: Genomics, Proteomics, Metabolomics

The term "omic technologies" refers to a series of techniques and methodological platforms which each aim to characterize biomolecules using approaches with a degree of generic applicability to a given type of biomolecule. In the process by

which biological information flows from DNA (gene sequences and non-transcribed regulatory elements), through to transcription of mRNA, translation into proteins (and their associated post-translational modifications) and the eventual effect of protein expression upon metabolite levels within the cell, "omics" technologies embrace the fields of: genomics (DNA), functional genomics (mRNA), proteomics (proteins) and metabolomics (metabolites) respectively (see Fig. 7.1). Each of these fields of "omic" research includes a wide variety of potential techniques and a thorough description of all the methods available for omic-research is beyond the scope of this chapter, however a general overview will be given. The information which each method can provide can include: (1) identification of the molecules involved, (2) quantification of the amount of biomolecules present within defined biological states/systems-quantitative omics approaches, (3) characterization of the molecular interactions between biomolecules and (4) identification and quantification of the molecular alterations which can diversify a given biomolecule into numerous isoforms. The information from omic-studies can provide several useful outputs of clinical utility including mechanistic insight into the development of disease and/or candidate biomarkers. The official NIH definition of a biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [4]. The discovery of biomarkers and of mechanistic insights into disease development are by no means mutually exclusive and key mechanistic players may indeed be biomarkers of disease.

7.2.1 Genomic Analysis

7.2.1.1 Methodology

Genomic techniques involve sequencing of DNA, the determination of gene sequences, base-substitution mutations within genes, sequencing and identification of gene fusions, and the detection of duplications and deletions of key areas of the genome and their relation to disease states. Genomic platforms have evolved to allow the sequencing of whole genomes (using paired end sequencing) [5] and the technology has developed to enable genomic sequencing from single cells [6]. In addition to sequence alterations cancers can also display gene copy number alterations. Normal cells are diploid containing two copies of every gene (one on each chromosome pair-with the exception of sex-linked genes on the X and Y chromosomes in males). Within many cancers regions of chromosomes are duplicated resulting in genes having more than two copies per cell and sometimes entire chromosomes are duplicated (polyploidy). Cancers can also harbour deletions resulting in less than two copies of genes per cell, and this can also encompass loss of entire chromosomes (aneuploidy). Copy number alterations within genes can be detected by array-based comparative genomic hybridization (aCGH) which enables the detection of copy number alterations

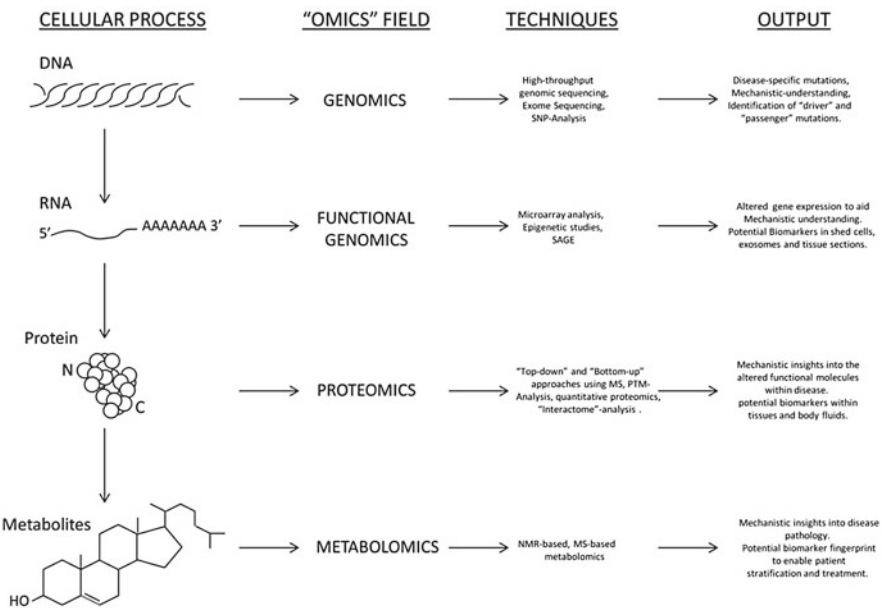

Fig. 7.1 "Omics" strategies within biomarker discovery and biological research-an overview: "Omic"-approaches apply molecular characterization methodologies to biomolecules within the flow of biological information from DNA, through to mRNA, protein and eventually alterations within cellular metabolites ("Cellular process"). Different classes of biomolecules are analysed within: genomics (for DNA sequence analysis), functional genomics (for mRNA analysis), proteomics (for protein analysis) and metabolomics (for the analysis of metabolites). The individual omic procedures each encompass a wide-range of different techniques which can produce different types of data pertinent to disease aetiology, prediction of clinical outcomes and guidance of treatment options. Genomic analysis (using techniques such as next-generation sequencing) can identify key genes mutated within disease, germline mutations which predispose towards disease or disease-associated single nucleotide polymorphisms (SNPs). Functional genomic profiling determines the level of gene-transcripts and in some cases provides useful fingerprints for molecular profiling of tumours enabling patient-centred treatment decisions for personalized medicine. Proteomics and metabolomics identify alterations in proteins and metabolites. The data arising from proteomics can be both qualitative (presence/absence of proteins) or quantitative depending upon the technique being used. Metabolomics provides quantitative information about the levels of metabolites within disease and this information can be used to supplement data from other molecular profiling strategies to provide an improved patient-diagnostic/prognostic/treatment-oriented decision tool to aid disease management. In addition to biomarker discovery all of these platforms have the potential to discover key molecules involved in disease which could function as drug targets

within genes and whole chromosomes [7]. Genomic techniques for molecular classification have begun to impact upon patient diagnosis and treatment. For instance within breast cancer the Mammaprint®, (Agendia, Irvine, CA, USA) microarray based kit [8], and the OncotypeDX®, (Genomic Health, Inc, Redwood City, CA, USA) PCR-based kits [9], are both approved for use in standard clinical treatment guidelines.

7.2.1.2 Applicability

Current state of the art methods for genomic analysis (i.e., next generation sequencing-NGS) require a cellular source of DNA which can be obtained from solid tumours or circulating cancer cells. Solid tumours are challenging due to their heterogeneity as well as the presence of normal, healthy cells within the tumour mass. For this reason most studies focus on tumours with >60 % tumour nuclei present [10]. For diffuse tumour-types, such as pancreas and prostate cancer, laser-capture microdissection (LCM) can be employed, however this approach is challenging due to the low yields of genomic DNA (<100 ng). Genomic sequencing has the potential to reveal mechanistic aspects of cancer development including the identification of somatic mutations predictive of poor disease outcome (e.g., in acute myeloid leukaemia-[11]), identifying the clonal origin and development of malignancy [12] and determining treatment options [13].

7.2.2 Functional Genomic Analysis

7.2.2.1 Methodology

Functional genomic methodologies study the products of gene expression, principally mRNA transcripts as well as regulatory RNAs such as microRNAs [14]. The main technological platform used within functional genomics have been microarrays. Microarray surfaces present a series of short impregnated oligonucleotides printed onto their surface which will hybridize along the length of specific mRNAs. More recently exon arrrays have been developed which present oligonucleotides specific to individual exons within genes. As exons are specific DNA regions which encode protein domains, and as these exons are frequently shuffled together in differing orders during gene expression (a process termed "alternative splicing")-exon arrays can provide information relevant to the expression of alternative protein isoforms. In addition to these array based methods deep-sequencing of mRNA (mRNA-seq) methods are becoming increasingly applied [15, 16]. By fluorescently tagging genetic material and using the principle of hybridization of complementary nucleic acid strands followed by the digital evaluation of fluorescent signals, microarrays allow the expression of tens of thousands of genes to be quantified simultaneously, and within pair-wise sample comparisons. Functional genomic studies can provide an assessment of the differentially expressed genes between two biological samples (e.g., healthy vs. cancer), as well as identifying alternative splicing events. This provides key mechanistic insights into the disease process as well as providing information relevant to patient stratification and guiding treatment options.

7.2.2.2 Applicability

Functional genomic screens profile cellular mRNA (the "transcriptome") and thus require either tumour derived cells, circulating cancer cells within the blood, or

released microsomes (small membranous vesicles reported recently to contain miRNAs [17]). The clinical value of functional genomic data is illustrated by the array of gene signature detection assays available to provide prognosis/prediction tools for breast cancer treatment [18]. Gene expression signatures can provide complementary information to histological tumour grade and patient health status to aid prediction of survival outcomes. Functional genomic profiling can also provide results aiding treatment decisions, e.g., the response to lenalidomide within del(5q) myelodysplastic syndromes (MDS) [19].

7.2.3 Proteomic Analysis

7.2.3.1 Methodology

A complete description of proteomic methods is beyond the scope of this book chapter however a review of these methods is provided within [20–22]. There are many different methodological platforms for proteomic analysis, and these can provide information including (i) identifying the proteins present within a biological sample, (ii) providing quantification of protein levels (and comparison of these levels amongst multiple samples), (iii) identification of protein-protein interactions ("interactomics"), (iv) identification of important regulatory post-translational modifications to proteins (e.g., phosphorylation), (v) profile temporal alterations in the levels of proteins within a biological system and (vi) identifying organelle and cellular localization. Whilst the number of proteomic hardware platforms and analytical strategies is great all methods use one of two different approaches: (a) "Top-down" proteomics-in which whole proteins and naturally occurring peptides are analysed and (b) "Bottom-up" proteomics-in which the proteins within a biological sample are digested into peptides in vitro using proteases (typically trypsin) and the resulting peptides analysed. Top-down proteomics is useful for identifying the range of Post-Translational Modifications (PTMs) within proteins-chemical modifications to the protein structure that are not part of the DNA encoded amino acid sequence (such as phosphorylation, glycosylation, ubiquitination) and alternative splicing/proteolytic isoforms within a sample, whilst bottom-up proteomics can generate larger data sets more rapidly due to the relative ease of identifying small peptides. Within biomarker discovery, proteomics has the advantage of identifying altered proteins, the class of molecules which are the target of almost all drug therapies. Furthermore altered protein expression cannot be inferred from genomic or functional genomic data sets.

7.2.3.2 Applicability

Proteomic approaches can be applied to tissue/cell-extracts, biological fluids (serum/plasma/urine) and more recently to tissue sections themselves. Each individual

sample type provides its own unique challenges-e.g., within serum/plasma the high level of a few major protein components makes detecting disease-specific proteins/peptides more difficult, a limitation partially overcome by using immunodepletion [23]. Proteomic data sets can provide mechanistic insights into disease processes as well as providing diagnostic, prognostic and treatment-decision orientated information to guide cancer management.

7.2.4 Metabolomic Analysis

7.2.4.1 Methodology

Metabolomic methods enable the identification and quantification of metabolites (e.g., salts, lipids, steroids, sugars, hydrocarbons and salts) within body fluids as well as tissues. Metabolomic studies involve metabolite extraction followed by separation of the metabolites and their identification. The separation of metabolites can be performed using liquid chromatography-LC [24] or gas-chromatography-GC [25], and metabolite identification can be performed using either mass-spectrometry (MS) or nuclear magnetic resonance (NMR) [26]. The advantage of using MS within metabolomics is sensitivity, whilst NMR provides relatively low sensitivity but high reproducibility. Metabolic alterations are a frequent phenomena within cancers via cellular alterations such as the Warburg effect-(increased glycolytic flux within cancers [27]) and the reverse-Warburg effect [28]. Other key metabolic alterations observed within cancer include: hypoxia, increased synthesis of proteins, fatty acids and nucleotides, altered *de novo* fatty acid synthesis and alterations within lipid metabolism. Metabolomic data can be combined with proteomic data to provide a more detailed diagnostic fingerprint of cancer development, thus increasing the specificity of cancer diagnosis [29]. One potential advantage of metabolomic alterations within disease monitoring arises from the fact that metabolic alterations are already being used within diagnostic/therapeutic tests-for instance mass-spectrometry is frequently used for measuring inborn errors of fatty acid and amino acid metabolism within newborn babies [30].

7.2.4.2 Applicability

Metabolomic analysis within cancer diagnosis currently faces some of the same hurdles and challenges as proteomics. Although body fluids can be analysed by both MS-based and NMR-based metabolomics, and solid tissue samples are also applicable (by magic-angle NMR) several key challenges remain. In order to reliably detect disease states the normal range and variability of metabolite levels requires an improved definition, and sample preparation procedures need a greater degree of standardization to enable comparison between studies [31]. Sample preparation for LC-MS based metabolomics using solvent extraction also faces the limitation that

each individual procedure samples only a sub-fraction of the entire metabolites present. Despite these limitations, metabolomics will provide biomarker signatures enhancing the diagnostic and prognostic utility of biomarkers discovered using other omic-platforms.

7.3 "Omic"-Strategies Within Bone-Metastatic Cancer

A summary of individual studies relating to cancers that metastasise to bone will now be presented. An overview of selected "omic"-biomarker studies is provided within Table 7.1.

7.4 Bone Metastasis in Multiple-Myeloma

7.4.1 Multiple Myeloma: Role of Epigenetic Regulation Within Bone Metastasis Revealed by Proteomic Profiling

The term "epigenetics" refers to a series of heritable modifications within the genome that do not consist of DNA-sequence alterations. Several forms of epigenetic modification have been identified within cancer including: (a) methylation of gene-promoter regions resulting in gene-silencing ("DNA-methylation") [32]; (b) post-translational modification of the histone-components that bind DNA within the nucleus "histone modification" [33]; (c) repositioning of the nucleosomes to different DNA regions ("nucleosomal repositioning") [34] and (d) the regulation of gene expression by short 18–25 nucleotide micro-RNAs ("miRNA") [35].

Several miRNAS have been discovered which play a role in the developmental pathway of multiple myeloma from normal plasma cells through to MGUS and MM, including miR-21, miR-106b-25 cluster, miR181a and b, miR-32 and mIR-17-92 cluster [36]. miR-21 has received particular attention as a micro-RNA frequently over-expressed in a wide range of cancers including numerous solid tumours (hepatocellular carcinomas, gastric cancer, cervical carcinoma, ovarian carcinoma, head and neck cancers and papillary thyroid carcinomas) as well as leukemic cancers and thus a miRNA which functions as a classical oncogenic miRNA or "OncomiR" [37]. Quantitative reverse-transcription-polymerase chain reaction (qRT-PCR) enables the amplification of mRNA transcripts into cDNA with incorporation of fluorescent groups and the ability to monitor the rate of fluorescence-incorporation in real time. The rate of incorporation of the fluorescent signal is proportional to the amount of mRNA in the sample enabling as estimation of the relative level of different mRNA transcripts and this approach can be applied to miRNAs as well. In a PCR-based study of myeloma cells it was observed that

Table 7.1 Summary of key "omics"-driven studies within bone metastasis research

"Omic" method applied	Source material	Biomarker(s) discovered/ mechanistic insight	Clinical utility	Reference
Multiple myeloma				
Functional genomics: Microarray analysis	Multiple myeloma cell-lines with varying levels of TACI-expression cultured with A-Proliferation Inducing Factor (APRIL) and B-Cell-Activating Factor (BAFF)	BM-environment-derived cytokines BAFF and APRIL signal via TACI receptor to promote plasmablastic development and BM-dependence	Potential antibody-based therapeutic target	[45]
Proteomics: SILAC-labelling of multiple myeloma cell-line	Multiple myeloma cell-line with altered expression of miR-21, combined with SILAC labelling	Identification of PIAS3 as a STAT3-regulator within multiple myeloma	Identification of a potential diagnostic marker and potential drug target	[39]
Proteomics: Array based protein analysis of phosphoproteins	Comparison of normal plasma cells and isolated multiple myeloma cells	Identification of differentially phosphorylated proteins including mTOR/p70S6K and ERK1/2	Identification of potential therapeutic drug targets	[105]
Proteomics: Phosphoproteomic profiling	MM cell-line treat with FGF1 + orthovanadate or FGF-inhibitor	Differential FGF-mediated phosphorylations identified, including RSK2, cytoskeletal proteins	Mechanistic insight into MM cell-signalling. Potential diagnostic tissue/serum-based biomarker	[50]
Prostate cancer				
Functional genomics: Gene-expression profiling, BeadChip™ (Illumina)	C4-2B Prostate cancer cells expressing WT or mutant doxycycline-inducible Runx2-transcription factor	Runx2 induces genes in cell-cycle, proteolysis, cytoskeleton, intracellular signalling and transcription factors	Identification of Runx 2 as a potential diagnostic, prognostic or therapeutic target	[66]
Proteomics: iTRAQ-based quantitative proteomics	Pooled serum samples from patients with bone metastasis, no metastasis but clinical progress of PCa, BPH etc.	Identification of differentially expressed proteins including eukaryotic translation elongation factor1 alpha 1 (eEF1A1) in PCa bone metastasis	Potential diagnostic biomarker	[76]

(continued)

Table 7.1 (continued)

"Omic" method applied	Source material	Biomarker(s) discovered/ mechanistic insight	Clinical utility	Reference
Proteomics: SELDI-TOF-MS of PCa sera	Serum from PCa patients with and without bone metastases	Serum amyloid protein-A (SAA) identified as differentially expressed with bone metastasis	Potential diagnostic biomarker	[77]
Metabolomics: GC-MS	Comparison of BPH vs. PCa metastasis tissues	Elevated sarcosine levels in metastatic prostate cancer	Potential diagnostic indicator for metastatic spread	[53]
Metabolomics: GC-MS	Comparison of BPH vs. PCa metastasis tissues	34 metabolites identified as differentially expressed within metastasis	Mechanistic insight into metabolic alterations within metastasis and possible diagnostic indicator	[54]
Breast cancer				
Functional genomics: Analysis of gene set enrichment analysis data sets	Deposited gene set enrichment analysis (GSEA) data	Role of cytokines and cytokine-receptors in breast cancer metastasis to bone	Identification of Noggin as bone metastasis-specific gene within breast cancer	[79]
Functional genomics and secretome profiling	MDA-MB-231 cell lines with varying degrees of metastatic potential	Cystatin-E/M (CST6) is down-regulated within bone metastatic breast cancer	Identification of key physiological suppressor of bone metastasis	[106]
Functional genomics: Microarray analysis of mouse model of breast cancer metastasis to bone	RNA from parental MDA-MB-231 cells and bone-homing variant	Identification of VCAM-1 as mediator of breast cancer metastatic growth within bone	Identification of potential antibody-based drug target	[93]
Functional genomics: cDNA-microarrays	RNA from breast primary tumour as well as patient matched metastasis	Primary tumour is very similar to the distant metastasis	Suggests that metastases occur via inherent features and not clonal selection	[91]
Proteomics: Cell-surface biotinylation and protein identification by LC-MSMS	MDA-MB-231 breast cancer cells and osteotropic variant MDA-MB-231-B02	Metastatic cells have lower class-I HLA expression and higher expression of αvβ3-integrin	Identification of potential antibody-based drug targets	[94]
Proteomics: Analysis of glycoproteins, cell-surface proteins and extracellular proteins from primary tumour and bone metastasis	Isolated primary tumour and bone metastasis from individual patient	Identification of differentially expressed proteins including Sushi-domain containing protein-2 (SUSD2) in bone metastases	Potential diagnostic and drug-targets within patient matched, isogenic samples	[95]

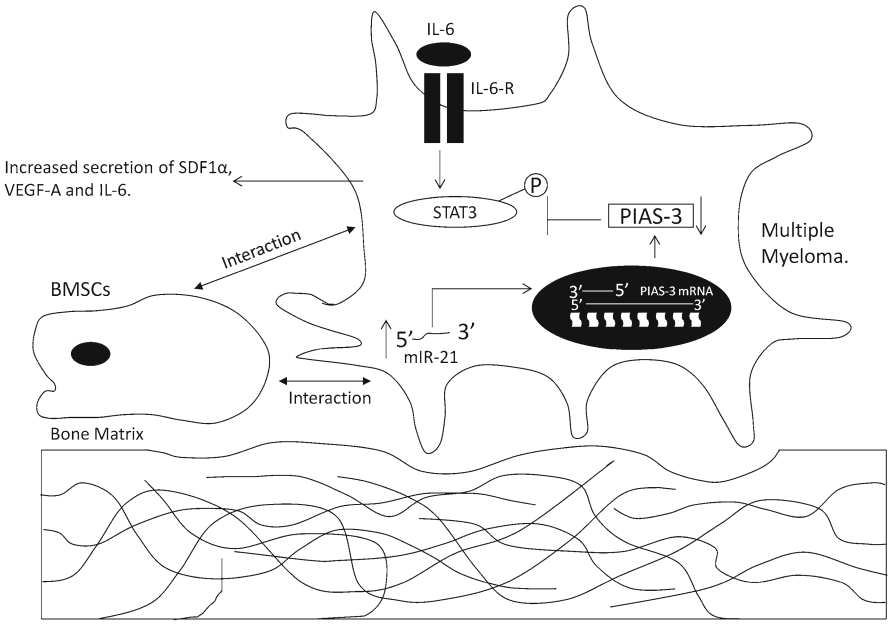

Fig. 7.2 Proteomic analysis of multiple myeloma cells identifies a regulatory network stimulating cancer cell proliferation: Multiple myeloma cells within the bone microenvironment are in contact with bone marrow stromal cells (BMSCs). The interaction with BMSCs promotes MM-cells to secrete several autocrine and paracrine factors including SDF1α, VEGF-A and IL-6. Contact with BMSCs also increases the level of miR-21 within bone-resident MM-cells. One of the targets of miR-21 action is the gene for PIAS-3. PIAS-3 decreases cell-proliferation by dephosphorylating STAT-3 downstream of the IL-6 receptor (IL-6-R). Contact with BMSCs thus activates MM-cell proliferation both by stimulating the release of proliferative autocrine and paracrine cytokines and growth factors from MM cells, but also by inhibiting a growth-inhibitory pathway acting via PIAS-3 and STAT3

miR-21 levels were increased when these cells were cultured in the presence of bone marrow stromal cells (BMSCs) [38]. The miR-21-induced alterations in protein expression occurring within MM cells were profiled by selective knockdown of miR-21 expression following transfection with a locked nucleic acid anti-miR-21 oligonucleotide (LNA-21) and in the control experiment transfection with a control oligonucleotide (LNA-cont) (see Fig. 7.2). SILAC-labelling of cells transfected with LNA-miR-21 and LNA-cont enabled the quantitative estimation of the global proteomic alterations occurring in response to the action of miR-21. Several proteins were identified as potential miR-21-targets including the Protein Inhibitor of activated STAT3 (PIAS3)-a negative regulator of Signal Transducer and Activator of Transcription 3 (STAT3) activity [39]. Constitutive STAT3 signalling has been strongly implicated in the development of MM [40] and PIAS3 has been demonstrated to negatively regulate IL-6-mediated STAT3-signalling within MM cells [41]. SILAC-based comparison of a MM-cell line before and after H1-parvovirus-mediated reversion of the malignant phenotype identified 379

proteins which were either increased or decreased during cell-reversion with STAT3 being the most significantly down-regulated, further pointing to a role of STAT3 in MM-progression [42].

In addition to a role in the regulation of miRNA-21 levels, binding or MM-cells to BMSCs also increases the secretion of cytokines such as stromal-derived factor-1α (SDF-1α), vascular endothelial growth factor (VEGF) and interleukin-6 (IL-6) which promote cell-survival, migration and angiogenesis. The bone environment thus promotes multiple myeloma cell survival via a number of mechanisms including cell-cell contact and receptor mediated signalling as well as epigenetic modification within metastatic MM cells themselves (see Fig. 7.2).

Functional genomic studies combined with SILAC-labelling and proteomic analysis have thus identified a key epigenetic switch responsible for the adaptation of multiple myeloma cells to growth within the bone metastatic niche. This work also identifies the IL-6/STAT3 signalling pathway as a potential drug target within multiple myeloma.

7.4.2 Functional Genomic Profiling Identifies a Gene-Signature Predictive of Dependence Upon the Bone-Microenvironment

The survival and proliferation of MM cells within the bone microenvironment is promoted by a number of autocrine and paracrine signalling systems which enhance tumour cell proliferation and inhibit tumour cell apoptosis. Several members of the tumour necrosis factor (TNF) family have been reported to be elevated within the serum of patients with MM, including B-cell Activating Factor (BAFF), and A Proliferation-Inducing Ligand (APRIL) [43, 44]. BAFF and APRIL are produced within the bone microenvironment with APRIL being a significant factor released by osteoclasts [45]. Several receptors for BAFF and APRIL have been identified within malignant plasma cells including the receptors TAC1 (Transmembrane activator and calcium modulator and Cyclophilin Ligand Interactor) and BCMA (B-Cell Maturation Antigen).

Gene expression profiling of purified MM cells from patients across a range of clinical grades, followed by hierarchical clustering identified two sub-groups of patients, a $TACI^{high}$ subgroup and a $TACI^{low}$ subgroup with a 659-gene signature differentially expressed between them [45]. $TACI^{high}$ MM cells displayed a gene signature more similar to that of mature plasma cells, with a preponderance of up-regulated transcripts encoding autocrine/paracrine signalling components and receptors responsible for interaction with the extracellular matrix (ECM) and bone microenvironment. In contrast $TACI^{low}$ MM cells express a gene signature with a preponderance of cell-cycle genes resembling the profile of plasmablastic cells. Treatment of purified MM-cells with BAFF/APRIL did not alter the expression pattern of the signature genes within the $TACI^{high}$/$TACI^{low}$ signatures suggesting

that these transcriptional profiles may arise from exposure to the bone microenvironment and not be directly regulated BAFF/APRIL transcripts themselves. $TACI^{low}$ patients have a higher proportion of advanced stage III MM cases, more frequent bone lesions and a decreased haemoglobin level and an overall worse prognosis than $TACI^{high}$ patients. In particular the $TACI^{high/low}$ status of patients did not correlate with other known clinical parameters and risk factors including levels of β2m/LDH or CRP, suggesting that TACI may well be an independent prognostic factor for outcome within MM. Stratification of MM cases into $TACI^{high/low}$ subclasses could also aid treatment decisions as many therapeutic agents target components of the bone microenvironment and autocrine/paracrine signalling components responsible for tumour cell survival.

7.4.3 Phosphoproteomic Profiling to Identify Key Signalling Components Within Multiple Myeloma Bone Metastases

Altered cellular signalling within MM could represent a potential target for future drug discovery. Several signalling networks involving tyrosine-phosphorylation are altered within multiple myelomas. A subgroup of MM cases harbour the t(4;14) chromosomal translocation which results in the activation of the fibroblast growth factor receptor-3 (FGFR3) [46] and a role for activation of FGFR3 has been identified within a variety of cancers including bladder, colon and cervical cancers as well as skeletal dysplasia's [47]. Signalling via FGFR3 occurs via a similar mechanism to many receptor tyrosine kinases (RTKs), in which ligand binding to the extracellular domain of the receptor triggers receptor activation and autophosphorylation of key tyrosine-residues within the cytoplasmic domain of the receptor. These phosphorylated sites can act as docking sites for key-signalling proteins which contain src-homology-2 (SH2) and protein-tyrosine-binding (PTB)-binding domains [48, 49]. The activated receptor tyrosine kinases can also phosphorylate other proteins in a signalling cascade. Phosphoproteomic identification of key proteins involved in FGFR3 signalling has been facilitated by use of an FGFR3-inhibitor PD173074, as well as by stimulatory treatment of MM cells with FGF1 and the pan-tyrosine-phosphatase inhibitor orthovanandate. Isolation of phosphotyrosine-containing peptides from the MM-cell line KMS11 treated with PD173074, or with FGF1+orthovanandate, followed by label-free quantification identified a series of protein phosphorylation sites which were increased by FGF1-treatment and inhibited by PD173074-treatment [50]. These candidate FGFR3-mediated targets included proteins within cell-signalling cascades (Ribosomal S6 Kinase 2-RSK2, proteins involved in endocytosis which may regulate FGFR3 signalling, cytoskelatal proteins and proteins which regulate growth factor signalling to MM cells) [50]. This phosphoproteomic study identified key proteins responsible for the FGFR3-mediated growth of multiple-myeloma. Targets such as RSK-2 may also be potential drug targets within multiple myeloma.

7.5 Prostate Cancer Metastasis to Bone

7.5.1 Metabolomic Alterations Within Prostate Cancer Metastasis to Bone

Metabolic alterations accompanying prostate cancer metastasis to bone could potentially be utilized to aid the prognosis of prostate cancer metastatic spread enabling more rapid application of drug treatments. Several metabolomic studies have been performed within prostate cancer including: (a) a reduction in citrate concentrations within primary prostate tumours compared to benign prostatic hyperplasia (BPH) or normal prostate tissues [51], as well as (b) a ^{1}H-NMR study which demonstrated statistically significant altered ratios of citrate/lactate, citrate/total choline, phosphocholine/total creatinine, choline/total creatinine, alanine/total creatinine, phosphoethanolamine/total phosphate, phosphocholine/total phosphate and glycerophosphoethanolamine/total phosphate within prostate cancer tissue samples compared to BPH samples [52]. In contrast here have been few metabolomic studies of prostate cancer metastasis to bone.

To date there have been a few metabolomic studies within prostate cancer metastasis. Using gas-chromatography-MS (GC-MS) Sreekumar et al. [53] identified elevated levels of sarcosine (an N-methylated derivative of the amino acid glycine) as being elevated in prostate cancer invasion. Within this study it was observed that reduction in the level of sarcosine (by knock-down of glycine n-methyltransferase) attenuated the invasive potential of prostate cancer cell lines. Similarly increasing the level of sarcosine (by knock down of the sarcosine degrading enzyme sarcosine dehydrogenase) increased the invasive potential of prostate endothelial cells [53].

Metabolomic profiling of normal-bone and prostate cancer derived bone metastases by GC-MS identified a panel of 71 metabolite peaks of which 34 were identifiable [54]. Validation of this data set was also performed by GC-MS analysis of plasma samples from prostate cancer patients with and without bone metastases as well as plasma samples from patients with benign prostate disease. In addition metabolomic profiling of both malignant and benign prostate tissue was also performed and the results also indicated increased cholesterol levels within bone metastatic prostate cancer [54]. A key metabolite observed to alter within bone metastatic prostate cancer was cholesterol, with statistically significant higher levels of cholesterol within prostate cancer bone metastases than from bone metastases derived from other forms of cancer. Increased immunostaining for the low-density lipoprotein receptor (LDL-R) as well as the scavenger receptor class B type I receptor (SR-B1) suggested an increased potential for bone metastatic prostate cancer cells to take up cholesterol containing lipoproteins. In addition increased immunostaining for 3-hydroxy-3-methyl-glutaryl-CoA-reductase (HMG-CoA-Reductase) was observed in osteoblasts situated adjacent to the metastatic prostate cancer cells [54].

This panel of metabolites identified in advanced, metastatic prostate cancer may enable the earlier detection of cancer spread to bone (particularly when

using high-sensitivity methods such as LC-MS). In combination with proteomic biomarker profiles this may facilitate the high-sensitivity, high specificity detection of malignant spread to bone.

7.5.2 *Transcriptomic Alterations Within Bone-Metastatic Prostate Cancer Cells*

Functional genomic studies of the altered gene expression profiles within bone metastatic prostate cancers have attempted to identify master transcriptional regulators of bone colonization. Several transcription factors have been implicated in osteoblastogenesis including the Runx-transcription factor family member Runx2 [55–57]. Runx2 transcriptional activity has been associated with expression of key-bone proteins including bone sialoprotein [58], MMP9 [59] and Runx2 expression induces the mineralization of prostate cancer cell-lines [60]. Gene expression analyses have identified a panel of genes which are Runx2 targets including: genes mediating anti-apoptotic protection of prostate cancer cells e.g., survivin and Bcl2 [61, 62], increases in prostate cancer cell survival via elevated expression of BMP7 [63, 64], as well as known genes involved in epithelial-mesenchymal transition (EMT), invasiveness, degradation of the extracellular matrix, bone breakdown and angiogenesis [59, 65–67] and osteoclast differentiation [59, 65, 66]. The combined effect of these transcriptional alterations is to promote prostate cancer growth within and adaptation to the bone environment (see Fig. 7.3).

The molecular events which trigger Runx2 expression and activation when prostate cancer cells metastasize to bone are a subject of intensive research. Recent studies revealed a role for SMAD5 phosphorylation within the signal transduction pathway leading to Runx2 activation [68]. Transcriptional activation of Runx2 with resultant increased RANKL production by metastatic prostate cancer cells requires phosphorylation of both SMAD5 and Runx2. SMAD5 phosphorylation increases when hyaluronan (a major component of the ECM within bone) binds to the cell surface receptor CD44 on prostate cancer cells [69]. Runx2 phosphorylation was observed to require ligation of the cell surface receptor αvβ3-integrin [68], and αvβ3-integrin has been demonstrated to bind osteopontin, a signalling component secreted by prostate cancer cells [70]. Increased bone resorption functions in concert with oestrogen receptor (ER) signalling to regulate Runx2 [71, 72] and there is evidence that Runx2 expression itself may be driven by a switch in the oestrogen receptor expression profile from the ERβ1 isoform (which suppresses Runx2 expression) to the ERβ2 isoform (which enhances Runx2 expression) [73] (See Fig. 7.3).

The transcriptomic profiling of bone-metastatic prostate cancer cells identifies a gene signature indicative of Runx2 transcriptional activation within bone metastases. Runx2 may therefore be a key target for therapies (including miRNA-mediated gene therapies) aiming to reduce prostate cancer spread to bone.

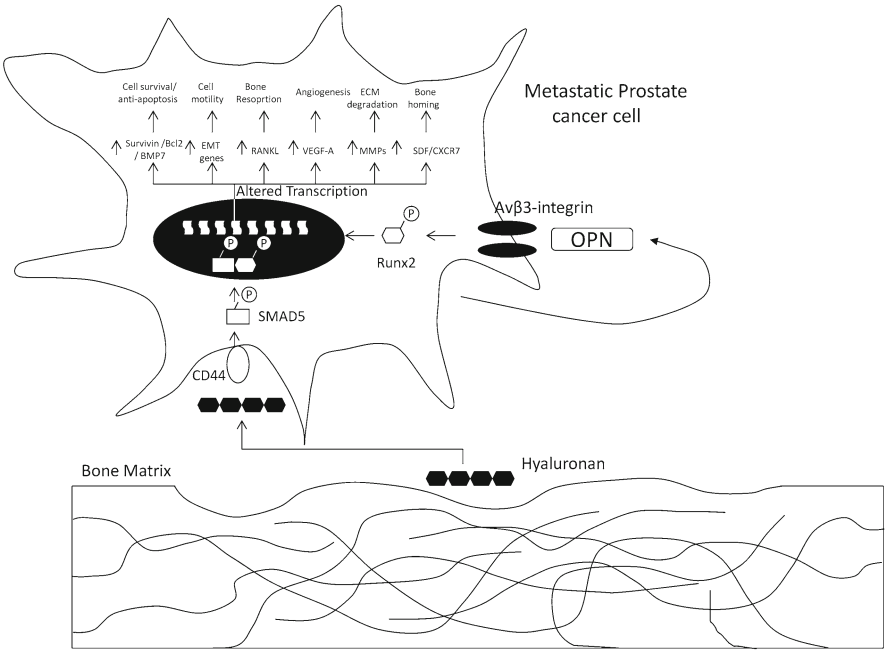

Fig. 7.3 Transcriptomic profiling identifies a key transcriptional regulator within bone-metastatic prostate cancer: Transcriptomic profiling has identified the Runx2 transcription factor as a key transcriptional regulator involved in prostate cancer metastasis to bone. Bone is a rich source of hyaluronan, a non-protein-containing glycosaminoglycan which binds to the receptor CD44 on metastatic prostate cancer cells triggering the phosphorylation of the SMAD5-transcriptional coactivator. Osteoprotogerin (OPN) which is secreted by metastatic prostate cancer cells, binds to the cell surface receptor αvβ3-integrin triggering phosphorylation of the transcription factor Runx2. The complex of phospho-SMAD5 and phospho-Runx2 can then activate the transcription and protein expression from genes involved in numerous aspects of prostate cancer metastasis to bone including: cell survival, increased bone resorption, extracellular matrix (ECM) degradation increased cell motility and osteoclast (OC) activation

7.5.3 Serum Diagnostic Markers for Prostate Cancer Metastasis to Bone

Diagnostic markers for prostate cancer metastasis to bone are urgently required to supplement current assessment procedures which typically involve isotope bone scanning (reviewed in [74]). Serum/plasma represents a potentially invaluable sample source for biomarker discovery as it can be obtained non-invasively. In the time course of prostate cancer development the failure of anti-androgen therapy initially presents as a biochemical failure characterized by rising serum prostate-specific antigen (PSA)-levels [75]. This biochemical failure predates the development of detectable bone metastases and metastasis-associated symptoms by a

median time of approximately 6-months [75]. Thus there is a window of time during which serum/plasma biochemical alterations predate the development of clinical symptoms of cancer-spread to bone. Earlier detection of bone micrometastases may enable more effective targeting of bone-directed therapies to target prostate cancer spread.

Proteomic profiling of prostate cancer serum samples using 4-plex iTRAQ was performed using 4 different groups of serum pools: (i) benign prostatic hyperplasia (BPH) samples, (ii) localised prostate cancer with no evidence of progression, (iii) localized prostate cancer with biochemical evidence of progression and (iv) serum from patients with confirmed bone metastases [76]. Of 122 proteins identified and quantified within this study 25 proteins were significantly differentially expressed between progressing vs. non-progressing cancer samples and 23 proteins were significantly differentially expressed between bone-metastatic and progressing samples. Within the 23 metastasis associated proteins eukaryotic translation elongation factor 1 alpha 1 (eEF1A1) was further validated by immunostaining of tissue microarrays and observed to be elevated within osteoblasts within close proximity to bone-metastases [76]. Low molecular weight-peptide-based biomarkers of prostate cancer metastasis to bone have also been identified by SELDI-TOF-MS, resulting in the identification of a series of serum amyloid protein A (SAA) isoforms with statistically significant elevated expression within serum from bone metastatic prostate cancer patients compared to prostate cancer patients without bone metastases, a result confirmed by immunoprecipitation assays [77].

"Bottom-up" proteomic analysis of prostate cancer serum samples, and characterization of the low-MW serum peptidome has thus identified potential early diagnostic markers for prostate cancer metastasis to bone.

7.6 Breast Cancer Metastasis to Bone

7.6.1 Breast Cancer Bone Metastasis: Transcriptional Profiling Reveals a Key Role for Transforming Growth-Factor-β (TGFβ)/Bone Morphogenetic Protein (BMP)-Signalling

Breast cancer primary tumours have been subject to extensive gene expression analysis using both commercially available microarray chips (i.e., Affymetrix) as well as using custom made chips, and the gene expression data from these studies are publicly available (via gene expression omnibus). These gene expression databases represent a potentially rich source of information for identifying key mediators of breast cancer development, relapse and metastatic spread. In a recent statistical analysis of these data sets a subset of genes were identified which correlated with

the risk of relapse. Members of this gene family subset displayed either increased or decreased expression levels correlating with risk of relapse across a panel comprising hundreds of breast cancer samples representing all stages of development and subtypes of breast cancer [78] and gene ontology analysis identified key members of this relapse- and metastasis-related gene family to be transforming growth factor-β (TGFβ) family cytokines and a key TGFβ-family member antagonist-Noggin [78, 79].

TGFβ has the ability to both inhibit as well as promote tumorigenesis depending upon the stage of cancer development [80–82]. The TGFβ-family of growth factors includes Bone morphogenetic Proteins (BMPs) which stimulate bone formation. Several BMP inhibitors have been identified which play diverse roles within developmental pathways, embryogenesis and cancer [83] including the BMP-antagonist Noggin. TGFβ-family cytokines play a variety of roles within breast cancer metastasis to bone in particular by altering the balance of bone formation and bone breakdown. Bone consists of mineralised extracellular matrix components, and numerous cell types including bone forming osteoblasts and bone-resorbing osteoclasts [84]. Osteoblasts secrete growth factors including Receptor of Activator of Nuclear Factor κB-Ligand (RANKL) which binds to the Receptor activator of Nuclear Factor-κB (RANK) on osteoclasts stimulating osteoclast maturation and bone degradation. Osteoblasts can also secrete osteoprotogerin (OPG) a soluble decoy receptor which inhibits RANKL function.

BMPs are members of the TGFβ-family of growth factors, a large family of growth factors with over 20 members with numerous diverse functions [85]. BMPs play key roles in bone-formation including the formation of the body-axis, and bone and cartilage formation [86]. Several BMP-family members promote bone formation by acting upon osteoblasts to increase their release of OPG and reduce the release of RANKL thereby inhibiting osteoclast mediated bone degradation. Within development BMP action is controlled by a series of secreted BMP-antagonists which also play key developmental roles [83]. Noggin is a key BMP-antagonist which is required for correct embryonic development [87] and gene-knockout studies have suggested that it plays a key role in skeletal development [88].

Mechanistic investigation of the role of noggin within breast cancer metastasis to bone revealed that high noggin-expression is strongly selected for within the bone environment (but not within metastases to the lung, liver or brain) [79]. Overexpression of noggin increased the growth rate of bone metastases within orthotopic mouse models as assessed by BioLuminescence imaging, furthermore shRNA-mediated gene silencing of noggin reduced the growth rate of bone metastases in the same study and modulation of noggin levels was observed to influence the ability of breast cancer cells to form tumourspheres-suggestive that noggin might also facilitate the re-initiation of metastases via inhibiting the differentiation of metastatic breast cancer cells [79]. In this way the BMP antagonist noggin may provide bone metastatic breast cancer cells with a double advantage for growth and colonization within the bone environment and be a potential drug-target for targeting of bone metastases.

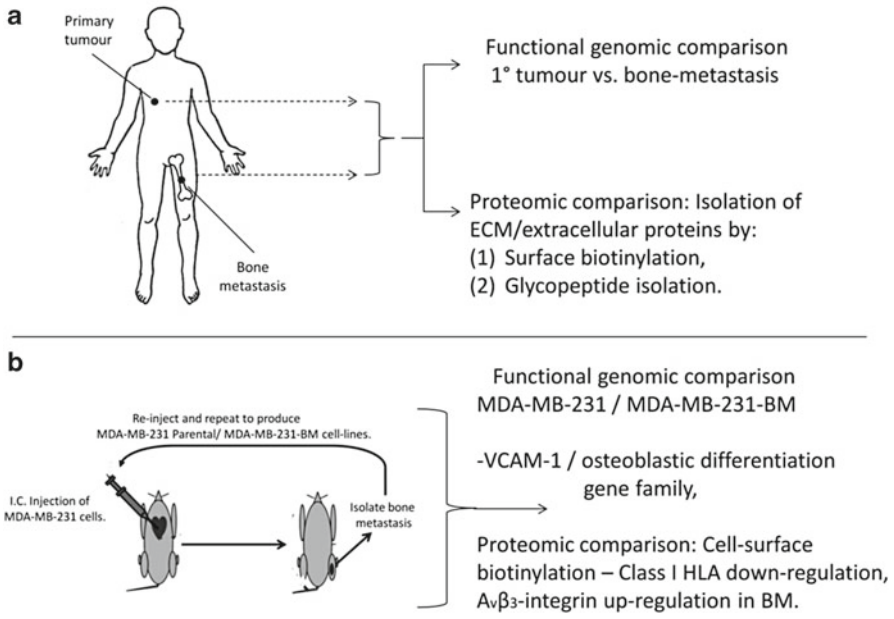

Fig. 7.4 Comparative molecular-profiling of primary tumours and matched bone metastases: Molecular profiling of patient matched primary tumours and bone metastases, as well as mouse model systems has the potential to identify functionally important molecules within bone metastasis. The common cellular-origin within the mouse-model, as well as the isogenic background for the patient-derived samples reduces the effect of inter-individual variability. This facilitates the identification of functional molecules within bone metastases. Functional genomic and proteomic studies have been conducted within such sample types identifying the up-regulation of osteoblastic differentiation genes, as well as the altered protein expression of cell-surface molecules such as Class-I HLA molecules and $\alpha_v\beta_3$-integrin

7.6.2 Breast Cancer Adaptation to the Bone-Metastatic Environment: Patient-Matched Genomic/Proteomic Studies

The adaptation of metastatic cancer cells to the bone microenvironment is a key step within cancer dissemination and a potential source of therapeutic targets. There have been few studies on primary tumours and patient matched metastases. This is partly due to the long time frame -breast cancer bone metastases often present years after the resection of the primary tumour and also due to logistical challenges in obtaining bone metastasis biopsy material [89]. Despite these limitations there have been a few omic-profiling studies of patient-matched primary-tumour vs. bone metastasis samples as well as studies within mouse-model systems for bone metastasis (see Fig. 7.4).

Genomic analysis of primary breast tumours and these tumours after their relapse to either brain or bone metastatic sites identified panels of genes which

clustered together according to the site of metastasis [90]. In total 22 transcripts were differentially expressed between the primary tumour and bone metastases and hierarchical clustering revealed similarity between the bone metastases and the primary breast tumour. Gene expression analyses such as these offer the hope that a diagnostic signature could be profiled within a primary tumour which will predict the site of future metastases, thus aiding treatment decisions [90, 91].

Functional genomic profiling has also been applied to mouse models of metastatic breast cancer. Microarray analysis of a breast cancer cell line (MDA-MB-231) and a bone homing variant obtained by intra-cardiac injection (MDA-MB-231-B02) identified the upregulation of a panel of 11 mRNAs with known roles within osteoblastic differentiation, including the increased expression of the osteoblast specific differentiation protein cadherin-11 [92]. A separate study involving functional genomic profiling of MDA-MB-231 breast cancer cells and a mouse-bone homing variant identified a functionally significant role for vascular cell adhesion molecule-1 (VCAM-1) in the recruitment of osteoclast progenitors into the site of bone micrometastases [93]. Anti-VCAM-1 antibodies had demonstrable ability to inhibit the development of bone metastases in this study [89].

Proteomic profiling of paired primary tumour/bone metastasis samples focussing on cell-surface and secreted proteins identified proteins implicated in cell-cell communication, and autocrine and paracrine signalling events. Cell-membrane proteins are attractive potential targets for antibody-based therapies. Surface biotinylation (a technique which enriches for cell-membrane proteins) has been employed in studies to date. Isolation of biotinylated membrane proteins from the osteotropic cell-line MDA-MB-231-B02 (a bone homing variant of MDA-MB-231) revealed the upregulation of the cell-surface receptor $\alpha_v\beta_3$-integrin, and the down-regulation of class-I HLA molecules within the bone homing cells [94]. Proteomic analysis of a primary human breast tumour and a bone-metastasis from the same patient, with identification of surface biotinylated as well as glycosylated proteins, revealed a decreased expression of tumour suppressive α2β1-integrin within the bone metastasis [95]. Numerous proteins involved in cancer cell motility and tumour aggressiveness were identified in this study as being elevated in bone metastasis including activated leukocyte cell adhesion molecule (ALCAM/CD166), whilst Sushi-domain-containing protein-2 (SUSD2)-a known tumour suppressor-had reduced expression with the bone metastasis samples [95]. Addition of these differentially expressed proteins to the current breast cancer biomarkers oestrogen-receptor (ER) and HER2 may improve treatment decisions. Tumours are currently classified according to histological criteria as well as the presence of differing receptor expression levels such as for oestrogen-receptor and HER2. Measurement of the levels of the differential proteins identified in these studies and their inclusion within the classification criteria may enable a more accurate subdivision of tumour types according to aggresiveness and response to therapeutic interventions.

7.7 Bone Metastasis Biomarkers: From Pre-clinical "Omics" Screens to Clinical Application

The application of genomics, transcriptomics, proteomics and metabolomics to biomarker-discovery within bone-metastatic cancers has generated large quantities of data and numerous potential biomarkers for further development. Whilst these studies are very promising the application of "omic"-strategies to the field of bone metastatic cancer is relatively recent and few omic-insights have been pursued as far as clinical utility.

One of the key challenges in the development of clinical biomarkers is revealed by recent data regarding the high degree of heterogeneity of tumours. High throughput genomic sequencing within breast cancer has identified extensive inter-tumour heterogeneity, with each individual tumour containing multiple cell clones each with a different pattern of mutations [96]. The genomic sequencing of gene fusion products within breast cancer also reveals considerable inter-individual heterogeneity [97] and this diversity may partly be explained by defects in the apparatus responsible for mismatch repair leading to genomic instability [98]. There is therefore a diverse family of subtypes within each organ-specific cancer and this makes it unlikely that an individual biomarker will predict outcomes in all cases of that cancer. A consequence of this is that currently used individual markers can have high sensitivity but low specificity. Prostate specific antigen (PSA) within prostate cancer is just one example of a biomarker with high sensitivity but low specificity [99]. The requirement for high specificity to prevent false positive results and consequent patient stress (and unnecessary treatment costs) has driven the search for multiple biomarker panels which should have improved diagnostic ability. In this approach successful biomarker development must therefore aim to identify a series of molecules which are involved in the key steps within the disease process with sufficient diversity to represent the full spectrum of subtypes within that cancer. The requirement for biomarkers enabling early diagnosis is particularly acute. In the early stages of cancer development alterations in protein and metabolite levels are likely to be of small magnitude and therefore multi-marker panels may also provide a compound assessment of disease progression. The development of diagnostic/prognostic decision tools arising from "omics"-research thus frequently focuses upon multi-marker panels.

The key steps involved in the translation of pre-clinical biomarkers into clinical utility are briefly outlined below and summarised in Fig. 7.5 (biomarker development for clinical utility has been covered in detail in several excellent reviews including [100]).

The translation of pre-clinical findings into improved early diagnosis tools for bone metastasis, as well as their incorporation into patient stratification nomograms and treatment option determinants involves a number of number of stages and challenges. Pre-clinical biomarker discovery using "omics"-technologies typically involves the use of time-consuming procedures and expensive technology

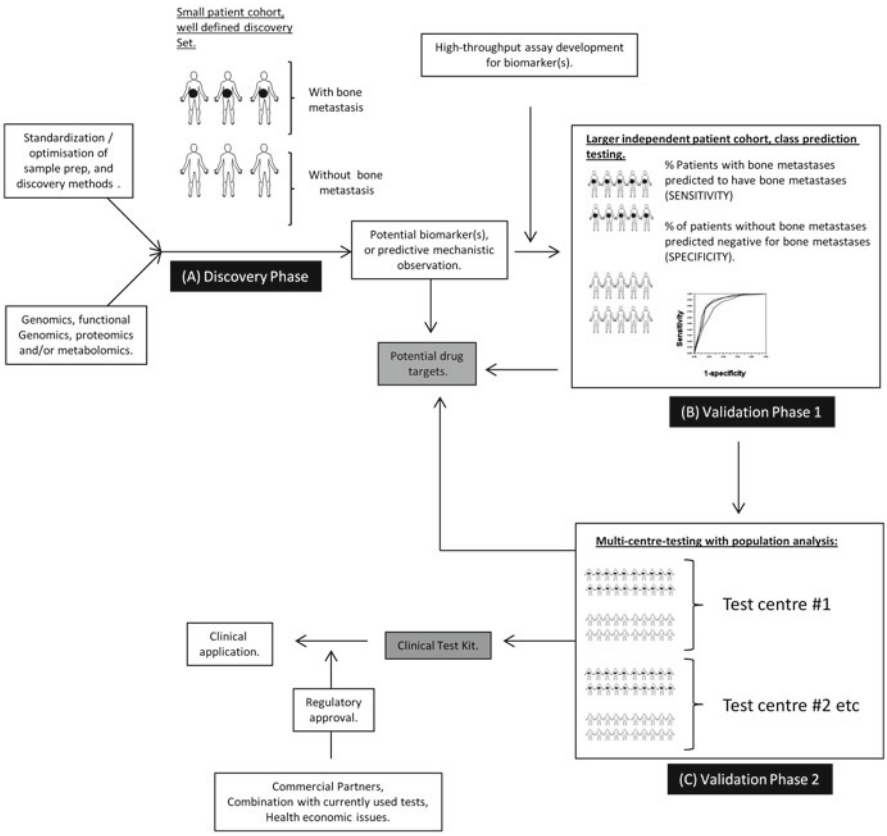

Fig. 7.5 "Omic"-strategies within cancer metastasis to bone: Workflow from the laboratory to clinical application: Omic strategies have the potential to impact upon patient diagnosis and treatment in several ways, most notably the development of new clinical tests for prognosis/diagnosis of disease as well as the discovery of new drug targets. (**a**) As the majority of "omic" discovery platforms are time-consuming and/or expensive initial discovery is usually performed in a small cohort of well-defined patients. (**b**) The results of this discovery phase can include potential disease biomarkers and/or drug targets. Validation of these biomarkers involves application of the potential predictive panels within class-prediction tests using a larger blinded panel of patients with or without the disease. This first validation phase frequently requires the development of high-throughput assays for the markers. (**c**) Further validation of the candidates discovered then proceeds through multi-centre testing of the biomarker(s) to ensure that the insight discovered by the original omics-based screen is applicable across multiple clinics and laboratories. Only when a biomarker panel or drug target has cleared these steps of development and received regulatory approval will the original omics-based discovery proceed to clinical applicability. Eventual clinical application depends upon health economic assessment and the new diagnostic marker is frequently combined with pre-existing markers to provide the final, improved patient-diagnostic tool

platforms, and for this reason they usually involve small patient sets. The putative biomarker candidates resulting from these small scale discovery projects require confirmation in blinded validation cohorts. A significant proportion of candidates fail this validation step and this may be due to the small number of samples originally analysed, sample biases, or in some cases the lack of robust sample preparation procedures. Quantification of biomarkers within large patient sets frequently requires the development of high-throughput assays for use in clinical chemistry laboratories.

In order to provide an effective clinical test the putative biomarkers discovered within pre-clinical studies must have demonstrable reproducibility between institutions. A challenge here to date has been the lack of standardization within the platforms used to discover potential biomarkers in pre-clinical studies such that biomarker panels may not be reproducible over time within an institution or between institutions. Validation of biomarkers at this stage requires the ability of the biomarker panel to accurately predict which patients have disease (or the disease-stage in question) within large, population-based, multi-institutional blind test cohorts (see Fig. 7.5). Biomarker candidates and panel-based diagnostic/prognostic tools that prove their utility across multiple institutions using these high-throughput assays provide a suitable biological basis for the development of clinical test kits. Eventual application of the clinical products (test kits or pharmaceutical drugs) to the sphere of patient treatment requires regulatory approval and input from healthcare professionals and health-economic advisors.

7.7.1 Genomics/Functional Genomics: Towards Clinical Applicability

Gene expression signatures have already made a significant contribution towards cancer treatment decisions and outcome prediction, as application of the 70-gene signature MammaPrint test and the 21-gene-signature OncoTypeDX kits within breast cancer illustrate [18]. There is evidence that as blood cells flow through tumour tissues signalling events modify the gene expression profiles of the blood cells. Whole RNA-based transcriptomics has recently identified gene expression signatures predictive of overall survival within castration-resistant prostate cancer [101, 102]. Therefore whole blood profiling of mRNA (and miRNA) expression levels within whole blood cells offers considerable promise for informing cancer treatment. These gene expression signatures may reflect the risk of bone metastasis as this is a major contributor towards the morbidity arising from these cancers. Gene expression profiling and correlation with overall survival does not always relate to bone metastasis however, as a recent study within breast cancer illustrates [103]. In the study of Rajski et al. 2012 MDA-MB-231 cells cultured in the presence of osteoblasts up-regulated two sets of genes, one set of interferon-response genes which strongly predicted overall survival, and another set of IL-6 related genes which did not

significantly change overall survival but was associated with a shorter time to bone metastasis [103]. Genomic profiling and gene expression analysis thus holds out significant promise for the mechanistic elucidation, and clinical management of bone metastatic cancers. Large multi-centre trials with careful data analysis (including patient associated meta-data) has the potential to reveal key insights into bone metastasis.

7.7.2 Proteomic/Metabolomic Signatures of Disease: Towards Clinical Utility

There have been many pre-clinical proteomic/metabolomic-studies performed to date which have identified potential protein and metabolic alterations which occur within bone metastatic cancer. None of these observations have to date impacted upon the treatment of bone metastatic cancer in the clinic, though some of these putative biomarkers are progressing through downstream biomarker validation. This validation relies on quantitative measurement of the candidates discovered within preclinical studies in much larger patient cohorts and this requires the development of robust, quantitative assays. Proteomic biomarker validation to date has principally involved use of immunoassays (i.e., ELISA), however MS-based quantitative methods for assaying proteomic biomarkers such as multiple-reaction monitoring (MRM) are increasingly being used [104]. Despite the current early stage of translation of proteomic/metabolomic markers into the clinic, multi-marker panels composed of these candidates have considerable potential to impact upon patient treatment in bone metastatic cancer in the future, particularly when combined with existing diagnostic markers (such as PSA) and clinical observations.

7.8 Conclusions

Post-genomic technologies are relatively recent additions to the arsenal of techniques being applied to the diagnosis and treatment of cancers that metastasise to bone. To date these technologies have contributed considerable insights into the disease-mechanisms and potential drug targets for bone metastatic cancers. Continual refinement of the techniques involved, for instance improved sensitivity within NMR-based metabolomic studies, the improved accuracy of transcriptome analysis using techniques such as mRNA-seq, and the expansion of functional genomics to include recently identified non-coding regulatory RNAs (such as miRNAs) will further increase the utility of omic-strategies within bone metastasis in the foreseeable future.

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Part III
Therapeutic Management

Chapter 8
Analgesic Treatment of Bone Metastases

Sebastiano Mercadante

Abstract The presence of bone metastases predicts the presence of pain and is the most common cause of cancer-related pain. Although bone metastases do not involve vital organs, they may determine deleterious effects in patients with prolonged survival. Bone fractures, hypercalcaemia, neurologic deficits and reduced activity associated with bone metastases result in an overall compromise in the patient's quality of life. A metastasis is a consequence of a cascade of events including a progressive growth at the primary site, vascularization phase, invasion, detachment, embolization, survival in the circulation, arrest at the site of a metastasis, extravasion, evasion of host defense and progressive growth. Once cancer cells establish in the bone, the normal process of bone turnover is disturbed. The different mechanisms responsible for osteoclast activation correspond to typical radiologic features showing lytic, sclerotic or mixed metastases, according to the primary tumour. The release of chemical mediators, the increased pressure within the bone, microfractures, the stretching of periosteum, reactive muscle spasm, nerve root infiltration and compression of nerves by the collapse of vertebrae are the possible mechanisms of malignant bone pain. Pain is often disproportionate to the size or degree of bone involvement. The use of analgesics according to the WHO ladder is recommended. The difficulty with incident pain is not a lack of response to systemic opioids, but rather that the doses required to control the incidental pain produce unacceptable side effects at rest. Opioids should be carefully used to balance background analgesia and breakthrough pain. Once analgesic optimization is achieved there are several options to treat breakthrough pain, including opioids with a fast onset.

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Invasive techniques are rarely indicated, but may provide analgesia in the treatment of pain resistant to the other modalities. Careful appraisal and the application of a correct approach should enable the patient with bone metastases to obtain an acceptable pain relief despite the advanced nature of their malignant disease.

Keywords Bone metasases cancer pain • Palliative care • Opioids

8.1 Introduction

Bone pain is a major problem in advanced cancer. Although bone metastases do not always cause pain, pain is often the first symptom of a bone metastatic disease. Moreover, bone metastases frequently give rise to complications that have an important impact on the patient. About 40 % of patients with cancer pain have bone metastases that may cause hypercalcemia, pathological fractures, radioculopathies and spinal compression, leading to severe pain and neurologic symptoms. Incidental pain, mostly associated with bone metastases, reduces the possibility of pharmacological pain control and is considered a negative prognostic factor for pain control [1]. Recent studies have revealed an alarming pattern in patients with body lower metastases, who reported substantial interference of activity even though pain levels were mild or moderate [2, 3].

8.2 Clinical Presentation

Cancer-induced bone pain usually increases in magnitude over the evolution of the disease and consists of background pain and movement-induced pain, a sub-type of breakthrough pain, also defined as incident pain. Ongoing background pain, which is commonly the first symptom of bone cancer, begins as a dull, constant in presentation and gradually progressive in intensity. The pain is usually localized to a particular area and is often experienced at night or on weight-bearing. Continuous pain may be moderate on resting, but may be exacerbated by different movements or positions, such as standing, walking, sitting, or pressure on the area of involvement. Pain from a vertebral pedicle may be associated with unilateral nerve root pain. Disease progression may lead to vertebral body collapse, with the development of spinal compression and their neurological symptoms, which are initially ambiguous and then progress to paraplegia. Muscular cramps often occur in muscles close to painful bone metastases. Anxiety, tension, and lack of activity because of pain or weakness also predispose to cramps and myofascial pains, particularly in the back and neck [1]. On a numerical scale, patients with bone metastases categorized their pain as mild if pain was ≤ 4, moderate if pain was 5–7, and severe if pain was ≥ 8 [4].

Intermittent episodes of extreme pain can occur spontaneously, or more commonly, after weight bearing and movement. There is a correlation between pain at rest and pain on movement [1]. Adequate management of incident pain is a very difficult

challenge and represents a serious problem due to its temporal characteristics, which means it is not always completely preventable. 'Incident pain' refers to intermittent exacerbations of pain that can occur spontaneously or in relation to specific activity. The difficulty with incident pain is not a lack of response to opioids, but rather that the doses required to control the incident pain produce unacceptable adverse effects when the patient is at rest or pain spontaneously stops. Thus, patients with pain from bone metastases on weight-bearing or movement may require a dose of opioids that causes excessive adverse effects for the patient at rest, as movement-related pain is likely to be repetitive and in some cases unpredictable [5].

8.3 Analgesic Treatment

Cancer-induced bone pain remains a clinically challenging problem to treat rapidly and effectively [5]. A multimodal approach to pain management is often necessary, as pain is not simply a physical sensation. In a prospective observational cohort study, several treatment modalities were employed, demonstrating the complex management of patients with bone pain [2]. Thus, attention should be paid to factors that modulate the pain threshold, such as anxiety, depression and fatigue. Other non-drug factors affecting pain threshold include general discomfort, insomnia, fear, anger, sadness, boredom, mental isolation and social abandonment. Much can be done to alleviate pain by explaining the mechanism underlying it and by showing concern for the patients. Thus, relief of other symptoms, facilitating sleep, relaxation, companionship and elevation of mood may help pain management. For example, massage therapy has been found to reduce general aches and pains especially in patients with bone metastases that were bed bound or with limited mobility, at least in some populations [6]. Relaxation techniques include simple focused-breathing exercises, progressive muscle relaxation, pleasant imagery, meditation and music/art assisted relaxation. These techniques are easy to learn without requiring special training and therefore they could reduce symptoms (such as nausea and vomiting, fatigue) and improve mood, sleep, and quality of life in cancer patients. Psychotherapy: should be offered to patients with history of psychiatric illness or who develop clinical signs of depression. Psychotherapy could also be used as an adjuvant to medical treatment to patients suffering from a history of addiction which makes their pain management a challenging task There are anticancer therapies providing important analgesic responses, which will be examined thoroughly in other chapters.

8.3.1 Pharmacological Treatment

Analgesic drug therapy is the cornerstone of cancer pain therapy. Current treatment is based on the analgesic ladder recommended by the WHO [7] which involves a stepwise approach to the use of analgesic drugs and is essentially a framework

of principles rather than a rigid protocol. Although the paucity of controlled studies [8], adherence to this basic approach may provide adequate analgesia in 80–90 % of patients experiencing cancer-related pain,. An adjuvant analgesic may be co-administered to improve analgesia or reduce adverse effects.

Step 1 analgesics are for patients with mild to moderate pain and involve the use of non-opioid analgesics, including paracetamol, and non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are drugs commonly used as a first step of the analgesic ladder. However, no clear guidelines on the use of NSAIDs with opioids for prolonged periods are available [9]. In specific circumstances NSAIDs may provide profound analgesia when administered with opioids [10]

Step 2 analgesics include low potency opioids like codeine and tramadol. Step 2 drugs have been indicated for those patients with mild to moderate pain who do not obtain adequate relief with non-opioid analgesics. However, data supporting the role of second step drugs were found to be insufficient to recommend their use in cancer patients with mild to moderate cancer pain [11]. High potency opioids can be used at relatively low doses for the same purposes [12].

When cancer patients experience severe pain, strong opioids are the mainstay of therapy (step 3 drugs). High potency opioids include morphine, oxycodone, hydromorphone, methadone, fentanyl, and buprenorphine. There is a large variety of options for the delivery of opioids in the management of cancer pain. In some instances, there are clear indications for using one preparation or delivery system over another, according to the ability of the patient to use a specific type of delivery system, the efficacy of that system to deliver acceptable analgesia, the ease of use by the patient and their family, and the potential or actual complications associated with that system. It is important to select the appropriate drug, dosage, and route of administration for the individual patient as well as to know how to titrate the dosage according to the analgesic response. Drug side effects should be anticipated and managed. A sequential trial of drugs may be appropriate if one medication is ineffective or the side effects unmanageable [13].

8.3.2 Routes of Administration

8.3.2.1 Oral Route

The oral route is the most common, least invasive, least expensive and easiest route for opioid administration for most patients with cancer pain. As most opioids are available in an oral formulation in patients who can take oral medications, this route is commonly considered preferential [14]. The main problem with the oral route is the first-pass biotransformation of opioids in the liver. All opioids given orally are absorbed via the gastric and duodenal mucosa and then transported to the liver via the portal venous system. In the liver, these medications undergo ‘first-pass metabolism’ before entering the systemic circulation. This has a major impact on the systemic plasma concentrations of drugs. Bioavailability is defined as the percentage

Table 8.1 Opioids used for moderate-severe intensity

Drug	Half-life (hrs)	Equianalgesic dose (mg)	Comments
Morphine	3–5	10	Available in sustained release form
Hydromorphone	3–5	2	Available in sustained release form
Methadone	15–24	1–2	Drug accumulates after several days, favored by hepatic dysfunction, potential interactions
Fentanyl		0.1	Available in transdermal patch Transmucosal formulation for breakthrough pain
Buprenorphine		0.14	Available in transdermal patches
Oxycodone	2–3	7	Available in sustained release form
Tapentadol	2–3	30	Available in sustained release form

of administered medication that reaches the systemic circulation. For example, the dose of an opioid given orally to a patient with cancer pain must be three times the intravenous or intramuscular dose of morphine.

Morphine, the most commonly used medication in the world to treat cancer pain, has a terminal elimination plasma half-life of about 3 h. To provide longer-lasting analgesia, several preparations have become available. Bioavailability of these slow-release preparations is the same as that of immediate-release preparations, but time to peak plasma drug concentrations is longer, and peak plasma concentrations are decreased. These preparations are recommended by the manufacturer to be administered every 8–12 h. Hepatic impairment may partially influence the pharmacokinetics of morphine, probably since there is a relatively large hepatic reserve for glucuronidation. Renal failure seems to be more determinant because it profoundly affects the elimination of the glucuronide metabolites of morphine. While morphine itself remains largely unaffected by renal failure, accumulation of both metabolites has been reported [15, 16].

Oxycodone is a semi-synthetic opioid agonist that can be used as an alternative to morphine in controlling chronic pain. Noroxycodone, oxymorphone and conjugated forms of oxycodone, are the major metabolites. Oxycodone provide similar efficacy with an equivalency ratio with morphine of about 1:1.5 [17].

Hydromorphone is more potent and soluble than morphine and, like morphine can be tailored to the needs of the patient. Hydromorphone is metabolized in polar substances eliminated by the kidney. Hydromorphone and its metabolites accumulate in renal failure, resembling the problems emerging with morphine and its metabolite elimination in such circumstances. The equivalence ratio with morphine is about 1:5 [17].

Tapentadol is a novel, centrally analgesic agent acting with two mechanisms of action: mu-opioid receptor agonism and norepinephrine reuptake inhibition. TP has been developed for the management of moderate to severe chronic pain. The moderate affinity at mu receptor and the opioid-sparing effect of inhibition of norepinephrine reuptake suggest that TP should produce fewer opioid-related adverse effects than

typical mu-agonists. TP has been shown to be effective in different pain models. In these models tolerance development was considerably delayed with tapentadol compared to morphine [18]. Few data exist in cancer patients. In an exploratory study, tapentadol started in doses of 100 mg/day was well tolerated and effective in opioid-naive patients with cancer pain, regardless of the pain mechanism. It could be considered as a flexible drug to be used in patients with moderate-severe pain [19].

Methadone is a low-extraction drug and is metabolized, mainly by N-methylation in the liver, to inactive metabolite. Its pharmacokinetics is highly variable, and there is evidence for pronounced interindividual differences in the proportion between renal excretion of the metabolite and the parent drug. This makes the use of the drug more complex, because of difficult predictability and the risk of accumulation. Differently from the previous drugs, methadone plasma concentrations do not change significantly in patients with abnormal renal function [15, 16].

Many patients will develop tolerance to most of the undesirable side effects of opioids (such as nausea/vomiting or sedation) over a period of several days. However, certain patients may not be able to tolerate oral medications because of oesophageal motility problems or gastrointestinal obstruction (e.g., head and neck or oesophageal cancer, bowel obstruction) or may present with nausea and vomiting, limiting the utility of the oral route. Finally, some patients are unable to swallow due to the site of their cancer or because they are neurologically impaired. Alternative routes, including the intravenous and subcutaneous, as well as the transdermal ones, have been advocated in such circumstances.

8.3.2.2 Parenteral Route

The intravenous route of administration is indicated for those patients whose pain cannot be controlled by a less invasive route or who already have a central venous access. The major disadvantage of this route is that it is more complex to manage, especially at home, and requires some expertise. On the other hand, this route is faster, allowing for an immediate effect in emergency conditions, and providing the best conditions for rapid opioid dose titration. For patients with very severe pain, the intravenous route is the fastest way to obtain analgesia and determine the patient's opioid requirements. The opioid is then converted into an equianalgesic oral dosage [20].

For patients requiring parenteral opioids who do not have in-dwelling intravenous access, the subcutaneous route can be used. This simple method of parenteral administration is quite popular in the palliative care setting. The limiting factor is the volume of fluid that can be injected per hour, often requiring more concentrated solutions. Most drugs used by intravenous route can also be used by subcutaneous infusion, except methadone, which can induce local toxicity. The main advantages of the subcutaneous over the intravenous route is that there is no need for vascular access, changing sites can be easily accomplished, and problems associated with in-dwelling intravenous catheters are avoided. The oral-parenteral ratio for morphine is 2:1 or 3:1 [21].

8.3.2.3 Transdermal Route

Transdermal route is a noninvasive option for patients unable to take oral medications. They maintain a relatively constant opioid plasma concentrations [22]. Transdermal delivery systems have several advantages over traditional routes of administration in the management of chronic pain. These include non-invasive administration and rate-controlled release; the active compound passively diffuses into the systemic circulation, allowing therapeutic serum levels to be maintained 48–72 h following a single application. Fentanyl and buprenorphine are available transdermally, because of their potency and lipophilicity. Upon initial application of the patch, a subcutaneous "depot" is formed as opioids saturate the subcutaneous fat beneath the patch. After approximately 12 h, steady-state plasma opioid concentrations are reached, and are maintained for 48–72 h. Fentanyl and buprenorphine, in doses of 25 μg/h and 35 μg/h, should be approximately equivalent to 60 mg or oral morphine [17]. These drugs are less influenced by an abnormal renal function, in comparison with morphine and hydromorphone, and may have a lower incidence of constipation as a side effect [15, 16].

8.4 Opioid-Related Adverse Effects

All opioids produce common adverse effects. The most common opioid side effects are constipation, sedation, dry mouth, delirium, nausea, respiratory depression, pruritus, convulsions and myoclonus. All opioid drugs have similar side effects, although an individual patient may tolerate one opioid better than another. Opioid adverse effects are preventable or treatable, and patients will develop some degree of tolerance to them. No precise guidelines on symptomatic treatment have been produced [23, 24]. The clinician must understand the mechanism and management of these effects in order to use opioids safely and effectively. The concomitant use of adjuvant drugs may minimize these effects in many circumstances.

Constipation is the most common and refractory opioid-related adverse effect. Opioids produce increased resting tone in the smooth muscle of the small and large intestine and reduce peristalsis. Stool softeners should be started when opioids are first prescribed. A combination of senna and docusate may be useful [25]. If constipation has already developed, stimulant laxatives or osmotic agents should also be used. It is likely that drugs with a specific mechanism, namely opioid-anatgonists, can be more effective than laxatives. A combination of naloxone and oxycodone in a 1/2 ratio has been recently developed to prevent opioid-induced constipation, based on the peripheral antagonism of naloxone in the gut [26]. In cancer patients this combination was effective in reducing opioid induced constipation, while maintaining adequate analgesia [27]. Alternately, breakthrough injections of an antagonists such as methylnaltrexone are available for constipation resistant to laxatives [28].

Opioid-induced nausea and vomiting may have multiple mechanisms, as opioids activate receptors in the chemoreceptor trigger zone of the dorsal medulla, reduce gastric emptying by increasing smooth muscle tone in the gastroduodenal sphincter and other intestinal sites, and sensitize the vestibular apparatus in the inner ear, particularly in young patients. Phenothiazines, metoclopramide or haloperidol, and scopolamine may be effective according to the presumed prevalent mechanism [23].

Any opioid may produce myoclonus. A decrease in opioid dose or adding clonazepam or gabapentin may be helpful. When opioids produce pruritus, it is usually from direct histamine release. Antihistamines may often be sufficient. However, if symptomatic treatments fail, switching the patient to a different opioid may remedy the situation [24].

Respiratory depression is the most feared opioid adverse effect. However, it most commonly occurs in opioid-naïve patients who receive high initial doses of opioids and is unlikely to occur in patients receiving regular therapeutic doses. Opioids may produce sedation, particularly when starting the medication in an opioid-naıve individual or when titrating the dosage upwards. Generally the sedation is not severe and tolerance will develop within a period of days.

8.5 Opioid Switching

As opioids act through different opioid receptor subtypes in the central nervous system and cross tolerance between opioids is incomplete, a shift from one opioid to another is a useful option when the side effect–analgesic relationship is no longer beneficial, and allows for the elimination of toxic metabolites which may have accumulated under the previous therapy. Patients who experience dose-limiting adverse effects during opioid escalation may benefit from a trial of an alternative opioid. In a switch from one opioid to another, the latter drug is often observed to be relatively more potent than would be anticipated, given published estimates [13, 29].

Specifically, methadone has been reported to be useful in restoring opioid responsiveness in patients whose pain ceases to be controlled by morphine or hydromorphine at doses much lower than those suggested by the opioid conversion charts among opioids. However, in comparison with other opiodis, methadone's potency may be much greater than expected when a switch is made from another drug because tolerance is reversed, probably due to its anti-NMDA effect, and strict surveillance is necessary when converting patients who are taking high doses of opioids. The clinical benefit will depend on the degree to which cross tolerance exists with respect to analgesia as well as to side effects. As the degree of cross-tolerance may change as opioid doses are escalated, it is advisable to proceed with caution when switching from any opioid to another in patients receiving very high opioid doses. Data suggest that switching to methadone using the currently proposed ratios (1:4) may lead to severe toxicity. A strongly positive correlation between dose ratio and previous morphine dose suggests the need for a highly individualized and cautious approach when rotating from morphine to methadone in

patients with cancer pain on high doses of morphine. The subsequent titration process should take into account the characteristics of the pain and the individual clinical situation [17].

8.6 Movement-Related Breakthrough Pain (BTP)

Patients with bone metastases have a specific type of BTP, namely incident pain, due to movement or burden [30]. BTP is a transitory flare of pain superimposed on an otherwise stable pain pattern in patients treated with opioids, is normally severe in intensity, has a rapid onset, and is considered as a negative prognostic factor. If BTP is more frequent and more severe in patients who have their basal pain not adequately controlled, it is essential to optimize the basal analgesia by an appropriate opioid titration to obtain the best balance between analgesia and adverse effects, also using different sequences of opioids, and combining analgesics and adjuvants when necessary. A careful titration may improve the basal analgesia. On the other hand, patients with movement-related pain due to bone metastases are often receiving basal medication for their pain which is otherwise considered acceptable, but are confined in the bed, with a limited mobility.

Patients presenting a relevant incident component may improve their physical activity with opioid dose increases despite having their pain at rest apparently controlled [31]. However, an increase in dose may also result in unacceptable toxicity, mostly sedation, during the period between incident pain episodes. Thus, optimization of basal opioid therapy should be attempted in cancer patients with bone metastases presenting with movement-induced pain who have apparently a well controlled pain condition at rest, but probably having a hypersensitivity to some innocuous stimuli, such as movement.

8.6.1 Management of BTP

Oral opioids can be useful in circumstances where they can be administered before starting activity in the presence of a predictable event, for example starting activity, or presenting with a slow onset. The onset of a clinical effect of an oral opioid can be expected 30 min after the administration. In other circumstances the onset of action of an oral dose may be too slow and will not overlap the onset and the offset of incident pain [32]. Different technologies have been developed to provide fast pain relief with potent opioid drugs such fentanyl, delivered by non-invasive routes. Transmucosal administration of lipophilic substances, obtainable in non-invasive forms, has gained in popularity in the last several years due to the rapid effect clinically observable 10–15 min after drug administration. Not all drugs are suitable for transmucosal administration. Fentanyl is a potent and strongly lipophilic drug, which favors its passage through the mucosa and then across the blood–brain barrier

Table 8.2 Characteristics of opioids used for BTP

	Analgesic onset	Availability	Dwell-time
Oral morphine	30–45′	30 %	NA
Oral oxycodone	30–45′	40–50 %	NA
OTFC	15′	50 %	15′
FBT	15′	65 %	15′
SLF	15′	70 %	2′
INFS	5–10′	70–90 %	NA
FPNS	10′	70–90 %	NA

to provide fast analgesia. All the studies performed with fentanyl-based products, commonly named rapid-onset opioids (ROOs), have recommended that these drugs be administered to opioid-tolerant patients receiving doses of oral morphine equivalents of at least 60 mg [33].

Oral transmucosal fentanyl citrate (OTFC) is a fentanyl-impregnated lozenge available in different dosage strengths. The lozenge is gently rubbed against the buccal mucosa until it has completely dissolved (which should take no longer than 15 min, if appropriately used). Active participation is required to correctly use the lozenge, and fFentanyl is absorbed in about 15 min through the oral mucosa. Mucositis, local infection, and dry mouth may affect absorption of the drug. Absolute availability is about 50 %. However, the percentage absorbed by mouth and immediately available for treating BTP is about 25 %. Several trials have shown that OTFC in doses ranging from 200 to 1,600 μg is an effective analgesic for BTP in patients already receiving maintenance opioid therapy for chronic cancer pain. This approach produces a faster onset of relief and a greater degree of pain relief than the placebo or oral morphine, at 15, 30, and 60 min [34].

Fentanyl buccal tablet (FBT) is a formulation of transmucosal fentanyl designed to provide rapid penetration of fentanyl through the buccal mucosa by using effervescence to cause pH shifts that enhance the rate and extent of fentanyl absorption. A reasonable level of salivation is needed to allow dissolution. FBT is absorbed in approximately equal proportions through the buccal mucosa and the gastrointestinal tract, whereas with OTFC the proportion absorbed through the buccal mucosa was lower (22 %) than that absorbed gastrointestinally (78 %). Thus, the drug immediately available from FBT to treat BTP is about double that of OTFC (48 % versus 22 %). Controlled studies have reported the efficacy and safety of FBT in opioid-tolerant cancer patients with BTP after 10–15 min [34].

The high vascularity and good permeability of the sublingual mucosa offer the potential for rapid absorption of lipophilic opioids such as fentanyl. Sublingual fentanyl (SLF) consists of a small, rapidly disintegrating tablet that contains an ordered mixture of micronized fentanyl adhered to the surface of water-soluble carrier particles (mannitol) that allow for a rapid disintegration and absorption of fentanyl. SLF demonstrated to be safe and effective in comparison with placebo providing analgesia within 10 min [34].

The intranasal route of administration is an alternative with several benefits, including fast systemic penetration and in cases of local buccal problems. Intranasal

fentanyl spray (INFS) has been associated with minimal local irritation in the nasal cavity. Studies have shown the effectiveness of INFS in comparison with pacebo or OTFC showing a fast pain relief (5–10 min). A pectin-based drug delivery system has been designed to gel when applied to mucosal surfaces. Fentanyl pectin nasal spray (FPNS) is delivered as a low-volume fine mist of uniform droplets that form a gel on contact with the calcium ions present in the mucosal membrane secretions. FPNS studies provided clinically meaningful pain relief faster than oral morphine or placebo [34].

8.6.2 Dosing

Many pioneer studies of OTFC and FBT have recommended titrating opioid doses for BTP [35]. The reasons why titration is necessary are not clear, considering that the presence of tolerance should suggest a dose proportional to those used for background analgesia. Moreover, dose titration may make the practical use of ROOs difficult in daily activity, particularly at home or in outpatients, and most patients may be reluctant to try ROOs because of concerns about the dose, preferring ultimately the traditional oral dosing of morphine [36]. However, none of these trials specifically examined the dosing problem, and the information gathered is just incidental to the study design aimed to demonstrate superiority of these preparations over placebo, oral morphine or standard oral opioids.

In a study reproducing a clinical scenario of patients receiving opioids for BTcP, the dose of oral opioids used as rescue medication was 18 % of the ATC opioid dose, whereas for OTFC, titrated to determine the effective dose, the rescue dose was about 35 % of the ATC dose [37], suggesting that the titration process mostly provides even higher doses that those proportional to the ATC regimen. A titration process with the lowest dose of ROOs is likely to produce a limited effect in patients who are receiving high doses of opioids regularly [33]. Observations from data pooled from the same trials of OTFC confirmed that, despite the study design, some relationship between BTP and ATC opioid dose exists, [38].

Recently a comparison of titration process with an approach using doses of ROOs proportional to the basal opioid regimen has shown that proportional doses are safe and more effective [39].

8.7 Adjuvants

Experimental studies suggest that adjuvant therapy is required to reverse the dorsal horn pathophysiology in bone cancer pain [40]. Some patients with bone metastases manifest bone pain with distinguishable neuropathic features, and these patients reported greater pain intensity [41].

Thus, drugs able to decrease the excitatory neuronal state in the spinal cord may be beneficial in this context. In an experimental bone cancer model gabapentin did

not influence tumour growth but it did attenuate both ongoing and movement-evoked bone cancer-related pain behaviours [42]. Anti-epileptic drugs are able to decrease the excitatory state in the spinal cord and may have some potential in bone cancer pain. However, apart from some occasional case reports, no appropriate studies have been performed to date [43]. Similarly, anticonvulsants, such as carbamazepine, phenytoin, valproate and clonazepam, have been reported to relieve pain in numerous peripheral and central neuropathic pain conditions, although contradictory results have been found. The efficacy of these drugs could be explained by their inhibitory effects on NMDA-receptors, and other mechanisms for some drugs, including sodium channel blockade. However, no conclusive clinical study has statistically verified these observations in cancer pain and conversely, open sodium channel blockers have been reported to relieve neuropathic pain states in other studies [43].

Corticosteroids possess analgesic properties for a variety of cancer pain syndromes, including bone pain, A number of studies have documented the positive effects of corticosteroids on various cancer-related symptoms, including pain, appetite, energy level, food consumption, general wellbeing and depression. Although analgesia in diverse pain syndromes has been reported in patients reporting a nerve compression or bone pain which has an important inflammatory component, most of the evidence for these effects is anecdotal [43].

Antidepressants may improve depression, enhance sleep and provide decreases in the perception of pain. The analgesic efficacy of the tricyclic antidepressants has been established in many painful disorders and has been suggested for neuropathic pain syndromes presenting with a superficial burning pain. The analgesic effect of amitriptyline is not directly related to antidepressant activity, and it is usually observed within 5 days. Alternative drugs with a lower incidence of side effects should be considered in patients predisposed to the sedative, anticholinergic or hypotensive effects of amitriptyline. Adverse effects are of concern. Common side effects of tricycic compounds include antimuscarinic effects, such as dry mouth, impaired visual accommodation, urinary retention, and constipation, antihistaminic effects (sedation), and anti-alpha-adrenergic effects (orthostatic hypotension). The potential benefits of amitriptyline are associated with a high rate of adverse effects, which can be particularly intense in advanced disease [44].

Other adjuvant analgesics that are potentially useful in this setting include calcitonin, bisphosphonate compounds, and selected radiopharmaceuticals. Their role is examined in other chapters.

8.8 Interventional Procedures

8.8.1 Spinal Route

A small number of patients may still fail to obtain adequate analgesia despite large systemic opioid doses, or they may suffer from uncontrollable side effects such as nausea, vomiting, or oversedation. These patients may be candidates for the

administration of a combination of opioids and local anaesthetics via the spinal (epidural or intrathecal) route. The goal of spinal opioid therapy is to place a small dose of an opioid and/or local anaesthetic close to the spinal opioid receptors located in the dorsal horn of the spinal cord to enhance analgesia and reduce systemic side effects by decreasing the total daily opioid dose. Use of this route to deliver opioids requires placing a catheter into the epidural or intrathecal space and using an external or implantable infusion pump to deliver the medications. Deciding between epidural vs. intrathecal placement or external vs. implantable pumps to deliver the opioid is based on multiple factors including duration of therapy, type and location of the pain, disease extent and central nervous system involvement, opioid requirement, and individual experience. Intrathecal opioid administration has the advantage of allowing a higher concentration of drug to be localized at the receptor site while minimizing systemic absorption, thus possibly decreasing drug-related side effects. Morphine remains the drug of choice for the spinal route, because of its relatively low lipid solubility. It has a slow onset of action, but a long duration of analgesia when given via an intermittent bolus. The starting dose is quite difficult to calculate and should take into consideration various factors, including the previous opioid dose, the age of the patient, and the pain mechanism. Adding a local anesthetic to morphine via the spinal route has been successful in providing good analgesia in patients whose pain was resistant to epidural morphine alone, despite high doses [45]. Of interest, the most frequent indication for a spinal treatment was incident pain associated with bone metastases, unresponsive to multiple trials of systemic opioids [46].

Further clinical studies and trials will still be required to judge the safety, efficacy, and extended role of the spinal route in chronic cancer pain and, more importantly, to define in which patients this technique is best indicated. Procedural and surgical complications, system malfunction, and pharmacological adverse effects are the main categories of complications associated with spinal drug delivery [45].

8.8.2 Minimally Invasive Treatments of Bone Metastases

Invasive procedures are possible options for the treatment of skeletal metastases in patients who are poor surgical candidates because of their age, comorbities, the extent of disease, or have been refractory to radiation therapy [1].

Image-guided percutaneous ablation of bone metastases is an effective, minimally invasive alternative to conventional therapies in the palliation of pain from metastatic disease. Ablative technologies applied in the treatment of skeletal metastases include radiofrequency ablation, cryoablation, microwave ablation, laser ablation, ethanol ablation, and, most recently, focused ultrasound. These ablative methods may be performed in combination with percutaneous cementoplasty to provide support and stabilization for metastases in weight-bearing bones at risk for pathologic fracture [47].

Patients who present with painful pathological vertebral compression fractures but no neurological compromise have the option of percutaneous vertebral

augmentation procedures. Vertebroplasty and kyphoplasty are minimally invasive procedures consisting of injection of bone cement (polymethylmethacrylate) in a fractured or disrupted vertebral body via a percutaneous cannula placed in the vertebral body through a uni or bipedicular approach. This will serve to provide structural support and minimize mechanical pain. In addition, the cement may have intrinsic analgesic and antitumor properties. Differently from vertebroplasty, for kyphoplasty the injection of the bone cement occurs after creation of a cavity in the vertebral body by inflation of a balloon, this will allow a low-pressure injection, therefore minimizing complications from extravasation [48].

Osteoporotic vertebral compression fractures and spinal tumors could be further indications. The safety and efficacy of these procedures has been made known in large, multicenter, randomized, controlled trials [49–51]. Residual pain after successful vertebral augmentation procedures may occur, possibly due to other pain generators, including degenerative changes in the adjacent structures such as facets and discs, causing persistent axial back pain and radiculopathy.

Radiofrequency ablation can provide effective palliation of painful bone metastases. The aim of radiofrequency ablation is to ablate tumors as widely as possible but not beyond the outer margin of the tumor. The mechanism by which radiofrequency ablation provides pain relief is multifold, including the destruction of local sensory nerves, the decrease of tumour burden, and prevention of tumor progression. Like radiofrequency ablation, percutaneous cryoplasty may provide pain relief by a cooling effect produced by the expansion of argon forced into the lesion, and subsequent generation of an ice ball. Cellular dehydration and cell death are the main mechanisms [52].

A percutaneous cordotomy is the interruption of the ascending spinothalamic tract, usually at the cervical level. A percutaneous cervical cordotomy by radiofrequency has been utilized in patients with unilateral bone pain below the C5 dermatome. Cordotomy may be indicated in a selected group of patients with refractory breakthrough pain due to bone metastases. The risk of serious complications, including mirror pain, general fatigue or hemiparesis, and respiratory failure, with a deterioration of the performance status, is high. Pituitary ablation has a potential role in patients with widely disseminated pain of bony metastatic origin, and in patients with a primary tumour which is hormonally responsive. Although the success rate has been quoted as 74–94 %, long-term follow-up to death has not been carried out successfully. High mortality rate (2–6 %) has also been reported with transient morbidity regarding rhinorrea, meningitis, visual disturbances, diabetes insipidus, headache and hypothalamic disturbances [1].

8.9 Conclusion

Patients with metastatic bone pain are challenging, because they present unique pain characteristics which are strongly dependent on the activity. The oral route of opioid delivery should be the first choice. If the oral route is unavailable, a noninvasive

alternative to the oral route is the transdermal route, which at present is available for administration of fentanyl or buprenorphine. For those patients in whom oral or transdermal opioids are not appropriate, intravenous or subcutaneous administration is effective, the latter route being easier to administer than the former. Opioid switching may be useful in improving the balance between analgesia and opioid-related adverse effects.

For treatment of incident-type BTP, other than oral opioids, which have a slow onset of action and could be used pre-emptively, fast delivery preparations of fentanyl are available, producing a more rapid effect than oral opioids. The spinal route can be attempted when oral and other parenteral routes have been unsuccessful. This route may be most successful when opioids and local anesthetics are used in combination. Whichever route is used, administration of opioids to manage cancer pain requires knowledge of potency relative to morphine and the bioavailability of the route chosen. Dose-equivalent tables are only close approximations and substantial interpatient variability is often observed. Therefore, patients should be closely followed and doses titrated to minimize side effects whenever the opioid, route, or dose is changed. Minimally invasive procedures have been proposed in recent years to provide pain relief Tables 8.1 and 8.2.

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Chapter 9
External Beam Radiotherapy and Bone Metastases

Candice Johnstone and Stephen T. Lutz

Abstract While the management of bone metastases requires multidisciplinary care, external beam radiotherapy (EBRT) remains an effective and efficient method by which to palliate pain and prevent pathologic fracture. Dose fractionation schemes ranging from 8 Gy in a single fraction to 30 Gy in ten fractions can provide equivalent relief with a minimal risk of side effects. Highly conformal or stereotactic body radiation therapy shows promise in the treatment of these patients, with its most appropriate niches to be determined through continued accrual to ongoing clinical trials. Treatment guidelines and quality measures have been developed to better define the use of EBRT in the setting of painful bone metastases.

Keywords External beam radiotherapy • Bone metastases • Fractionation • Pain • Highly conformal therapy • Stereotactic body radiation therapy

9.1 Introduction

Bone metastases are a common manifestation of malignancy, and they require multidisciplinary collaboration to determine the optimal palliative regimen. Radiation is useful in the treatment of both symptomatic and asymptomatic osseous lesions. Bone metastases often result from primary tumors that have arisen in the breast,

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prostate, lung, thyroid, kidney, and bone marrow (in the form of multiple myeloma) [1]. Primary tumors from other sites can metastasize to the bone as well, though less frequently. Symptoms caused by bone metastases commonly present earlier in the clinical course of metastatic neoplasm than do symptoms caused by visceral metastasis. As described elsewhere in this textbook, patients who experience bone metastases may suffer a wide range of clinical symptoms ranging from localized pain or pathologic fracture to functional deficits from compression of the spinal cord, nerve roots or peripheral nerves. The manifestation of these symptoms relates to the anatomic location of the affected bone and the osseous and extraosseous extent of the lesion [2, 3]. A bone is weakened both by the direct effects of tumor invasion as well as by perturbations in the normal remodeling mechanisms mediated by the interplay between osteoblasts and osteoclasts. This may result in the inability to bear a load, therefore leading to microscopic or even larger, macroscopic fractures. Spine bones that suffer decreased integrity can compress, with their decrease in height causing the adjacent muscles to spasm in an effort to augment spinal stability. Alternatively, nerve compression or invasion by tumor can create pain with different characteristics that radiates to another anatomic site. The perception of pain may therefore include descriptions by the patient such as “sharp”, “burning”, “shock-like”, “cramping”, “achy” or “unrelenting”. Systemic effects may include nausea, vomiting, fatigue, anorexia, and psychological changes caused by hypercalcemia. Bone metastases that are asymptomatic may also require treatment if there is impending spinal cord compromise or significant involvement of weight bearing bones. This may especially be true in the management of lesions of the acetabulum, where surgical options are limited.

9.2 Radiotherapy for Pain

Estimates suggest that 50–75 % of radiographically evident bone metastases cause discomfort at some point during the patient’s disease course. The treatment of painful bone metastases remains the most common use of palliative radiotherapy, and external beam radiotherapy (EBRT) provides effective and time-efficient pain relief with a low risk of complications. EBRT provides at least partial pain relief in 60–80 % of affected patients, with a complete response in 25–30 % [4]. Though some have suggested that tumors from soft tissue or kidney origin are less responsive to radiotherapy, painful metastases caused by those histologies may still respond quite well to treatment.

Pain relief from bone metastases of any histology may not begin until several days after the initiation of EBRT and may take several weeks to reach its full palliative relief. In the Dutch Bone Metastasis Study, the mean time to the onset of pain relief in both arms was 3 weeks [5]. Thus, pain medicine regimens must be initiated and properly maintained during the time until the effects of radiotherapy are manifested. In addition, patients must be reasonably comfortable lying flat for 15–20 min so that radiation therapy can be delivered. The stepwise approach of pain medicine dosing

described by the World Health Organization should be employed to achieve sufficient pain relief during this interval [6]. Depending upon the intensity or nature of the pain, pain medicine regimens may include non-steroidal anti-inflammatory agents, narcotic analgesics, or adjuvant pain medicines such as corticosteroids, nerve-stabilizing medicines, or anti-depressants.

The duration of pain control or pain response varies, but is typically several months. In the Dutch Bone Metastasis Study, a subgroup analysis was performed on patients surviving more than 52 weeks [7]. The mean duration of response in both arms was approximately 29–30 weeks. Unfortunately, approximately 55 % of patients had progression of pain at the treated site at a mean interval of 16–17 weeks. If pain recurs, retreatment can be considered (see Retreatment, Sect. 9.7 below).

The mechanisms of radiotherapy effects on normal and cancerous cells are well known. Linear accelerators create photons that interact with DNA and other molecules, such as water, to create double-stranded DNA breaks. These double stranded DNA breaks are more easily repaired by normal cells than cancer cells and interfere with the replication of cancer cells. Pain relief following EBRT may occur faster than tumor cell death, suggesting a more complex phenomenon which may include a decrease in the tumor cell production of factors, e.g. cytokines, that can lead to stimulation of nocioceptors on adjacent nerves, as outlined in Chap. 3.

9.3 Impending or Pathological Fracture

Patients with documented bone metastases should be actively evaluated for radiographic findings that suggest a risk for pathologic fracture. The chances for morbidity and mortality of a completed fracture are much higher than would are true for a properly managed impending fracture. Unfortunately, even a diligent clinician cannot always definitively determine the true risk of pathologic fracture from clinical and radiographic information [8, 9]. Analysis from prospective studies and ongoing research into computer risk models do suggest promising improvements in the prediction of fracture risk. Pathologic fractures most commonly occur in weight-bearing bones that experience torsional forces, though bones which are significantly weakened may fracture even in bed-ridden patients who simply readjust their position in their sleep. Surgical stabilization of weakened bones can prevent pathologic fracture with EBRT of 20–30 Gy given afterwards to promote tumor lysis which can allow for healing and minimize persistent pain [10, 11].

Radiation when given to a bone that is at risk for a pathologic fracture decreases the tumor burden and promotes healing of the normal bone. Bisphosphonates also play a role in preventing pathologic fracture. These modalities are complementary and are often used in combination.

One reason commonly cited against the use of higher dose per fraction radiation regimens is the potential for pathologic fracture. In the analysis of the RTOG 97-14, there was no difference in the long-term risk of pathologic fracture with the single fraction regimen compared to multi-fraction regimen [12].

9.4 Dose Fractionation

Many different fractionation schemes have been used to treat metastatic bone pain, with one survey showing that over 100 regimens are in use worldwide [13]. Multiple prospective, randomized trials have been completed to analyze equivalency of specific regimens during the past three decades. Most of those studies have compared single-fraction regimens such as 8 Gy in a single fraction to other multi-fraction regimens. Short-term pain relief, mean time to response, mean duration of response are equivalent with courses of 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, and a single 8 Gy fraction. Table 9.1 compares the four largest randomized trials of fractionation.

The advantages of the single fraction treatment include greater patient and caregiver convenience as well as fewer short-term side effects [12]. Many physicians believe that this technique should be reserved for patients with a short life expectancy; however, an unplanned subgroup analysis of patients surviving >52 weeks in the Dutch Bone Metastasis trial suggests that higher total doses offer no additional benefit over a single fraction [7, 14]. In addition, both in that study and in RTOG 97-14, physicians routinely overestimate patient survival [7, 15]. Another theoretical advantage of the higher dose per fraction is the increase in double stranded DNA breaks seen with increased dose per fraction and the potential to overcome the relative radioresistance of certain tumor histologies, e.g. renal cell carcinoma. There is limited data in this setting as the majority of patients enrolled in these trials have breast, lung or prostate primary tumors.

The circumstances when a higher total dose of 20–30 Gy could be considered include bone metastases with a large extraosseous component or osteolytic lesions with impending pathologic fracture in those who are medically inoperable [16]. The goals of the longer course in these circumstances are to maximize tumor control and remineralization, issues that are more relevant for those who will likely survive for several months. A single trial of patients with neuropathic pain from bone metastases did not show superiority for either 20 Gy in 5 fractions or a single

Table 9.1 Summary of the largest randomized trials of single vs multiple fraction palliative radiation therapy

Trial, year [Ref]	Randomization dose/fraction number	Response rate SF (%)	Response rate MF (%)	Retreatment rate SF/MF	Complete response SF	Complete response MF
Bone Pain Trial Working Party 1999 [37]	8 Gy/1 vs. 20 Gy/5	274/351 (78 %)	257/330 (78 %)	23 %/10 %	57 %	58 %
Dutch Bone Metastasis Study 1999 and 2004 [5, 38]	8 Gy/1 vs. 24 Gy/6	395/556 (71 %)	396/543 (73 %)	24 %/6 %	37 %	33 %
Hartsell et al. 2005 [12]	8 Gy/1 vs. 30 Gy/10	187/455 (41 %)	188/443 (42 %)	18 %/9 %	15 %	18 %

SF Single Fraction, *MF* Multi-fraction

8 Gy fraction, though the proper fractionation for this clinical circumstance remains somewhat controversial [17].

A single fraction course is more commonly associated with re-treatment to the same painful site than fractionated courses, with rates of 20 % versus 8 %, respectively. This may be due in part to reluctance on the part of radiation oncologists to give additional fractionated radiation after a fractionated course. In addition, there has been less reported benefit to retreatment after multi-fraction regimens than after single fraction regimens [5].

9.5 Process of Radiation Therapy Planning and Delivery

Radiation oncologists commonly consult on patients with bone metastases following a definitive diagnosis and evaluation by other oncology physicians. Therefore, the radiation oncologist must gather and interpret all of the relevant clinical data and radiographic studies while optimizing communication with those other healthcare providers. Once EBRT has been determined to be appropriate by the radiation oncologist and has been accepted in an informed fashion by the patient, they are scheduled for a simulation or radiation planning session. One purpose of the simulation is to establish a reproducible patient position that allows treatment of the affected area without giving unnecessary radiation dose to other body parts, e.g. the arms. At simulation, the patient's body shape and anatomy is captured in the treatment position either by fluoroscopy or a quick CT scan to allow for dose calculation and reproducible set-up for subsequent treatment(s). While simulation may be completed by clinically assessing bony landmarks or using fluoroscopy to visualize bony anatomy, the most common mechanism for simulation involves a 20–30 min appointment which includes obtaining a CT scan of the patient in the same position that treatment will be delivered. The dosimetry, or dose planning, is completed next and involves computerized measurement of the best means by which to deliver dose to the intended target while minimizing treatment to adjacent normal tissues. For patients who do not live near a radiation facility or who suffer pain with transfer to and from CT scanners and treatment tables, it is most efficient to complete the consultation, simulation, and initiation of single fraction therapy during the same day. There are physicist and physician review of the radiation plan to ensure accurate delivery of radiation. Prior to treatment, portal images are obtained to verify that the set-up of the patient is correct and that the correct area is in the treatment field. The delivery of radiotherapy commonly takes only 10–15 min per dose, and it is painless other than discomfort that may be associated with transfer to fraction lying on the treatment table.

9.6 Side Effects of EBRT

Radiation therapy for bone metastases may cause acute side effects that are most often predictable, mild, manageable with conservative measure; and dependent upon the area of the body which is irradiated. Fatigue is the main systemic side

effect associated with treatment, though the fatigue from radiotherapy is usually less significant than that which is caused by the disease or other treatment modalities. Local side effects can include skin irritation, gastrointestinal complaints like nausea or diarrhea, or dysphagia. Factors such as the daily dose and total dose delivered can influence the risk for acute, sub-acute, and long-term toxicity. Previous trials have suggested a slightly higher risk of acute side effects following multiple fractions of radiotherapy when compared to a single, larger fraction for bone metastases [14, 18]. Tumor cell kill can cause a transient increase in bone pain around the time of the first few fractions of radiotherapy in 20–40 % of patients [19]. When it occurs, this pain flare may be minimized by the use of non-steroidal anti-inflammatory drugs or oral dexamethasone.

The late effects of radiotherapy, which by definition occur several months to years after treatment, are relatively rare but can be more serious than acute side effects. While the acute effects of treatment depend mostly upon the total dose of delivered radiotherapy, the late side effects of radiation depend upon both the total dose delivered and the size of dose delivered per treatment. In other words, larger daily doses of radiation correlate with a higher risk of long-term side effects. Patients with bone metastases have historically not lived a sufficiently lengthy time to commonly suffer late side effects. Improvements in systemic treatment have allowed some patients with bone metastases to live longer and potentially put them at risk for long-term toxicity that can be associated with short course, high dose per fraction therapy. To date, this has not been clinically significant given the relatively short survival in metastatic cancer and modest total dose delivered when larger fraction sizes are used. In the Dutch Bone Metastasis, a separate stratification and randomization was performed for patients who were thought to have a better prognosis, after 1 year, only 53 % of those patients were alive [7]. On average, physicians overestimated the survival of patients with metastatic cancer by 3 months. Factors that are associated with improved survival include histology (breast or prostate), absence of visceral metastasis, Karnofsky Performance Status and the Functional Assessment of Cancer Therapy (FACT) [15].

9.7 Retreatment with EBRT

Patients who have been previously treated with EBRT receive re-treatment to that same painful site with some frequency. If the first course of palliative radiation was a multi-fraction course, the retreatment rates are about 8 %. For those whose first course was a single fraction of 8 Gy, the retreatment rate is 20 % [4]. Approximately 55 % of patients experience recurrent pain at the treated site. At least one trial demonstrated less benefit from retreatment after initial multi-fraction regimens [5]. The true incidence of recurrent pain is uncertain, given that retreatment in those trials was given at the discretion of the treating physician. In general, both patients and physicians are more likely to accept re-treatment after an initial single fraction versus

a more prolonged radiotherapy course [5]. Recent consensus conference groups have therefore begun to better define the criteria by which re-treatment should be considered. Given that pain sometimes recedes slowly following radiotherapy over a period of days to weeks, the minimum interval before re-treatment should be considered is 4 weeks [20]. There is little prospective data available to predict the risk for combined side effects from initial treatment and re-treatment of painful bone metastases, though retrospective studies suggest that re-treatment can be given with relatively safety and a 50–70 % chance for pain relief [21]. A prospective international study did not demonstrate any non-interiority for a single 8 Gy retreatment versus 20 Gy in 5 fractions. The multifraction re-treatment course was associated with more side-effects [22].

9.8 Highly Conformal Therapy

Several emerging technologies are capable of producing EBRT that is considered highly conformal [23]. The goal of these techniques is to deliver high doses to the target while minimizing damage to adjacent structures. These approaches include intensity modulated radiation therapy (IMRT), which uses an inverse planning process with dose constraints for organs at risk (OAR) in the treated volume. Stereotactic body radiation therapy (SBRT) involves the delivery of large, highly conformal doses with fastidious attention paid to dose planning, patient set-up, and localization. This technique may be especially useful in the re-treatment of an area where the spinal cord has reached tolerance due to their initial definitive course of radiation therapy. Image guided radiation therapy (IGRT) can help to optimize patient positioning [24]. Proton beam therapy takes advantage of spatial qualities of radiation dose delivery to maximize dosing to the intended target [25].

SBRT has been used for painful bone metastases involving the spine, both as a primary treatment and as a method for delivering re-treatment to spine bones that have previously received standard external beam radiotherapy [26]. Treatment regimens studied include 30 Gy in 5 fractions, 27 Gy in 3 fractions, 40 Gy in 5 fractions or 16–24 Gy in a single fraction [27–29]. The results of these early trials are promising with prospective, randomized data likely to further define the best use of this technology [30] SBRT may be used for the primary treatment or retreatment of spine metastases. However, the relative lack of information about the long term effects of very large single doses through innovative delivery systems may create a higher risk of long term side effects than would be true for more established treatment approaches, so care must accompany this approach [31]. Routine use should not be employed until sufficient evidence from clinical trials justifies the substantive increase in cost when compared to standard external beam radiation therapy. Figure 9.1a–c Illustrates treatment of a shoulder metastasis with 8 Gy in a single fraction in the axial, coronal and sagittal planes. Figure 9.2a–d Illustrates SBRT to a vertebral body metastasis with 16 Gy in a single fraction.

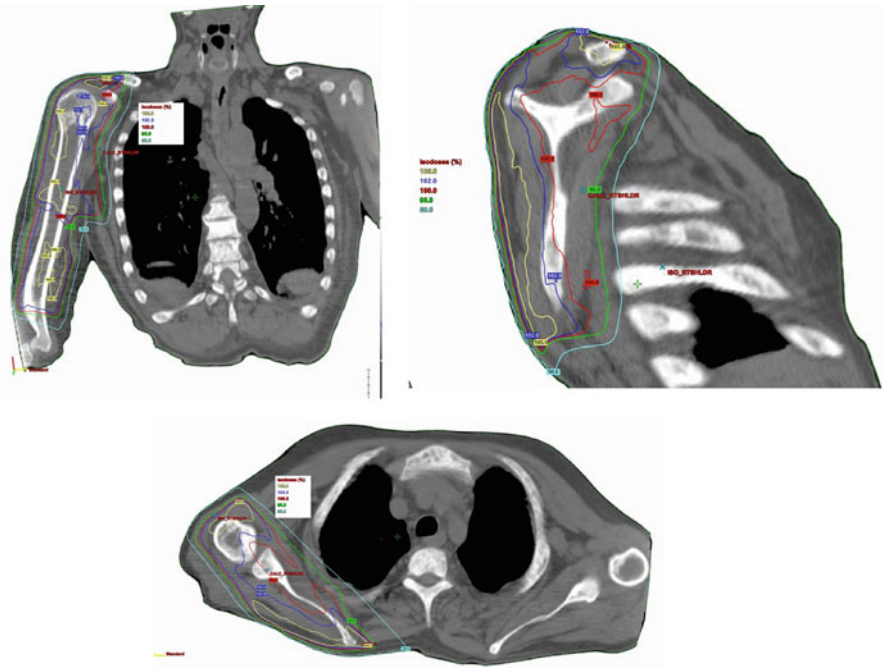

Fig. 9.1 Coronal, Saggital and Axial CT dosimetric images for a single fraction of 8 Gy using 3D conformal radiotherapy

9.9 Guidelines and Quality Measures

Though the optimal treatment of bone metastases with radiotherapy has been evaluated in multiple prospective randomized trials, there has been a great deal of variability in the dose fractionation regimens employed by radiation oncologists. One survey revealed that 101 different dose fractionation schemes were employed worldwide for this single clinical circumstance [13]. These disparities have led to the formation of treatment guidelines by the American Society for Radiation Oncology (ASTRO) and the American College of Radiology (ACR) [32–34]. These guidelines confirm that the available data reveal four fractionation schemes that are equivalent in the successful management of painful bone metastases: 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, and a single 8 Gy fraction. The guidelines acknowledge a trade-off between increased convenience and a higher re-treatment rate with single fraction therapy. Additionally, the publications differentiate between treatment approaches that have proven to be effective through clinical trials and those approaches that require further investigation before being used in a routine, non-protocol setting. The use of one of the four approved fractionation schemes is considered a measure of quality as determined by the

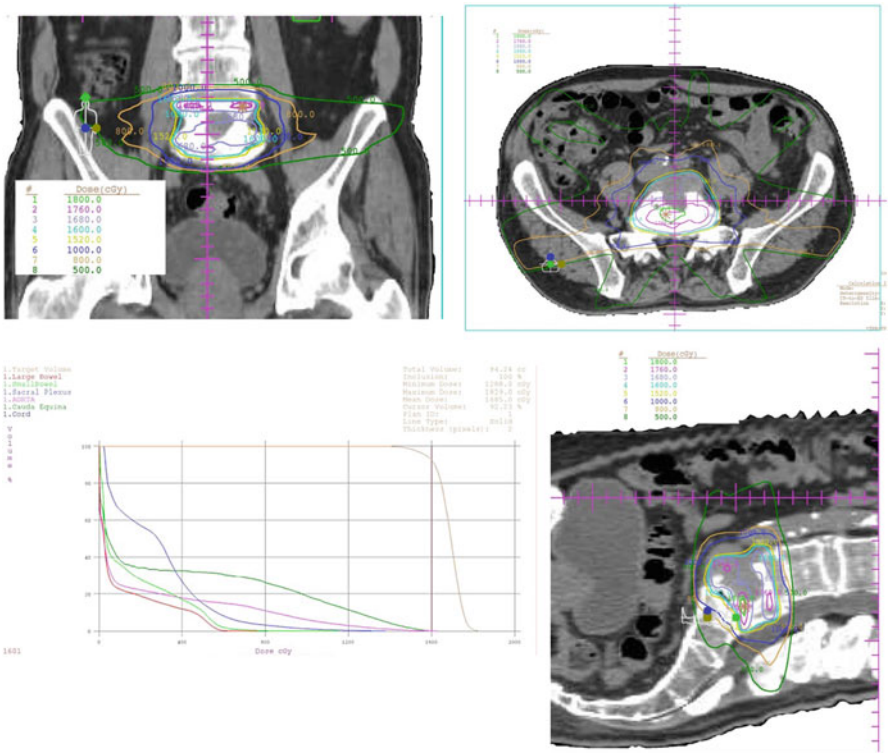

Fig. 9.2 Coronal, Saggital and Axial CT dosimetric images for a single fraction of 16 Gy delivered with stereotactic spine radiation therapy with the accompanying Dose Volume Histogram

National Quality Forum (NQF) [35]. The NQF is a non-profit organization that is tasked to assess healthcare priorities in the United States while providing a means to measure and report on the performance of healthcare providers and healthcare facilities. Furthermore, the choice to offer appropriate length fractionation schemes for patients with painful bone metastases is under review in an initiative called "Choosing Wisely" [36], a program started to help physicians become better financial stewards of healthcare use.

9.10 Summary

Bone metastases continue to be a significant clinical problem, with pain being the most common symptom requiring intervention. External beam radiation therapy continues to serve as the main form of treatment for painful bone metastases, with good coordination required between the radiation oncologist and other specialists including medical oncologists, surgeons, palliative medicine specialists, and physiatrists.

Short course treatments effectively provide symptom relief, with many patients best treated by a single fraction. The acute- and long-term side effect rates from EBRT are minimal and usually self-limited. Highly conformal therapy for bone metastases shows great promise, especially in patients with recurrent pain in the spine after previous conventionally fractionated curative therapy. Bone metastases treatment guidelines and quality measures provide data-derived direction to the management of patients with this clinical condition.

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Chapter 10
Radionuclide Therapy

Fabio M. Paes

Abstract Bone pain due to skeletal metastases constitutes the most common type of chronic pain among patients with cancer. Almost 65 % of patients with prostate or breast cancer and 35 % of those with advanced lung, thyroid and kidney cancers will have symptomatic skeletal metastases. Painful osseous metastases are known to significantly decrease the patient's quality of life and are associated with co-morbidities such as spinal cord and nerve injury, hypercalcemia, depression and pathologic fractures. The treatment of bone pain is challenging and involves a multidisciplinary approach with a combination of therapeutic modalities. In patients with extensive osseous metastases, systemic radionuclide therapy should be part of the adjunctive therapy for pain palliation. In this chapter, we discuss the most common approved and clinically used radionuclides for bone pain palliation, focusing on indications, patient selection, efficacy, and different biochemical characteristics and toxicity. We will cover Strontium-89 chloride (Sr-89), Samarium-153 lexidronam (Sm-153) and Rhenium-186 etidronate (Re-186). A brief discussion on the available data on Rhenium-188 (Re-188) is also presented focusing on its major advantages and disadvantages. In the end, we perform a concise appraisal of the available data on combination therapy of radiopharmaceuticals with biphosphonates or chemotherapy.

Keywords Radionuclide therapy • Samarium-153 • Strontium-89 • Rhenium-186 • Radiopharmaceuticals • Flare phenomenon

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10.1 Introduction

Unfortunately, the majority of cancer patients will develop pain at some point during the course of the disease. Painful osseous metastasis constitutes the most frequent cause of pain among all cancer patients. It is commonly detected in the advance stages of the disease and drastically decreases the patient's quality of life. Bone pain is distinct from neuropathic, visceral or other types of somatic pain (such as inflammatory and arthritic pain) with particular characteristics during its course: initially it is dull and mild, and progresses to a chronic painful state with intermittent severe breakthrough episodes of acute pain. Generally, the pain exacerbates at the end of the analgesics scheduled interval and it is often difficult to treat without being accompanied by significant, unwanted side effects.

The pathophysiology is not well understood and multiple mechanisms are postulated and discussed in the literature [1]. In summary, tumor-induced cytokines, stimulating factors released by tumor cells, and direct nerve injury have all been proposed as mechanisms that mediate skeletal pain. Infiltration of the bone matrix and trabeculae by tumor cells stimulating osteolysis also generates skeletal pain. This explains in part the positive results of biphosphonates in the treatment of bone pain due to its known inhibitory osteclastic effect [2]. Peripheral nerve endings are also triggered by various substances produced by cells in response to the tumor (e.g., Prostaglandin-E, Interleukins, Substance P, GABA, Transforming growth factor, etc.), and by the tumor cell itself (Tumor Necrosis Factor); leading to sensitization of the peripheral nervous system and causing allodymia and hyperalgesia [3]. Other possible mechanisms are the development of microfractures, spinal cord compression, entrapment and nerve injury due to weakening of bone by tumor growth.

The prevalence of painful osseous metastases varies among the different types of cancers. Approximately 65 % of patients with prostate or breast cancer and 35 % of those with advanced cancers of the lung, thyroid and kidney will develop symptomatic skeletal metastases. In clinical practice, breast and prostate cancers are responsible for more than 80 % of cases with bone metastases [4]. Metastatic bone involvement may be the first and only sign of solid tumor spread; detected in many instances before the primary site. Due to the high prevalence of osseous metastasis in prostate and breast cancers, screening whole body bone scintigraphy has become part of the initial staging and follow up algorithm of the majority of these tumors. Even in the presence of known osseous metastasis, skeletal scintigraphy has additional value in the oncologic work up as it also helps delineate the extension and severity of skeletal involvement, and can classify lesions as predominantly osteoblastic, lytic or mixed type. This information is crucial in the correct treatment plan as discussed later in this chapter.

10.1.1 The Challenge of Managing Bone Pain

The appropriate management of painful skeletal metastasis is complex, costly, and should be carried out by a multidisciplinary approach [5–7]. Most of the therapies targeted to kill the tumor cells are effective methods of pain control,

Table 10.1 Available therapies for the treatment of metastatic bone pain

Tumoricidal	Non-tumoricidal
1. Surgery	1. Analgesics
2. External beam radiation	2. NSAIDs
3. Chemotherapy	3. Opiods
4. Radionuclide therapy	4. Biphosphonates
5. Radiofrequency ablation	5. Hormones and anti hormones

Table 10.2 Barriers for adequate bone pain management

Cause	Intervention
1. Lack of familiarity of the available treatment options	1. Consider multidisciplinary approach referring the patients to Pain specialist, Nuclear Medicine Physician and Radiation Oncologist
2. Poor assessment and unreliable report of patient's pain	2. Establish a solid and trustworthy doctor-patient relationship
3. Variable documentation of patient's pain	3. Use of validated pain measurement instruments: Visual Pain Scale (VAS), Opioid and Pain dairy

like chemotherapeutic agents, external beam radiation (XRT), radiofrequency ablation (RF), and surgery. However, they are often invasive (i.e. surgery and RF), arduous to administer (i.e. chemotherapeutic regiments), provide incomplete pain control or are accompanied by unwanted side effects, particularly in patients with extensive metastatic disease. Medications without tumoricidal effect targeted to diminish the pain associated with metastasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), steroid or opiates are equally useful but also have dose limiting side effects [8]. A summary of available treatment options is provided on Table 10.1.

Sadly, even with this vast armamentarium, patients are still inadequately treated for bone pain. It has been reported that at least 45 % of cancer patients receive unsatisfactory pain control. Two of the most frequently identified obstacles for appropriate pain management are poor assessment of the patient's pain and physician's lack of knowledge of all treatment options (Table 10.2).

Symptomatic pain assessment must be performed by utilizing standardized measurement tools administered at appropriate intervals. It is important to assess and document periodically the patient's pain on each clinical consult and keep an open channel for communication with the patient and his family. The goal is to anticipate the worsening of the symptoms, evaluate the current treatment side effects and the quality of life to trace the best strategy for palliation.

On the research arena, consistent pain measurement and standardized recording of analgesic use across clinical trials is of ultimate importance to enhance comparability of findings, and facilitate the development of evidence-based guidelines for the management of bone pain. For instance, a consensus on palliative endpoint measurements in bone metastases has been in use for external beam radiotherapy trials and it can be used as a reference in future trials of other palliative modalities [9].

Furthermore, the physician caring for these cancer patients should understand that no single method is capable of offering adequate pain control for most individuals and frequently a combination of the systemic and local treatment is necessary,

particularly to avoid debilitating side-effects of either treatment modality. Curative options are not available for multiple skeletal metastases, and so, all available treatments are palliative.

In this chapter, it is reviewed the current approved radiopharmaceuticals for metastatic bone pain palliation, focusing on indications, patient selection, efficacy, and the different biochemical characteristics and toxicity. We examine the data on Strontium-89 chloride (Sr-89), Samarium-153 lexidronam (Sm-153) and Rhenium-186 etidronate (Re-186). A succinct discussion on Rhenium-188 (Re-188) is presented, focusing on its major advantages and disadvantages over the other available radiopharmaceuticals. We also present a concise appraisal of the available data on combination therapy of radiopharmaceuticals with biphosphonates or chemotherapy.

10.2 Systemic Radionuclide Therapy with Bone Seeking Radiopharmaceuticals

Systemic radionuclide therapy has proved its value in the management of painful bone metastasis in current clinical practice [5, 8, 10, 11]. Even though, these so called "bone-seeking agents" have been used in the treatment of oncological and non-oncological disorders for the past few decades, they remain a relatively unknown treatment modality for many physicians, even for those working on the oncologic and pain palliation fields. One of our goals is to change that.

The firsts bone-seeking radiopharmaceuticals approved for the treatment of painful bone metastases were the radioactive isotopes of Phosphorus-32 (P-32) and Strontium-89 (Sr-89). These elements preferentially incorporate into the sites of active osteoblastic bone metastases at rates 2–25 times greater than in normal bone. The clinical use of P-32 has decreased since the 1980s in favor of Sr-89 and newer alternatives, due in part to higher myelotoxicity from higher-energy decay and longer beta particle range in tissue [12]. Newer beta-emitting isotopes were developed for palliation of cancer-induced bone pain and are administered using chelated complexes with more efficient pharmacokinetics, better decay properties and a shorter beta range (Table 10.3).

Samarium-153 (Sm-153), Rhenium-186 (Re-186) and Rhenium-188 (Re-188) are categorized as newer bone-seeking radioisotopes [5, 12, 13]. They have been extensively studied in the treatment of painful bone metastasis, particularly in breast and prostate cancer. Samarium-153 has been approved for use in the USA and Europe for more than a decade, whereas Rhenium-186 has only been approved in Europe. Rhenium-188 is still under clinical investigation and shows a promising accessibility profile since it can be obtained from a generator [13, 14].

All the beta-emitting radioisotopes differ significantly in their physical properties, even though they have shown practically the same efficacy in pain palliation. The clinical experience and amount of data regarding those radioisotopes also vary, with

Table 10.3 Newer radiopharmaceuticals for pain palliation

Radiopharmaceutical	Max. Beta energy MeV	Gamma energy KeV (%)	Half-life (days)	Max. tissue range (Average)	Standard dose (SI)	Notes
Sr-89 Chloride	1.46	910 (0.01 %)	50.5	6 mm (2.4 mm)	4 mCi (148 MBq)	FDA approved longest half-life
Sm-153 EDTMP	0.81	103 (28 %)	1.9	2.5 mm (0.6 mm)	1 mCi/kg (37 MBq/Kg)	Most commonly used in the USA
Re-186 HEDP	1.07	137 (9 %)	3.8	4.5 mm (1.1 mm)	35 mCi (1,295 MBq)	Approved for clinical use in Europe
Re-188 HEDP	2.12	155 (15 %)	0.7	10.4 mm (3.1 mm)	30–118 mCi (1.1–4.4 GBq)	Experimental, $^{188}W/^{188}Re$ generator

at least twice more clinical trials involving Samarium-153, Strontium-89 and Rhenium-186 than Rhenium-188.

Besides the current use for bone pain palliation, other indications for these agents have been studied with promising results including treatment of hemophilic arthropathy [15, 16], conditioning therapy prior to bone marrow transplantation in acute leukemias [17–19], and radioimmunotherapy using radiolabeled antibodies against different tumors [20–23]. Those therapeutic indications are beyond the scope of this book.

10.2.1 Radiopharmaceuticals: Efficacy, Physical and Biological Characteristics

10.2.1.1 Strontium-89 Chloride

Sr-89-chloride (Metastron®) was the first FDA approved radiopharmaceutical for bone pain palliation. Strontium is a divalent cation and, like calcium, is incorporated into hydroxiapatite in the bone after intravenous injection. It has a half-life of 50.5 days, decays to stable Yttrium-89 emitting high-energy beta particles (Emax = 1.46 MeV) and 0.01 % of gamma-rays (910 keV). The beta particles are responsible for its therapeutic effect and have an energetic penetration range within 6–7 mm in soft tissues and 3–4 mm in the bone [24]. The short penetration range explains why minimal radiation escapes the body. Therefore, there is no radiation risk to others, even family members, after Sr-89 administration and the patients can be treated on an outpatient basis. Studies of Sr-89 pharmacokinetics demonstrated a variable plasma clearance (between 1.6 and 11.6 L/day) with overall total body retention of 20 % in a healthy population 90 days after injection, particularly in the normal skeleton. Osteoblastic lesions show up to five times greater radiopharmaceutical uptake and a prolonged retention time than areas of normal bone in the same patient (lesion/normal bone ratio 5:1) [4, 25].

The standard recommended dose of Sr-89-chloride is a single intravenous injection of 4 mCi (148–150 Mbq). No direct dose response relationship has been documented in the literature.

There is extensive data on the efficacy of Sr-89 for bone pain palliation (Table 10.4). As seen with other radiopharmaceuticals, patients with osseous metastasis from breast and prostate cancer were the predominant subjects in most clinical trials. The value of Sr-89 for the treatment of metastatic skeletal pain is discussed and exemplified below.

In an open label prospective study by Pons and colleagues [26], a total of 66 patients (50 males with prostate carcinoma and 26 females with breast cancer) were evaluated and treated with 4 mCi (148 MBq) of Sr-89. The efficacy of Sr-89 was evaluated using Karnofsky score, pain and analgesic scales at 3 months of treatment. The overall response rate was 89 % in the prostate and 92 % in the breast cancer patients. A good duration of the response was achieved and ranged

Table 10.4 Summary of efficacy studies on Sr-89, Sm-153 and Re-186

	Pain relief %	References	Dose (SI)	No. of patients	Cancer	Year
Sr-89 Chloride	92 %	Fuster et al. [82]	4 mCi (148 MBq)	40	Breast	2000
	78 %	Kraeber-Bodere et al. [28]	4 mCi (150 MBq)	94	Prostate	2000
	63 %	Turner et al. [83]	4 mCi (150 MBq)	93	Prostate	2001
	59.80 %	Dafermou et al. [33]	4 mCi (148 MBq)	527	Prostate	2001
	81 %	Ashayeri et al. [84]	4 mCi (150 MBq)	27	Prostate and breast	2002
	82 %	Zorga et al. [85]	4 mCi (148 MBq)	33	Prostate, breast, bladder and renal cell	2003
	88 %	Baczyk et al. [86]	4 mCi (148 MBq)	70	Prostate	2003
	57 %	Gunawardana et al. [87]	4 mCi (148 MBq)	13	Prostate	2004
	72 %	Liepe et al. [65]	4 mCi (148 MBq)	15	Prostate and breast	2007
	83.60 %	Ma et al. [88]	40–60 uCi/kg (1.48–2.22 MBq/kg)	116	Prostate	2008
Sm-153 EDTMP	62–82 %	Serafini et al. [39]	0.5–1 mCi/Kg (18.5–37 MBq/kg)	118	Prostate, breast, others	1998
	84 %	Tian et al. [44]	1 mCi/Kg (37 MBq/kg)	105	Prostate, breast, others	1999
	70 %	Dolezal et al. [89]	1 mCi/Kg (37 MBq/kg)	33	Prostate, breast, others	2000
	78 %	Wang et al. [90]	1 mCi/Kg (37 MBq/kg)	9	Prostate, breast, others	2003
	76 %	Sapienza et al. [42]	1 mCi/Kg (37 MBq/kg)	73	Prostate, breast	2004
	78 %	Etchebehere et al. [91]	1.0–1.6 mCi/kg (37–59.2 MBq/kg)	58	Prostate, breast, others	2004
	65 %	Sartor et al. [41]	1 mCi/Kg (37 MBq/kg)	152	Prostate	2004
	73 %	Tripathi et al. [92][a]	1 mCi/Kg (37 MBq/kg)	86	Prostate, breast, others	2006
	61.50 %	Ripamonti et al. [93]	1 mCi/Kg (40 MBq/kg)	13	Prostate	2007
	73 %	Liepe et al. [65]	1 mCi/Kg (37 MBq/kg)	15	Prostate and breast	2007
	75 %	Dolezal et al. [94]	1 mCi/Kg (37 MBq/kg)	32	Prostate	2007

(continued)

Table 10.4 (continued)

	Pain relief %	References	Dose (SI)	No. of patients	Cancer	Year
Re-186 HEDP	50 %	Kolesnikov-Gauthier et al. [95]	35 mCi (1,295 MBq)	26	Prostate and breast	2000
	79 %	Tennvall et al. [96]	70 mCi (2,590 MBq)	14	Prostate	2000
	67.50 %	Kucuk et al. [97]	35 mCi (1,295 MBq)	31	Prostate, breast, rectum, lung and nasopharynx	2000
	80 %	Sciuto et al. [55]	38 mCi (1,406 MBq)	60	Prostate and breast	2000
	92 %	Sciuto et al. [31]	38 mCi (1,406 MBq)	25	Breast	2001
	86 %	Dafermou et al. [33]	35 mCi (1,295 MBq)	58	Prostate	2001
	65 %	Han et al. [54]	35 mCi (1,295 MBq)	43	Prostate	2002
	62 %	Leondi et al. [98]	35 mCi (1,295 MBq)	24	Lung	2004
	67 %	Liepe et al. [65]	35 mCi (1,295 MBq)	15	Prostate and breast	2007

[a] Breast and prostate cancer had response rates of 80.3 % and 80.5 %, respectively. One case each of Wilms tumor, ovarian cancer, germ cell tumor testis, multiple myeloma, primitive neuroectodermal tumor and esophageal cancer, did not respond to therapy

from 3 to 12 months (mean 6 months). The most common side effect was a decrease in leukocyte and platelet counts after the 1st month of treatment, with a gradual partial to complete recovery within 6 months. Also, in the patients who were retreated with the same regiment, the effectiveness was as good as after the first dose of Sr-89 with similar safety profile.

Other dose regiments for Sr-89 were tried. Baziotis and colleagues [27] reported on 64 patients with painful bone metastasis from breast cancer who were treated with 54 uCi/kg (2 MBq/kg) of Sr-89 chloride as a single intravenous injection. The response was assessed during a 6-month follow-up period, and 52 of 64 patients (81 %) showed at least moderate improvement. A dramatic decrease in bone pain was carried by 18 out of the 52 responders (35 %). Twenty-one (40 %) presented a satisfactory response and in 13 cases (25 %) the response was considered moderate. Only 12 patients (19 %) from the whole group did not feel any improvement on pain. These findings, like many other published, prove the effectiveness of Sr-89 in the treatment of bone metastasis from breast cancer.

Kraeber-Bodere and his group [28] used a different approach in the evaluation of Sr-89 efficacy. They examined the relationship of therapeutic response and the degree of bone involvement and flare phenomenon in patients with metastatic prostate cancer who were treated with Sr-89. Flare phenomenon refers to expected worsen of the painful symptoms with corresponding scintigraphic findings usually in the first weeks after the radionuclide injection. They evaluated 94 patients (totalizing 117 single injections of 4 mCi) and compared the efficacy of treatment according to the extent of bone involvement (moderate and extensive). Improvement in the quality of life was obtained in 65 % of subjects, decrease in pain in 78 % (31 % complete response) and reduction of analgesics in 60 %. Efficacy was significantly better for pain decrease ($P=0.005$) and reduction of analgesics ($P=0.018$), and response was significantly longer ($P<0.0035$) in patients with moderate bone involvement than in patients with extensive osseous disease. In this study, the flare response observed in 23 % of cases was not predictive of pain response ($P=0.919$) or reduction of analgesics ($P=0.353$). Because patients with moderate metastatic involvement demonstrated better response, the authors recommended considering radiopharmaceutical agents earlier in the progression of osseous disease, which could lead to prolonged pain-free period and delayed transition to other therapeutic approaches, particularly high dose opioids.

Others, such as Laing and colleagues, have described the flare phenomenon (usually lasting 2–4 days) as a predictor of good therapeutic response. In their multicenter trial, they evaluated 83 patients with hormone refractory prostate cancer treated with at least 40 uCi/kg (1.5–3.0 MBq/kg) and obtained a 75 % therapy derived benefit and 22 % pain free response. Better results were more common in the group of patients who developed flare phenomenon. Most of responses occurred within 6 weeks with a mean effect duration of 6 months (range of 4–15 months) [29].

A systematic review of the available literature published by Finlay and colleagues showed a percentage of complete responders to Sr-89 ranging from 8 % to 77 %, with a mean value of 32 %, and no responders ranging from 14 % to 52 % (mean 25 %).

In general, 44 % of patients had some degree of response to Sr-89 treatment, giving a mean overall response of 76 % [10].

Another important question for patients with limited life span is how soon and for how long we should expect a response. An early phase I/II study showed a median time to response of 9 days (range 3–25 days) and an average duration of response of 1.6 months (range 1–4 months) in patients who received doses ranging from 1.0 to 4.0 mCi [30]. Several other authors reported greater mean duration of pain relief of about 6 months [31, 32]. In the systematic review, the overall time from the Sr-89 injection to measurable response was between 4 days and 28 days, with response duration of up to 15 months [10].

It is important to mention that, although limited data is available, some authors have described a few predictive factors of better response to Sr-89 therapy. Patients with limited skeletal involvement, with higher performance status, and those with predominantly osteoblastic lesions on bone scintigraphy demonstrated greater pain relief with a longer duration [33, 34]. These positive prognostic factors are likely valid for the other radiopharmaceuticals.

10.2.1.2 Samarium-153 Lexidronam

Samarium-153-EDTMP (Quadramet ®) is the most commonly used radiopharmaceutical for bone pain palliation in USA cancer centers. Sm-153 is produced by neutron irradiation of Samarium-152 oxide which can then be quelated with the calcium salt of ethylenediaminetetramethylene phosphonic acid (EDTMP-Lexidronam) to produce ^{153}Sm-EDTMP. Sm-153 is a radionuclide that emits mostly beta particles (E_{max} = +640; 710 and 810 KeV) with maximum energy of 0.81 MeV; it has a physical half-life of 46.3 h, and an average penetration range of 0.83 mm in water [35]. Its purity is practically 100 %. Contrary to Sr-89 and P-32, the beta-decay of Sm-153 is accompanied by 28 % emission of 103.2 keV gamma rays which can be detected by Anger cameras and used for imaging (Fig. 10.1). Sm-153-EDTMP forms a complex that selectively accumulates in skeletal tissue in association with hydroxyapatite, particularly in areas where the rate of bone turnover is high. The total skeletal dose of Sm-153 is unpredictable and ranges from 15 % to 95 % depending of the osteoblastic activity. Like with other radiopharmaceuticals, bone metastases retain about five times more Sm-153 than healthy bone tissue, so that adjacent malignant cells are selectively exposed to very high doses of radiation. Sm-153 is rapidly cleared from the blood with a half-life of 5.5 min leading to less than 1 % of the dose remaining in the circulation 1 h after administration. Urinary excretion is the main route of elimination and is complete within 6 h.

Dose escalation trials were performed in the early 90s and demonstrated similar distribution of activity in doses ranging from 1 mCi/Kg to 3 mCi/kg. Skeletal doses ranged from 20,000 to 32,000 mrad/mCi (5,300–8,800 Gy/MBq). Marrow doses ranged from 4,600 to 7,500 mrad/mCi (1,200–2,000 Gy/MBq) and urinary bladder doses ranged from 1,300 to 4,700 mrad/mCi (360–1,300 Gy/MBq) [36, 37]. Nonskeletal sites received negligible doses. Total absorbed marrow doses estimated

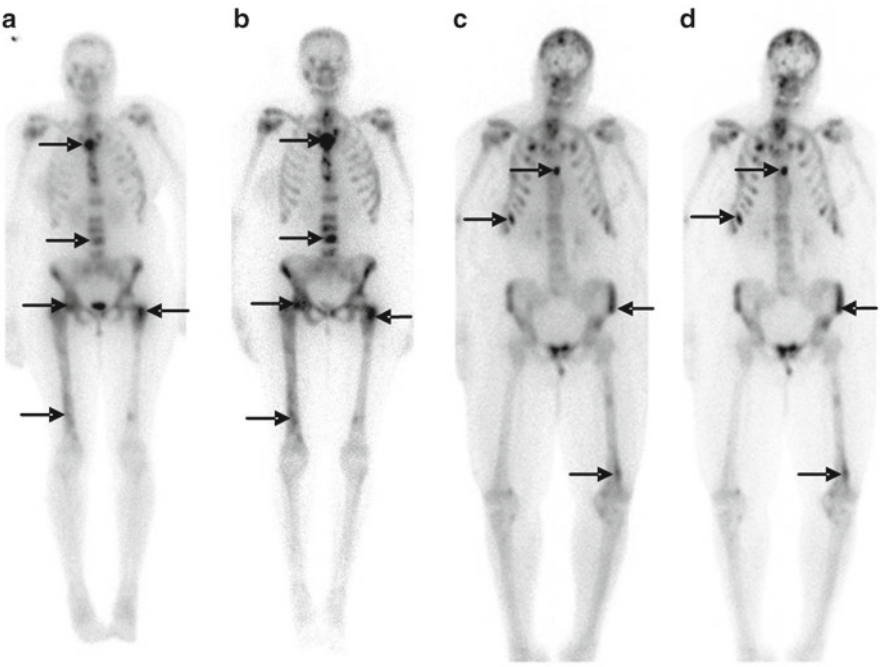

Fig. 10.1 Targeting of osteoblastic metastases with Sm-153-EDTMP scintigraphy. Anterior whole body bone scan images of two patients with metastatic breast cancer demonstrating several osteoblastic lesions in the axial and appendicular skeleton (*arrows*). Images (**a**) and (**c**) were acquired 4 h after injection of Tc-99 m-MDP whereas images (**b**) and (**d**) were acquired 1 h after a therapeutic dose (70 mCi) of Sm-153-EDTMP. All areas of osteoblastic metastases are matched between the whole body scans

by Eary and colleagues ranged from 1,277 to 2,250 rad in the 3.0 mCi/kg dose, with only two of four patients experiencing mild hematotoxicity [37]. The standard used dose of Sm-153-Lexidronam is 1 mCi/Kg administered intravenously, which has been proven safe and effective, causing only mild reversible bone marrow suppression in patients with normal blood counts.

After several open label studies in animals and humans [38], prospective controlled trials were conducted in a large number of patients in North America, Europe, South America and Asia [39–44] evaluating the efficacy of Sm-153 for the treatment of painful bone metastasis (Table 10.4). A summary of these data is discussed below.

In the first double-blind placebo-controlled study, 118 patients with painful bone metastases from a variety of primary tumors were randomized to placebo, 18.5 MBq/kg (0.5 mCi/kg), or 37 MBq/kg (1.0 mCi/kg) of Sm-153-lexidronam [39]. The efficacy was evaluated and documented using visual analog scale (VAS), physician's global assessment (PGA), and daily opioid analgesic use. In this study, the mean VAS score decreased from baseline in each of the 4 weeks following administration with

both active doses, with greater decreases in the higher dose group. The scores remained essentially unchanged from the baseline in the placebo group. A mild, transient, dose-related myelosuppression was the only side-effect noted. The 1.0 mCi/kg dose of Sm-153 provided a relatively rapid onset of pain relief, within 1 week of administration, compared to placebo and allowed an early reduction in the use of opioid analgesics. In addition, the effects were durable because more than half of the patients who were responders at week 4 were still judged as having some pain relief 16 weeks after the radionuclide administration according to the PGA [39].

A Phase III double-blind randomized controlled trial performed by Sartor and colleagues enrolled 152 men with hormone-refractory prostate cancer and painful bone metastases to assess the effectiveness of Sm-153 [41]. They were randomized (2:1) to radioactive (Sm-153) versus nonradioactive (Sm-152) Lexidronam complexes. Sm-153-Lexidronam had positive effects on measures of pain relief compared with control within 1–2 weeks. There was statistically significant improvement in pain and reduction of analgesic consumption for patients treated with Sm-153-Lexidronam. The analgesic use was statistically decreased at 3 and 4 weeks. Both the VAS and Pain Discomfort Scale (PDS) showed significant improvement in the Sm-153 group. For the PDS score, improvement was noted at weeks 1, 2, 3, and 4. For the VAS score, improvement was noted at weeks 2, 3, and 4. A statistically significant correlation ($r = 0.78$; $P < 0.0001$) was found between the VAS and PDS scores. The difference for the change in analgesic use between the groups was statistically significant at weeks 3 and 4 ($P < 0.0284$). Because non-responders were unblinded at week 4, statistical comparisons between the arms beyond week 4 were not possible. Again, mild, transient bone marrow suppression was the only adverse event and blood counts recovered to baseline after approximately 8 weeks. No grade 4 platelet or white bloods cell toxicity was documented [41].

Another multicenter trial, now from China, studied the efficacy and toxicity of single-dose Sr-153 as a palliative treatment for painful skeletal metastases [44]. One hundred and five patients with painful bone metastases from various tumors were treated with a dose of 1 mCi/kg (group I) or 0.5 mCi/kg (group II). The effects were evaluated according to change in daily analgesic consumption, pain and Karnofsky scores (KS) among other parameters, conducted regularly for 16 weeks. Of 72 patients who had been receiving analgesics, 63 reduced their consumption. The KS increased from 58.54 (+/−25.90) to 71.67 (+/−26.53), indicating improved general conditions, but there was no significant difference between both groups. Seventeen patients showed no response or serious side effects. Response and side effects were both independent of dose. In this trial, a dose of 1 mCi/kg of Sm-153 provided effective palliation in 83.8 % of patients with painful bone metastases [44]. These studies, along with many others, established the 1 mCi/kg dose of Samarium-153-EDTMP as a valuable option for metastatic bone pain palliation.

Whenever a patient demonstrates a good response to a single dose of Sm-153, repeated treatment should be considered. Retreatment has been proven safe, feasible, and efficacious. Menda and colleagues [45] reported the results of a patient with metastatic prostate cancer retreated with a total of 11 doses of 1 mCi/kg of Sm-153-Lexidronam, over a period of 28 months. With the first five doses, the

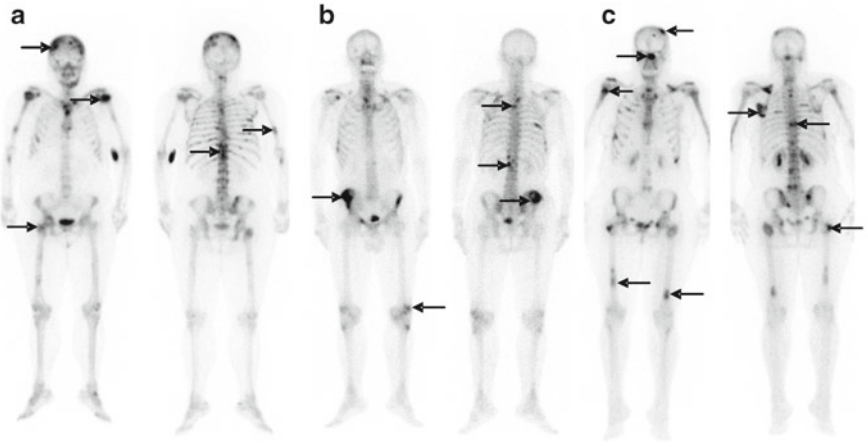

Fig. 10.2 Post treatment anterior and posterior views of whole body scans acquired 1 h after therapeutic doses of Sm-153-EDTMP of patients with different types of metastatic cancers (*arrows*—osteoblastic metastasis). (**a**) 57-year-old male with metastatic prostate cancer treated with 73 mCi. (**b**) 63-year-old male with metastatic adenocarcinoma of the lung treated with 74 mCi. (**c**) 46-year-old male with metastatic nasal spindle cell sarcoma treated with 71 mCi

patient clearly reduced his bone pain and improved his quality of life as determined by pain assessment scores and the impact of pain on daily living. With doses 6–11, the beneficial effects were maintained but were not as apparent or durable. The pain scores were lower but the use of opioid had also increased. During the 28 months of treatment, Sm-153 produced transient decreases in WBC and platelet counts which were not severe enough to cause clinical concern.

Sartor and his group also reported the safety and efficacy of repeated doses of Sm-153 in patients with metastatic bone pain [46]. They prospectively analyzed 55 patients receiving two or more 1.0 mCi/kg doses of Sm-153. Pain scores, adverse events, and hematologic parameters were assessed after each dose. Mild, transient suppression of platelets and white blood cell counts were the commonest adverse events after treatment. Nadirs were approximately half of baseline at 4 weeks with recovery in 90 % of patients by week 8. Temporary grade 3 thrombocytopenia occurred in 11 %, 12 %, and 17 % of patients after the first, second, and third drug administration, respectively. Significant decreases in pain scores ($P < 0.001$) were observed at Week 4 after each of the first three doses and maintained at Week 8 after the first two doses ($P < 0.003$) but not after the third dose. Decreases in pain scores were observed in 70 %, 63 %, and 80 % of patients, respectively, at Week 4 after the first 3 administrations.

Sm-153-Lexidronam is the radiopharmaceutical of choice for pain palliation in most practices in the USA due to its shorter half life, adequate safety profile and vast clinical experience for single or repeated treatment of patients with metastatic bone disease from different primary tumors (Fig. 10.2).

10.2.1.3 Rhenium-186 (Re-186) HEDP

Originally developed in the USA at the University of Cincinnati, Re-186 HEDP has been studied extensively and is widely used in Europe for bone pain palliation and treatment of other benign conditions [15, 16]. Re-186 is produced by irradiating Re-185, demonstrates chemical properties similar to Tc-99 m and can be readily complexed with HEDP with a relatively high radionuclide and radiochemical purity. With a physical half life of 89.3 h (approximately 3.7 days), Re-186 HEDP decays by the emission of a beta particle with energy of 1.07 Me. It is rapidly cleared from the blood (plasma half-life of 41 h), predominantly by renal excretion, with 70 % eliminated within 72 h.

Re-186 also decays by 137 keV gamma-emission (9 % abundance), used for imaging and dosimetry, having a body distribution similar to that of 99mTc-methylene diphosphonate (MDP) on bone scintigraphy [47]. A high effective dose rate was found with injected dose of 1,295 MBq (35 mCi) on dosimetric studies, with a mean tumor lesion midpoint dose to the tumor lesions of 35.3 Gy, and a mean midpoint marrow dose of 0.012 Gy. The tumor-to-marrow dose ratios have a high therapeutic index, with a mean value of 34:1, and a median value of 20:1 [48]. The maximum tolerated dose (MTD) of Re-186 for females with breast cancer and males with prostate cancer and symptomatic bone metastasis was 2,405 MBq (65 mCi) and 2,960 MBq (80 mCi) in the dose escalation studies performed by de Klerk's group [49, 50].

Recent guideline published by European Association of Nuclear Medicine (EANM) recommended a intravenously injected dose of 1.295 MBq (35 mCi) for treatment with Re-186 HEDP [51]. The efficacy of Re-186 HEDP for the treatment of painful osseous metastasis was also investigated by several groups in different clinical trials (Table 10.4).

A small double blind controlled trial by Maxon and his co-workers [52] was one of the first to show the beneficial effect of Re-186 in pain palliation. They evaluated a group of six patients treated with 1.258 MBq of Re-186 HEDP (34 mCi) and compared to seven patients who received 666 MBq of Tc-99 m-MDP (18 mCi) as a control group. Preliminary results demonstrated response in five patients of the six who received Re-186 HEDP, but in only one of the seven of the control group. Myelotoxicity with the Re-186 was minimal, with transient myelosuppression, returned to baseline within 8 weeks. Flare response only occurred in one patient 2–3 days after the injection, with complete resolution of the related pain within 1 week. In this pivotal study, a single intravenous administration of Re-186 was associated with a rapid and major pain relief in about 80 % of such patients.

On a larger open label trial using a single intravenous administration of approximately 1,258 MBq of Re-186 (34 mCi), the same group led by Maxon documented significant improvement in pain in 33 of 43 treated patients (77 %) following a initial injection, and in 7 of 14 patients (50 %) following a second treatment. Patients responding to treatment experienced an average decrease of 60 % in pain, with one in five treatments resulting in a complete resolution of symptoms. Again mild transient increase in pain within a few days following injection was the only noted

clinical adverse effect. Statistically significant but clinically unimportant decreases in total white blood cell counts and total platelet counts were observed within the first 8 weeks following the injection; no other toxicity was apparent [53].

The largest double-blind placebo controlled trial performed for evaluation of the efficacy of Re-186 in the treatment of metastatic prostate cancer, the PLACORHEN study [54], enrolled initially 111 patients of which 79 were evaluated (43 treated, 36 placebo). The total response of the patients treated with Re-186 varied from 0 % to 96 % (mean, 27 %). In the placebo group, the total response varied from 0 % to 80 % (mean, 13 %, $P<0.05$). The number of patients who needed pain palliation with radiotherapy was higher in the placebo group (67 %) than in the Re-186 (44 %).

Higher overall response rates to Re-186 were reported in the literature. Sciuto and colleagues demonstrated in two consecutive trials [31, 55] response rates of 80 % and 92 % respectively. In the first study, 60 patients with painful bone metastases from different tumor types were treated with 1,406 MBq (38 mCi) Re-186. After treatment, the patients were followed up clinically at weekly intervals for the first month and monthly thereafter up to 1 year, until death or pain relapse. Overall, 80 % of the subjects experienced prompt relief of pain, with 31 % having complete, 34 % partial, and 15 % minimal responses. The degree of pain response did not correlate with any pretreatment variable. The duration of pain relief ranged from 3 weeks to 12 months and correlated positively with the degree of response ($P=0.02$). High pretreatment scintigraphic scores and alkaline phosphatase levels correlated with a shorter response ($P=0.02$). Transient grade 1–2 WHO hematologic toxicity was documented, with a decrease in the mean platelet (32 %) and mean leukocyte (18 %) counts at 3 and 4 week, respectively. In the second trial, 25 patients with metastatic breast cancer treated with 1,406 MBq (38 mCi) of Re-186-HEDP were evaluated. The global response rate was 92 % (23/25). The duration of pain relief ranged from 1 month to 12 months (mean of 107 days with a median value of 60 days). Mild myelotoxicity was again seen with platelet and white blood cell counts returning to baseline levels within 6 weeks after administration. The differences in overall response among clinical trials are partially explained by the variability of used pain scales and response criteria.

Multiple consecutive treatments with Re-186 have been tried with a goal of prolonging the duration of response [56]. Most of the authors concur that further pain relief can be expected on repetitive treatments when patients respond to an initial injection. The subsequent doses should be administered at least 8 weeks apart, to ensure that the hematological parameters returns to normal range.

10.2.1.4 Rhenium-188 (Re-188) HEDP

Contrary to Re-186, Re-188 has gained major clinical interest due to its easy availability and lower cost from a Tungstein-188/Re-188 generator which has a long useful shelf-life of several months [13]. Re-188 can be complexed to diphosphate ligands such as HEDP for bone pain therapy, to lipiodol for intra-arterial tumor

embolization [57, 58] or to antibodies for radioimmunotherapy [20, 22, 59]. The chemical and biodistribuition characteristics of Re-188 HEDP are comparable with Re-186 HEDP. Nevertheless, it has the highest beta emission energy (maximum of 2.12 MeV) among the bone-seeking agents, with the shortest mean effective biological half-life in the bone (17 h). Due to its high-energy beta particle, Re-188 has also the highest penetration range in the bone of 10.4 mm. It also decays by gamma-emission of 155 keV, with 15 % abundance, which is sufficient for imaging. The gamma-emission has a relative short-half life of 16.9 h limiting the radiation hazard to bystanders. More than one third of the activity is excreted in the urine within 8 h.

Re-188 is still an investigational radioisotope with most of its clinical experience derived from metastatic bone pain therapeutic trials. Palmedo and colleagues from University of Bonn performed the initial dose escalating study with Re-188 for bone pain palliation. They evaluated 22 patients with metastatic prostate cancer treated with a single injection of escalating doses of Re-188-HEDP [1.3 GBq (35 mCi), 2.6 GBq (70 mCi), 3.3 GBq (90 mCi) and 4.4 GBq (120 mCi)]. Only patients with a WBC count exceeding 3×10^9/L, platelets over 100×10^9/L, a serum creatinine below 1.4 mg/dl and without previous chemotherapy or wide field external-beam radiation were included. Blood counts and biochemical parameters were measured weekly over a total of 8 weeks. Clinical follow-up studies including methods of pain documentation (medication, pain diary) were performed for 6 months after treatment. No hematological toxicity grade 3 or 4 was seen in the first three cohort groups. Thrombocytopenia grades 3 or 4 were only seen in three patients from the 4.4-GBq (120 mCi) group, with baseline platelet count $< 200 \times 10^9$/l. The overall nadir of thrombocytopenia was at 4 weeks. The maximum percentage decrease in platelet count was 17 % in the 1.3 GBq, 40 % in the 2.6 GBq, 60 % in the 3.3 GBq and 86 % in the 4.4 GBq group. Pain palliation was reported in 64 % of patients, with mean response duration of 7.5 weeks. As expected, the response rate increased with higher doses, reaching 75 % in the 4.4 GBq group. The group concluded that the maximum tolerated dose of Re-188 HEDP was 3.3 GBq (90 mCi) for all patients. Also, in patients with baseline platelet counts exceeding 200×10^9/L, the administration of 4.4 GBq (120 mCi) was safe [60].

The efficacy of Re-188 HEDP therapy in bone pain palliation was further evaluated by Liepe and colleagues. A group of 27 patients with hormone refractory prostate carcinoma was treated with doses of 2.7–3.4 GBq (70–90 mCi) of Re-188. They showed a response rate of 76 % with significant improvement of the Karnofsky Performance Scale, reduction of analgesic intake and pain intensity [61]. In another trial from Palmedo and colleagues, they evaluated the pain control and antitumor effects of repetitive administrations of Re-188-HEDP in metastatic prostate cancer patients. Sixty-four patients were randomized to either a single injection of 2.7–3.4 GBq (70–90 mCi) of Re-188 HEDP or two injections (interval, 8 weeks). They demonstrated an additive effect of repetitive injections with an increased response rate of 92 % after 8 weeks, versus a 60 % response rate after the single injection. The duration of pain relief was also prolonged from 2.6 months after a single injection to 5.7 months after repeated injection. Interestingly, they also

observed that a second injection with Re-188 HEDP was sometimes effective in relieving pain, in patients who did not respond to the first injection. In addition, they showed statistically significant reductions in the prostate specific antigen (PSA) levels ($P<0.01$), increase of the time to progression ($P=0.0013$) and median overall survival ($P=0.043$) in patients who received repeated injections and not in the single Wcer patients, there is available evidence of pain relief response to Re-188 HEDP in other tumors such as breast, lung, renal, pharyngeal and bladder cancer [63].

10.2.2 Comparative Studies Among the Radiopharmaceuticals

The overall pain palliation response rate and duration have been similar for all clinically used radionuclides with no clear advantage of a specific agent among the others.

In a comparative trial, 100 patients (60 with prostate cancer and 40 with breast cancer) were treated with 150 MBq (4 mCi) of Sr-89 (50 patients) or with 37 MBq/kg (1 mCi/Kg) of Sm-153 (50 patients) [64]. Complete pain relief was evident in 40 % of women and 40 % of men treated using Sm-153, and in 25 % of women and 33 % of men treated with Sr-89. No analgesic effect occurred in 20 % of patients. In the case of osteoblastic metastases, the complete response measured by means of the VAS score was achieved in 42.9 % of patients treated with Sr-89 and in 48.6 % of patients treated with Sm-153. In patients with mixed metastases the complete response was not achieved in any of the patients treated with Sr-89, and was present only in 20 % of patients after therapy with Sm-153. Although the difference of analgesic effect between both radionuclides was not statistically significant in patients with sole osteoblastic metastasis ($P>0.05$), patients with mixed metastases experienced better efficacy with Sm-153 compared to Sr-89 ($P=0.06$).

The most recent comparative study performed by Liepe and his group evaluated the effect of treatment with Re-188-HEDP, Re-186-HEDP, Sm-153-EDTMP and Sr-89 Chloride on pain symptoms, quality of life, and bone marrow function on 79 patients (31 patients with Re-188, 15 patients each with Re-186 and Sm-153, and 18 patients with Sr-89) [65]. In total, 73 % of patients reported pain relief (77 % after Re-188, 67 % after Re-186, 73 % after Sm-153, and 72 % after Sr-89; $P=0.268$–0.846). Fifteen percent of patients could discontinue their analgesics and were pain-free. Pain showed a decrease from 3.6 +/− 1.7 to a maximum of 2.2 +/− 1.8 at VAS ($P<0.01$). Patients described an improvement on the Karnofsky score from 70 +/− 10 % to 78 +/− 14 %, 12 weeks after treatment ($P=0.15$). There were no significant differences in pain palliation, Karnofsky performance status (KPS) and bone marrow toxicity between the different radionuclides ($P=0.087$–0.449).

The bone seeking agent of choice has yet to be determined. Since all the commonly used radiopharmaceuticals have comparable efficacy, the agent should be selected in a case based fashion taking into account the availability, toxicity and goal of therapy. A close discussion between the clinical oncologist and nuclear medicine physician is necessary to determine the appropriate radiopharmaceutical.

10.3 Indications

Intravenous injections of Sr-89 chloride, Sm-153-lexidronam and Re-186-etidronate are currently approved for the treatment of bone pain due to osteoblastic or mixed osseous metastasis from prostate and breast carcinomas (commonest indications) and other tumors presenting with painful osteoblastic lesions. The lesions must be documented with whole body skeletal scintigraphy performed within at least 8 weeks prior to therapy and the pain should correlate to the areas of abnormal radiotracer accumulation [11, 51, 66].

Most patients treated with radionuclide therapy have failed pharmacological therapy or developed limiting side effects, and are not candidates for external beam radiation for reasons previously mentioned. Although these bone seeking radioisotopes have been habitually reserved for the palliation of diffuse osseous lesions late in the disease process, they should preferably be administered early in the metastatic phase to increase the rate of therapeutic response [28]. The paradigm of using systemic radionuclide therapy as a last resort should be avoided. A common misconception is that the use of radiopharmaceutical will preclude or limit the use of systemic chemotherapy or external beam radiation in the patient with metastatic disease [67, 68]. If treated early, such patients can still be treated with systemic or localized therapies without significant side-effects. Another theoretic advantage of early treatment is that the radionuclide can deliver radiation selectively to subclinical tumors and to metastases that are too small to be imaged and treated by surgical excision or local external beam radiotherapy [69].

The appropriate choice of radiopharmaceutical is based on physical characteristics in relation to the extent of the disease, bone marrow reserve, and its availability in different countries [10, 70].

10.4 Patient Selection and Contraindications

Theoretically, any patient with documented osteoblastic bone metastasis by bone scintigraphy with associated uncontrolled pain is a candidate for radiopharmaceutical therapy for pain palliation. However, in practice, only patients with more extensive metastatic bone disease that could not be controlled by localized external beam radiation are sent for radionuclide therapy.

Preexisting cytopenia constitutes a relative contraindication since bone seeking radiopharmaceuticals can cause further myelotoxicity, aggravating low blood cell counts. Blood transfusion and colony stimulating grow factors (G-CSFs) may be used either prior to therapy or following radionuclide therapy in certain situations to salvage or stabilize patients until bone marrow recovery occurs spontaneously [10, 35, 36, 47]. Most institutions consider the following blood cell count as minimum low values for therapy: Hemoglobin (Hb) equal or greater than 9 mg/dl; Absolute White Blood Cell (WBC) count equal or greater than 3,500/dl and Platelet (PLT) count equal or greater than 100,000/dl. These values must be stable prior to therapy.

Patients may occasionally be treated with lower levels if chronic disseminated intravascular coagulation (DIC) is excluded. Even patients with lower values of WBC and PLT but greater than 2,400/dl and 60,000/dl respectively may be given consideration to receive systemic radionuclide therapy [10, 35].

Bone marrow involvement should not be considered a contraindication per se, unless the blood counts are significantly low. The presence of a "superscan" appearance suggests limited bone marrow reserve, but it does not constitute per se an absolute contraindication for therapy. As long as the blood counts are stable above the expected ranges, these patients can be treated with radiopharmaceuticals. They may be treated with lower dose levels or with fractionated smaller doses.

Pregnancy and breastfeeding are two absolute contraindications for therapy with bone seeking radiopharmaceuticals. Pregnancy test should be obtained for all female patients of reproductive age. They should also be advised against conceiving for at least 6 months after a therapeutic dose. Breastfeeding must be totally discontinued before the radiopharmaceutical is administered [51].

The plasma clearance of these agents is dependent on renal function. Patients with impaired renal function (GFR < 30 ml/min) should not receive the radiopharmaceuticals due to a higher risk of myelotoxicity. Although there is no clinical data on patients undergoing dialysis, the risk of contamination and radiation exposure in the dialysis unit constitutes an absolute contraindication for the therapy. By consensus, patients with moderate renal failure (GFR 30 > and <50 ml/min) should have their dose lowered by 50 %. The radiopharmaceuticals Sm-153-lexidronam and Re-186-etidronate are preferred due to their lower physical half-lives, even though there is currently no significant data regarding their safety and toxicity.

10.5 Administration and Precautions

The use of radiopharmaceutical for metastatic bone pain is becoming more frequent. Thus, it is important to understand the radiation risks and the appropriate precautions to be taken before and after administration. The use of radiopharmaceutical for bone pain palliation is safe for patients, administering personnel and contact relatives as long as the safety measures are followed. The recommendations for the patients should include avoid pregnancy for at least 6–12 months, avoid contaminating shared toilets, double toilet flushing for at least 1 week, bladder catheterization before injection for an appropriate period of time (Sr-89 = 4 days, Re-186 = 2–3 days and Sm-153 = 24 h) if incontinent, and avoid sexual contact for at least 1 week after injection. Once the patients are appropriately educated by the treating physician, the risk of radiation hazard is significantly minimized.

The administering physician must obtain an informed consent and use universal safety apparel during injection and handling of patients. The calculated dose of the radiopharmaceutical is administered on an out-patient basis with an injection over 1–2 min through a peripheral intravenous line which is subsequently flushed with 10–20 ml of saline. Patients should remain in the nuclear medicine department for 4–6 h post injection, to be monitored for rare injection reactions and side effects.

Table 10.5 Check list before therapy with radiopharmaceuticals, contraindications and post therapy recommendations

Pre-treatment clinical and imaging requirements	Positive bone scintigraphy within 8 weeks
	Positive correlation between osteoblastic lesions and painful sites
	Severe pain despite analgesics or analgesic side effects
	Not a candidate for local control with External Beam Radiation (XRT)
	Exclude active disseminated intravascular coagulation (DIC)
	Cervical spine involvement—consider pre-treatment with steroids
	No chemotherapy or large field XRT in the past 4–12 weeks
	Signed informed consent
Contraindications (*Absolute)	*Pregnancy: obtain pregnancy test the day of injection
	Breastfeeding: stop permanently
	*GFR < 30 ml/min or dialysis
	Spinal cord compression: needs XRT first
	*Low bone marrow reserve: low blood counts. ("superscan"—relative)
	*Life expectancy less than 4 weeks
	Incontinence: establish an urinary catheter
Laboratory	Hemoglobin >9.0 mg/dl
	Absolute WBC > 3,500/dl
	Absolute neutrophil >1,500/dl
	PLT > 100,000/dl
	Glomerular filtration rate > 50 ml/min
Safety precautions after treatment	Avoid pregnancy for at least 6–12 months
	Avoid contamination of shared toilets
	Rigorous double toilet flushing for at least 1 week
	Bladder catheterization (Sr-89 = 4 days, Re-186 = 2–3 days and Sm-153 = 24 h) if incontinent
	Avoid sexual contact for at least 1 week after injection

Post-therapy bone scintigraphy, when feasible, may be of value to check tumor extent, radiopharmaceutical distribution and to perform dosimetric calculations.

It is vital to inform the patient and the referring physician what they should expect after the radiopharmaceutical is given. Onset of pain relief may occur within days or weeks and its duration may also vary according to extent or metastatic bone disease. In general, radionuclide therapy is not recommended in patients with a life expectancy of less than 4 weeks, because the onset of pain relief may be delayed for more than a month. Flare response with increase pain has been described to occur in 10–15 % of patients, often within 72 h but, rarely, up to 21 days after injection and lasting 2–5 days. Flare is unusual after the second week, is thought to be related to the release of cytokines and may be helped by the temporary use of analgesics and steroids. The summary of patient selection criteria, contraindications and basic recommendations are listed in the Table 10.5.

10.6 Toxicity, Side-Effects and Follow Up

The toxicity profiles of the radiopharmaceuticals are similar and dictate the appropriate follow up schedule. When the osseous metastasis involves the cervical spine, a small chance of spinal cord compression post therapy exists and prophylactic corticosteroids should be considered. Transient myelosuppression with blood cell count drop, particularly of platelets and white-blood cells, is expected and frequently observed. The nadir of myelosuppression is usually 6–8 weeks for Sr-89 and 4–5 weeks for Sm-153 and Re-186 which is delayed when compared to chemotherapeutic agents [71]. The occurrence of severe bone marrow toxicity is dependent of patient's marrow reserve and previous myelotoxic therapies. In most patients, the blood cell counts returns to baseline levels over a 8–12 weeks period following radionuclide therapy. This may occur in less time if patients were never treated with chemotherapy or wide field radiation. After the radiopharmaceutical infusion is complete, the patients should follow-up with their referring or treating physician for management of flare phenomena, pain medications and other symptoms. It is also recommended close monitor of myelosuppression with weekly CBC between the 3rd and 8th weeks after treatment or until the blood counts return to baseline levels [10, 11, 51].

10.7 Combining Radiopharmaceuticals and Chemotherapy

Combining treatment with chemotherapeutic agents is a well-known method of improving efficacy of any radiation-based therapy. The cytotoxic effect of chemotherapy makes the tumor cells more susceptible to radiation damage. There is growing interest in improve the overall efficacy of the bone seeking agents with chemotherapy as radiosensitizer.

Unfortunately, limited data evaluating the effect of the concomitant use of radiopharmaceuticals with chemotherapy is available. Most, if not all, clinical trials have used Sr-89 as the combining radionuclide agent. Sciuto and his group were the first to utilize low-dose carboplatin (100 mg/m^2 at 7 and 21 days) as a radiosensitizer in 15 patients with osseous metastasis treated with Sr-89 [72]. The study design comprised a control group of 15 patients who received only Sr-89. Pain palliation was assessed 8 weeks post-injection with continued follow-up of 1 year. Improved osseous metastasis pain was observed in 20 of 27 (74 %) patients. The pain response in the patients treated with Sr-89 and carboplatin was superior to that seen in the control group ($P=0.025$), whereas survival was only marginally better in the combined treatment group (8.1 vs. 5.7 months, $P=0.19$). No clinically significant adverse effects or myelosuppression by carboplatin were observed.

Another randomized phase II trial published by Tu and colleagues [73] evaluated 103 patients after 2–3 cycles of induction chemotherapy (ketoconazole and doxorubicin alternating with estramustine and vinblastine) for hormone refractory prostate cancer. The 72 patients stable or responders after induction chemotherapy were

randomly assign to receive doxorubicin with or without strontium-89 (Sr-89) every week for 6 weeks. Overall, 62 of the 103 (60 %, 95 % CI 50–70) patients had a 50 % or greater reduction in serum PSA that was maintained for at least 8 weeks, and 43 (42 %, CI 32–52) had an 80 % or greater reduction. Almost 52 % patients with bone pain at trial enrollment had complete resolution of pain. For the group randomly assigned to receive Sr-89 and doxorubicin, the median survival time was 27.7 months (4.9–37.7 months). For patients who received doxorubicin only, the survival rate was 16.8 months (4.4–34.2 months) (P=0.0014). In this study, Sr-89 given as a consolidative therapy combined with doxorubicin after induction chemotherapy, improved overall survival in patients with stable or responding metastatic prostate cancer.

Questions arose about the possible effectiveness of combining therapy in controlling metastatic prostate cancer with osseous disease. A multicentric trial by Akerley and colleagues [74] evaluated 44 patients with metastatic prostate cancer treated with estramustine, vinblastine and 2.2 MBq/kg (0.59 mCi/Kg) of Sr-89 (repeated every 12 weeks). Response assessment was based on a change in the serum PSA levels, correlated with change in measurable disease and bone scan appearance of osteoblastic metastasis. A greater than or equal to 50 % decline in PSA for at least 6 weeks was observed in 21 patients (48 %, CI: 33–62 %) with a median duration of response of 23 weeks (range, 6–70.8 weeks). The median survival was 13 months with 1- and 2-year survival rates of 55 % and 25 %, respectively. After completion of therapy, a retrospective review showed that only nine patients received subsequent palliative external beam radiation after progression. Although preliminary, it was shown that the addition of Sr-89 to the regimen of estramustine and vinblastine could be delivered safely and in repeated doses, providing effective palliation.

A small preliminary phase I/II study [75] combining 2 Mbq/kg (55 uCi/kg) of Sr-89 and gemcitabine for the treatment of patients with androgen resistant prostate carcinoma evaluated maximum tolerated dose of this regiment and possible efficacy. Eleven of 15 patients received 13 courses at dose Level 2 (gemcitabine 800 mg/m^2) and only one patient developed dose limiting Grade 4 thrombocytopenia. There were no laboratory responses, as measured by prostate specific antigen concentration, although six patients (40 %) had stable disease.

Finally, Amato and his group [76] recently published a phase II clinical trial investigating the additional value of Sr-89 to an alternating weekly regimen of doxorubicin, ketoconazole, paclitaxel and estramustine in 27 patients with metastatic prostate cancer. A greater or equal 50 % reduction in PSA level was maintained for at least 8 weeks in 77.7 % of the patients at 16 weeks and in 66.6 % at 32 weeks. The median progression-free survival was 11.27 months (range, 1.83–29.53), and the median overall survival was 22.67 months (1.83–57.73). Two patients died during the course of the study due to disease progression. Overall, the chemotherapeutic regiment combined with Sr-89 demonstrated a prolonged progression-free and overall survival with acceptable toxicity when compared to historical data.

The use of bone-seeking radiopharmaceuticals in combination with chemotherapy is still not recommended in current clinical practice. Instead, unless in a experimental trial exploring the anti-tumoral effect of combining therapies, hematologic toxic

chemotherapy should be discontinued at least 4 weeks before the administration of Sr-89, Sm-153 or Re-186 and withheld for 6–12 weeks post therapy to avoid concomitant myelosuppresion [10, 77]. Most of the time, patients treated with radiopharmaceuticals can resume chemotherapy after the blood counts recovers to acceptable levels, usually after 12 weeks.

10.8 Combining Radiopharmaceutical and Biphosphonates

The data regarding the use of biphosphonates concomitantly with bone seeking agents is limited and conflicting. The hypothesis is that a competitive interaction of biphosphonates and radiopharmaceuticals at the hydroxyapatite crystal surface at the skeleton could decrease the uptake and clinical effect of both.

To answer this question, the biodistribuition and skeletal uptake of Sm-153 were evaluated in patients with hormone-refractory prostate cancer treated with a combined regiment using zoledronic acid [78]. After analyzing the urinary excretion, toxicity and scintigraphic data, the study showed that zoledronic acid treatment did not influence Sm-153 skeletal uptake and suggested that combined treatment was both feasible and safe.

Further studies were undertaken looking into the efficacy of combining therapy. In one study, Storto and his group [79] evaluated 49 patients with painful osseous metastasis from prostate and breast cancer. Twenty-five patients chronically treated with zoledronic acid, underwent bone pain palliation with 150 MBq (4 mCi) of Sr-89 chloride, given at least 6 months after the biphosphonate therapy begun (group A), 13 patients received Sr-89-chloride alone (group B) and 11 patients were treated over a period of time and continued to receive only zoledronic acid therapy (group C). All three groups had similar characteristics at baseline. Improvement of discomfort and bone pain in group A was significantly greater as compared to group B ($P < 0.01$) and group C ($P < 0.01$). Also, during the monitored period, clinical condition of the patients was significant better in the group A as compared to both groups B and C. These findings suggested that combined therapy of Sr-89-chloride and zoledronic acid in patients with painful bone metastases was more effective in treating pain and improving clinical status than Sr-89-chloride or zoledronic acid used separately.

In the study by Marcus and colleagues, skeletal uptake of Sm-153 EDTMP before and 1–4 days after pamidronate infusion was compared in three patients with breast cancer metastatic to bone [80]. In two of these patients, they followed the Sm-153 EDTMP uptake at approximately 1, 2, 3, and 4 weeks after pamidronate infusion. There was no difference in skeletal uptake of Sm-153 EDTMP before or after pamidronate infusion.

Considering the available data, there is no evidence of biological competition between biphosphonates and bone seeking agents and, therefore, they may be used concomitantly.

10.9 Conclusion

Bone pain palliation using radiopharmaceuticals is effective and safe with consequent decrease in morbidity and improvement in the patient's quality of life. Whenever possible, they should always be considered in the earlier stages of osseous metastasis dissemination rather than as a last resort. Ultimately, the responsibility to disseminate the proven efficacy of this therapy and advocate for the more widespread use of these agents lies with the combined work of the clinical oncologist, radiation therapy and nuclear medicine physician.

Several issues regarding bone seeking radionuclide agents still require further clarification, such as the possible beneficial effect of combining them with chemotherapy or biphosphonates, the true predictive factors of good response, and their safety profile in patients with extensive bone marrow involvement ("superscan" patient). Additional clinical trials are necessary not only to elucidate these questions, but also to evaluate the radiopharmaceutical use beyond palliation, towards improvement in survival. This may be possible with the combinations of various radiopharmaceuticals and radiosensitizers resulting in both tumoricidal as well as palliative effects [5, 6, 81].

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Chapter 11
Bisphosphonates in Bone Metastatic Setting

Grazia Armento, Marco Imperatori, Vladimir Virzì, Giuseppe Tonini, and Daniele Santini

Abstract Bisphosphonates (Bps) are a class of drugs approved for treatment of bone metastases. There are two classes, the Nitrogenous-containing and non-Nitrogenous-containing Bps. They act on osteoclasts, inhibiting malignant osteolysis which causes skeletal-related events. These events are defined as pathological fractures, spinal cord compression, bone pain requiring palliative radiotherapy, orthopaedic surgery (such as vertebroplasty, kyphoplasty, and cementoplasty) and malignant hypercalcemia (HCM). In this chapter we will describe the mechanism of action of Bps and the major preclinical and clinical studies which evaluated the efficacy of these agents for the treatment of bone metastases from solid tumors. We will also describe the clinical data on the adjuvant role of Bps in breast and prostate cancer.

Keywords Bisphosphonates • Bone metastases • Zoledronic acid • Clodronate • Pamidronate • Skeletal related events • Breast cancer • Renal cancer • Prostate cancer • Quality of life • Etidronate • Ibandronate

11.1 Introduction

Bps are a class of drugs approved for treatment of osteoporosis, multiple myeloma and bone metastases from solid tumors, primary hyperparathyroidism, osteogenesis imperfecta and Paget disease of the bone [1–4]. They are called Bps because they contain two phosphonate (PO3) groups and are similar in structure to pyrophosphate (PPi). Like their natural analogue PPi, Bps have a high affinity for bone mineral because they bind to hydroxyapatite crystals blocking its

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breakdown. In fact Bps accumulate in the mineralized bone matrix, released during bone resorption and they are ingested by osteoclasts. There are two classes of Bps: the Nitrogenous-containing (NBPs) and non-Nitrogenous-containing Bps (nNBPs). The two types of Bps act differently on osteoclasts. The non-nitrogenous Bps (such as clodronate) are metabolised in the cell to compounds that replace the terminal pyrophosphate segment of ATP, forming a nonfunctional molecule which competes with adenosine triphosphate (ATP) in the cellular energy metabolism (it inhibits mitochondrial ATP/adenosine diphosphate translocase causing loss of the mitochondrial membrane potential) leading to the osteoclast apoptosis [5]. NBPs (such as zoledronic acid, pamidronate, and ibandronate) act on bone metabolism by binding and blocking the enzyme farnesyl diphosphate synthase in the HMG-CoA reductase pathway (also known as the mevalonate pathway). Inhibition of the HMG CoA-reductase pathway leads to the prevention of the formation of two metabolites (farnesyl and geranylgeraniol) that are essential for connecting proteins of the skeleton of the cellular membrane (this process is called protein prenylation). This can affect osteoclastogenesis, cell survival, and cytoskeletal dynamics. In particular, the cytoskeleton is important for maintaining the "ruffled border" that is required for the link between a resorbing osteoclast and bone matrix surface. It has also been supposed that NBPs lead to disruption to the lipid modification of Ras, Rho, Rac proteins. N-BPs also induce production of an intracellular ATP analogue known as Apppi (triphosphoric acid 1-adenosin-5′-yl ester 3-[3-methylbut-3-enyl] ester), which may directly induce apoptosis similar to the metabolite of clodronate [6]. Bps are poorly absorbed by the gut and are therefore mainly administered intravenously. They are not metabolised and those not accumulated in the skeleton are rapidly cleared from the circulation by renal excretion [7, 8].

11.2 Efficacy of Bisphosphonates for the Treatment of Bone Metastases

Bone metastasis occurs in 75 % of patients with breast and prostate cancer and in approximately 40 % of patients affected by lung cancer, bladder cancer and malignant melanoma [9]. Bone metastasis confers a high risk of developing skeletal-related events (SREs) defined as: pathological fractures, spinal cord compression, bone pain requiring palliative radiotherapy, and orthopaedic surgery (such as vertebroplasty, kyphoplasty, and cementoplasty) and malignant HCM. In the absence of bone-specific therapies, SREs occur in 46–68 % of patients with bone metastases from solid tumors [10, 11]. Bps are currently used for treating the malignant osteolysis induced bone turnover which causes SREs. This also brings about a reduction of involved bone pain and the need for analgesics or palliative radiotherapy [12, 13]. However, relatively a few Bps have demonstrated efficacy for broad application in the oncology setting, and most are approved only for use in breast cancer or prostate cancer metastatic to bone [14–19].

11.2.1 Efficacy in Metastatic Breast Cancer

In 1995 i.v. pamidronate was approved for the treatment of patients with metastatic breast cancer based on data from a trial that demonstrated a decreased risk of skeletal complications [20]. A metanalysis demonstrated that Bps compared with placebo reduced non vertebral fracture risk (OR 0.80; 95 % CI: 0.64–0.99), fracture risk (OR 0.75; 95 % CI 0.61–0.63), need for radiotherapy (OR 0.65; 95 % CI: 0.54–0.79) and risk for HCM (OR 0.43; 95 % CI 0.29–0.63) [21]. In nine studies involving 2,189 women with advanced breast cancer and bone metastasis the use of Bps (clodronate, intravenous and oral ibandronate, pamidronate and zoledronic acid) reduced the risk of bone complications by 21 % (RR 0.79 %; 95 % CI 0.74–0.86) [22].

Moreover in the studies with oral clodronate, pamidronate, iv ibandronate and zoledronate versus placebo there was a significant delay in the appearance of bone events [22]. In the comparative study between pamidronate and zoledronate there were no differences in the time until the first skeletal event, but in the subgroup of patients with osteolytic metastasis treated with hormonal therapy, zoledronate extended the time to the development of bone complications (136 days versus 45 days) ($p<0.01$) [23].

Several trials demonstrated the analgesic effect of Bps in patients with bone metastases. In two large trials with breast cancer patients pamidronate was shown to improve pain scores and reduce the need for palliative therapy as compared with placebo ($p<0.001$) [24–26]. In trials comparing the efficacy of zoledronic acid and pamidronate involving patients with breast cancer and bone metastasis, zoledronic acid significantly reduced the need for radiotherapy ($p=0.037$) and improved pain [23].

Overall global health status was shown to be improved in a trial comparing the use of zoledronic acid in community versus hospital setting, confirming quality of life benefits with the administration of Bps in advanced breast cancer patients with bone metastases [27]. The maintenance of mobility, self-sufficiency and pain control are important parameters of quality of life and are associated with reduction of skeletal complications.

The choice of bp is based on evidence derived from clinical trials as well as patient's condition and preferences. Trials comparing pamidronate (90 mg) with clodronate demonstrated that intravenous pamidronate achieves an increased symptomatic relief, better clinical response and improved pain relief [28]. The comparison between zoledronic acid and pamidronate shows an advantage of the prior in patients with osteolytic lesions, delaying the time to the first skeletal complication ($p=0.013$). Additionally the same was valid for patients treated with hormonal therapy ($p=0.013$) [22]. The efficacy of iv and oral ibandronate was evaluated in three placebo-controlled trials. The MF4265 trial randomized 466 patients to receive either iv ibandronate or placebo showing a significant benefit in the ibandronate group in terms of skeletal morbidity period rate ($p=0.004$), the number of new SREs and the time to first SRE [29]. Other two smaller phase III placebo-controlled trials disclosed the efficacy of oral ibandronate (50 mg/day) [30].

Table 11.1 Efficacy data for single bisphospfonate (Bp). RR = relative Risk; RRR relative Risk Reduction to develop an SRE during Bp therapy in women with bone metastasis from breast cancer compared with placebo

Bp	Trial	SREs RR (CI 95 %)	SREs RRR (%)
Zoledronic acid	Kohono et al. [32]	0.59(0.42–0.82)	41
Pamidronate	Hortobagyi et al. [33] Theriault et al. [25]	0.77 (0.69–0.87)	33
Ibandronato ev	Body et al. [34]	0.80 (0.67–0.96)	20
Ibandronato os	Body et al. [30]	0.86 (0.73–0.02)	14
Clodronate	Kristensen [35]	0.69 (040–1.20)	31
Clodronate	Paterson et al. [111]	0.83 (0.68–1.02)	17
Clodronate	Tubiana—Hullin et al. [36]	0.92 (0.92–1.19)	8
	Metanalysis	0. 85 (0.77–0.94)	15

Adapted from Bertoldo [31]

In a Cochrane metanalysis 34 clinical trials were evaluated. In seven of them it was shown that the use of Bps compared with placebo reduced the SRE risk by 15 % (RR 0.85 %; IC 95 % 0.77–0.94 $p < 0.001$) [22] (see Table 11.1).

There is no evidence indicating an improved effect on skeletal complications with the switch from one aminobisphsphonate to another [31].

11.2.2 Efficacy in Metastatic Prostate Cancer

Prostate cancer has a high propensity for bone which is affected in 80–90 % of men with castration resistant metastatic prostate cancer.

Bone metastases from prostate cancer are commonly osteoblastic and are a major cause of morbidity [37].

Ten trials were analyzed in a review to assess the analgesic effect of bps [38]. One trial used etidronate [39], seven clodronate [40–45] one pamidronate [46] and one zoledronic acid [47]. The pain response rate was approximately 28 % for the Bps group versus approximately 20 % for the control group; the skeletal events rate was approximately 38 % for the Bp group and 43 % for the control group. Therefore in addition to preventing SREs Bps should be considered as a therapeutic modality for managing metastatic bone pain. Three randomized trials assessed the efficacy of Bps in the metastatic castration—resistant prostate cancer (CRPC). The zometa 039 trial randomized 643 patients with CRPC to receive zoledronic acid or placebo to evaluate the rate of SREs. At 15 months, 33.2 % patients of the zoledronic acid group experienced SREs as compared with 44.2 % of the control group ($p = 0.009$) [48]. Median survival was 546 days for the zoledronic acid group versus 464 days for the placebo group ($p = 0.091$). Zoledronate was approved as therapy for bone-metastatic prostate cancer and disease progression after first-line hormonal therapy [49].

The NCIC CTG PR.6 trial assessed the analgesic benefit of clodronate in patients with CRPC and symptomatic bone metastases. 209 patients were enrolled to receive mitoxantrone and intravenous clodronate or placebo. Palliative response was accomplished in 46 % patients of the pamidronate group and in 39 % of the placebo group ($p = 0.54$). Subanalysis showed that patients with severe pain benefited the most [50]. The CPG032 and INT 05 trials evaluated the efficacy of i.v pamidronate versus placebo for pain relief and in reduction of SREs. Pain scores and SRE rates were similar between the two groups [47]. The results of these three studies demonstrated that zoledronic acid, but not pamidronate and clodronate, decreases the risk of skeletal complications in CRPC with bone metastasis patients.

The MRC PR05 trial evaluated Bps in the castration-sensitive metastatic prostate cancer setting. In this trial 311 patients with prostate cancer and bone metastasis were enrolled. All patients were managed with Androgen Deprivation Therapy (ADT). They were randomized to receive oral clodronate or placebo during hormonal therapy. No differences were found in bone progression-free survival (primary study endpoint) and overall survival (secondary endpoint). After long-term follow-up a benefit in overall survival for the clodronate group was evident (8-year OS of 22 % in clodronate group versus 14 % of placebo group; HR 0.77; 95 % CI 0.60–0.98, $p = 0.032$) [51].

An ongoing trial (CALBG/CTSU 90202) is studying the role of zoledronate in metastatic prostate cancer patients receiving first-line hormone therapy (castration sensitive setting). Men are randomized to receive zoledronic acid (4 mg every 28 days) or placebo; the primary study endpoint is to compare the time to first skeletal-related event; the secondary endpoint is overall survival [52] (see Table 11.2).

11.2.3 Efficacy in Metastatic Renal Cancer

Current knowledge shows that the employment of zoledronic acid reduces the risk of SREs and improves quality of life of patients with bone metastases. Zoledronic acid has been shown to reduce bone pain in patients with renal cancer and bone disease; notably 50 % of patients receiving zoledronate reported stable or reduced pain scores for up to 24 months.

In a subanalysis of the phase III trial evaluating zoledronic acid in bone metastatic patients, it has been shown that in the renal cancer patients ($n = 46$) zoledronate achieved a reduction of SREs and prolonged the time to first SRE as compared to placebo [53, 54].

Zoledronic acid was also studied in a retrospective study with 23 patients receiving radiotherapy ± zoledronate. The use of the bp reduced the percentage of patients developing an SRE ($p = 0.003$) and prolonged the time to first SRE ($p = 0.046$) [55] (see Table 11.3).

Table 11.2 Studies of Bp use in bone metastic prostate cancer

Trial	n	Arms	Results
Zometa 039	643	4 mg zoledronic acid vs. placebo, every 3 weeks for 15 months	Significant decrease in SREs(33.2 % vs. 44.2 %); established zoledronic acid as standard of care in this setting
INT05/CGP032	350	90 mg pamidronate vs. placebo, every 3 weeks for 27 weeks	No significant difference in pain or SREs
NCIC CTG PR.6	209	Mitoxantrone and prednisone ± 1,500 mg clodronate, every 3 weeks until progression	No significant difference in palliative response, duration of response, progression-free survival, overall survival, overall quality of life
MRC PR05	311	2,080 mg daily oral clodronate vs. placebo, for 3 years maximum	Trend toward improved bone progression-free survival (P-0.066); significantly improved 8-year overall survival (22 % vs. 14 %, HR = 0.077; P = 0.032)
CALBG/CTSU 90202	680	4 mg zoledronic acid vs. placebo, every 4 weeks until progression to CRPC or first SRE, then cross-over to open label	Ongoing

Adapted from Lee et al. [49]

Table 11.3 Zoledronate Vs placebo in bone metastasis renal cell carcinoma

Reduced proportion of patients with ≥1 SRE	41 % versus 79 %; $p = 0.011$
Prolonged median time to first SRE	424 versus 72 days; $p = 0.007$
Reduced risk of developing an SRE	58 % (HR = 0.418; $p = 0.010$)
Reduced bone pain score	20.0 versus 37.3 units

Adapted from "Aapro and Saad [110]

11.2.4 Efficacy in Metastatic Lung Cancer

The efficacy of zoledronic acid was evaluated in a study involving non-breast and non-prostate cancer patients with metastatic bone disease [56]. The subgroup of patients (n = 280) with NSCLC receiving zoledronic acid achieved a non significant reduction of SREs as compared with placebo (45 % Vs 42 %, p = 0.55). The risk of SREs was reduced by 30 % (HR 0.706, p = 0.036); no statistical differences were found in pain scores and quality of life [56].

Therefore Bps should be considered for the treatment of metastatic bone disease from lung cancer to reduce the probability of developing skeletal complications and to control bone pain. Patients with poor prognosis may be excluded from receiving Bps since benefits are questionable.

11.3 When to Start, How Long to Continue, When to Stop

Bone pain is the earliest and commonest symptom of bone metastases and it can have debilitating effects on a patient's quality of life. Consequently treatment after pain develops may not be the optimal strategy. Identification of patients at risk for bone metastases, early diagnosis, and early treatment for bone metastases may be beneficial. The appropriate time to start bp administration is once a bone metastasis has been identified, and not after symptoms develop [57]. But to date there is no clear evidence about the use of long term treatment with Bps and there is limited data about their administration beyond 2 years.

A trial showed that intravenous ibandronate administered for up to 2 years in patients with bone metastases from breast cancer significantly reduced the mean number of new SREs ($p=0.032$) and significantly increased the time to the first SRE ($p=0.018$) as compared with placebo [58]. Other studies showed that intravenous pamidronate administered for up to 2 years significantly reduced the incidence and delayed the onset of SREs as compared with placebo [3]. It should be noted that these studies did not separate the possible benefits of Bps during the first year from those possibly gained during the second year of treatment.

However the Lotuz Study showed that SREs did not increase in patients with solid tumors or multiple myeloma receiving zoledronic acid beyond 2 years of treatment [59]. Another multicenter retrospective review evaluated 92 patients who received pamidronate or zoledronic acid for more than 24 months. This trial showed that patients had a reduced frequency of SREs without significant toxicity [60].

Other exploratory analyses of the zoledronic acid database from the phase III efficacy trial of prostate cancer demonstrated that the risk of SREs in patients receiving zoledronic acid during months 16-24 was significantly reduced as compared with the placebo group ($p=0.022$). Bp treatment also continues to provide clinical benefits after a patient experiences an SRE ($p=0.011$). Additionally among patients who had experienced an SRE before study entry, zoledronic acid reduced the proportion of patients who experienced an on-study SRE and provided a significant reduction in mean skeletal morbidity rate (SMR) as compared to placebo [61, 62] . Moreover, in patients who experienced an SRE before study entry, zoledronic acid significantly reduced the proportion of patients who experienced an on-study SRE as compared with pamidronate ($p=0.039$). Moreover the SMR was reduced by 24 % relative to pamidronate ($p=0.038$).

Analyses of the subset of patients with bone metastases from several solid tumors demonstrated that zoledronic acid significantly reduced the risk of developing an SRE by an additional 41 % as compared with pamidronate ($p=0.026$) during the second year of treatment [63] . A meta-analysis that included 12 randomized trials of bisphosphonate therapy for patients with bone metastases from various malignancies showed that the risks of nonvertebral fractures, vertebral fractures, radiotherapy, and episodes of HCM were reduced to 65 %, 69 %, 67 %, and 54 %, respectively, in comparison to rates of placebo-treated controls. A temporal analysis found no significant reduction in skeletal morbidity until after 6 months of treatment. After that both episodes of HCM and the need for radiotherapy were

Table 11.4 Antitumor effects of bisphosphonates

Antitumor effects of bisphosphonates	Mechanisms
1. Activation of apoptosis program	Activation of caspases
2. Inhibition of angiogensis	Modulation of proangiogenic factors
	Inhibition of capillary-like tubules
	Reduction of circulating VEGF levels
3. Macrophages phenotype polarization	Reduction of pro-M2 citokines
4. Inhibition of bone matrix degradation and cell adhesion	Inhibition of MMP
	Inhibition of cell adhesion to ECM

significantly reduced. After 12 months of treatment, significant reduction in vertebral fractures was noted. A progressive reduction in the need for orthopaedic surgery became significant at 24 months [64].

So bp treatment is indicated for at least 2 years and continuation beyond 2 years should be considered by balancing and evaluating the cost, potential benefit and involved toxicity.

11.4 Antitumor Effects of Bisphosphonates (Preclinical Data)

Preclinical studies demonstrated that bps exhibit antitumor activity in several tumor cell lines. In fact in vitro studies showed that they cause dose and time-dependent inhibition of proliferation and induce apoptosis of myeloma, breast cancer, prostate cancer, pancreatic cancer, lung cancer, and osteosarcoma cell lines in vitro [65–70]. In vitro studies have also shown that N-BPs combined with a variety of standard anticancer agents have an additive or synergistic antitumor effect against several tumor cell lines [71–76]. Moreover zoledronic acid and ibandronate were shown to inhibit progression of established bone metastases and development of new bone metastases in two models of breast cancer [21, 30].

The mechanisms responsible for those antitumor effects are not completely understood; bps appear to make the skeleton a less favorable site for tumor cell growth through the inhibition of osteoclast-mediated bone resorption and osteoclastogenesis because they reduce the release of several growth factors and directly inhibit tumor cell growth, survival and the ability of tumor cells to colonize bone.

In fact bps act as antitumor agents through different mechanisms (see Table 11.4).

11.4.1 Activation of Apotosis

Both N-BPs and non-N-BPs induce apoptosis of osteoclasts and tumor cells through the activation of caspases [77, 78]. Bps are metabolized in ATP analogues which can disrupt mitochondrial ATP/ADP translocase leading to release of cytochrome c from mitochondria and subsequent caspase-3 activation [79].

11.4.2 Antiangiogenic Mechanism

In vitro and in vivo studies showed that systemic administration of zoledronic acid in mice resulted in potent inhibition of angiogenesis [80, 81]. Moreover it modulates integrin expression (such as αVβ3) that are involved in angiogenesis [82] and are required for tumor cell adhesion to the bone. Several clinical studies showed that zoledronic acid also modulates serum levels of proangiogenic growth factors [83–85].

11.4.3 Macrophages Phenotype Polarization

Macrophages are the major component of inflammatory infiltrate of the tumor stroma. The exposure to the tumor cells-derived molecules such as IL-4, IL-13, TGFβ-1 and PGE2 (Prostaglandin E2) lead to development of "M2 polarized" macrophages [86, 87]. M2 macrophages secrete proangiogenic factors, mainly help repair sites of injury stimulating tissue remodeling and finally support the growth, migration and metastatic potential of tumor cells [88]. M1 macrophages guard against infection and defend against tumor cells. It has been shown that zoledronic acid reverses the polarity of peritoneal and tumour-associated macrophages from M2 to M1 [89, 90].

11.4.4 Inhibition of Bone Matrix Degradation and Cell Adhesion

Bps have also been shown to inhibit adhesion of tumor cells to extracellular matrix (ECM) proteins and to inhibit the process of tumor cell invasion and migration. In vitro studies showed that zoledronic acid and ibandronate could cause a dose-dependent inhibition of tumor cell invasion and motility through the Matrigel at extremely low concentrations, and this activity was enhanced by standard chemotherapy [91, 92]. Moreover matrix metalloproteinase (MMP) activity was inhibited by bp administration [93–96]. In vivo studies using murine models have reported inhibition of invasion and migration of breast cancer cells by zoledronic acid. Moreover, histological examination showed a significant decrease in bone, lung and liver metastases in mice that were repeatedly treated [97].

11.5 Prevention of Metastasis: The Role of Adjuvant Bisphosphonates

There is clear evidence to suggest that both tumor cells and host tissue play important roles for a "successful" metastatic process. A specific subpopulation of cells with tumor-initiating and migratory capacity can selectively migrate toward sites that are able to promote survival, and/or proliferation through a modification of

microenvironment. Bone plays a pivotal role in this process, acting not only as a preferential site for cancer cells' homing and proliferation, due to a complex interplay between different cellular phenotypes such as osteoblasts and osteoclasts, but also as a source of bone marrow precursors that are able to facilitate the metastatic process of extra-skeletal disease. In addition, bone microenvironment has the unique capacity to retain cancer stem cells in a quiescent status, acting as a reservoir that is able to cause a metastatic spread many years after the resection of the primary tumor.

Moreover, many chemotherapies and endocrine therapies support bone turn over and release of growth factors, increasing cancer stem cells growth in the bone microenvironment.

Targeting the bone metastatic process means preventing the cascade of the pathogenic process from the 'bone preneoplastic niche' to the 'visceral preneoplastic niches' [98].

11.5.1 Breast Cancer

Bps have a crucial role for protecting bone health in women receiving adjuvant therapy for breast cancer; indeed, most therapies, which have led to an increase in disease free survival, decrease estrogen levels that is associated with elevated rates of osteolysis because of the integral role of estrogens in maintaining skeletal homeostasis. Some trials suggest that women with breast cancer and elevated rates of osteolysis are at higher risk of bone metastases [99].

Bps inhibit osteoclast-mediated bone resorption, can delay the spread of skeletal metastases and may also inhibit tumour growth outside the skeleton by inducing apoptosis and inhibiting proliferation, adhesion, invasion, and angiogenesis of tumour cells [100].

Several clinical trials assessed the ability of adjuvant Bps in reducing disease recurrence in women with early- stage breast cancer.

In three large clinical trials planned to improve bone health in patients with early breast cancer, zoledronic acid was been shown to play a central role in improving clinical outcomes.

Azure trial assessed the anticancer effect of zoledronic acid plus adjuvant therapy (chemotherapy or endocrine therapy) in early stage breast cancer patients ($n=3,360$). Women received standard therapy alone or with zoledronic acid. The primary endpoint (DFS) was not improved by the use of zoledronic acid in the adjuvant setting, but a subset of patients receiving neoadjuvant therapy plus zoledronic acid ($n=205$) had a reduction of mean residual invasive tumor size by approximately 43.4 % as compared with chemotherapy alone ($p=0.006$) [101].

Moreover a predefined subanalysis evaluated the anticancer effect of zoledronic acid in at least 5 years post menopausal patients showing an improved DFS ($p<0.05$) [102]; this data suggest an improved anticancer effectiveness in a low-estrogen setting.

Table 11.5 Zoledronate in patients undergoing adjuvant therapy for I-III stage breast cancer

	ABCSG-12		AZURE		ZO-FAST
	Total patients	Patients > 40 years old	Total patients	>5 years postmenopausal status	Total patients
N	1,803	1,390	3,360	1,101	1,065
DFS benefit	P = 0.021	P = 0.013		P = 0.05	P = 0.0375
OS benefit	P = 0.042	P = 0.018	P = 0.85	P = 0.017	No

Adapted from Gnant and Hadji [100]

In ABCSG-12 trial premenopausal women with endocrine-responsive breast cancer were randomized to receive tamoxifen or anastrozole plus gosereline with or without zoledronic acid. After a median follow-up of 62 months (more than 2 years after treatment ended), zoledronic acid reduced the risk of disease free-survival events by 32 % (p = 0.009) [103].

Z-FAST, **ZO-FAST**, and **E-ZO-FAST** partner trials are been designed to evaluate the activity of zoledronic acid for preventing aromatase inhibitor-associated bone loss in postmenopausal women receiving adjuvant letrozole therapy [104–106].

These three studies were not planned to estimate the anticancer effect of zoledronic acid: indeed DFS and disease recurrence were only secondary endpoints. The biggest (ZO-Fast trials that enrolled 1,065 early breast cancer patients) demonstrated a reduction of DFS risk events (34 %) comparing upfront with postponed zoledronic acid (p = 0.0375) [107].

The two smaller trials (Z-Fast and E-ZO-Fast) did not demonstrate a significant difference between upfront and postponed zoledronic acid (probably it was due to a lower event rates that made impossible to analyze DFS) (Table 11.5).

11.5.2 Prostate Cancer

Androgen deprivation therapy is an element for intermediate or high risk early stage prostate cancer radio-treated or recurrent disease after surgery or radiation. The purpose of Androgen deprivation therapy (ADT) is the achievement of hypogonadism defined as serum testosterone level of less than 20 ng/mL. The hypogonadal condition influences osteoclast activity producing a decrease of bone mineral density with a consequent rise for the risk of fracture. Many Bps (such as alendronate, pamidronate, neridronate and zoledronic acid) have been shown to improve bone health in men receiving ADT.

Two studies investigated the efficacy of Bps to prevent bone metastasis in men with non metastatic prostate cancer.

ZOMETA 704 trial evaluated the efficacy of zoledronic acid in averting bone metastasis in patients with non-metastatic castration resistant prostate cancer with a

biochemical recurrence. Patients were randomized in two arms: the first arm to receive zoledronic acid and the second to receive placebo. No differences were displayed between the two groups in terms of time to first bone metastasis [108].

MRC PR04 was planned to evaluate the efficacy of clodronate to prevent symptomatic bone metastasis in high risk prostate cancer patients. The trial enrolled 508 patients randomized to receive oral clodronate or placebo for 5 years. After a 10 years follow up there were no statistical differences between the two groups concerning the development of first bone metastasis and overall survival. In contrast with these data, clodronate significantly improved overall survival in men with castration- sensitive metastatic disease [109].

ZEUS, **RADAR** and **STAMPEDE** are on ongoing trials that evaluate the effect of zoledronic acid on prevention of metastasis in patients with high risk prostate cancer.

The first one randomly assigned patients to receive standard therapy with or without zoledronic acid putting as primary endpoint the time to first bone metastasis after 48 months of treatment. Secondary endpoints are overall survival, symptomatic disease progression, PSA doubling time and biochemical markers of bone turnover.

The second one is designed to demonstrate that 18 months of bp therapy will prevent bone loss caused by androgen deprivation therapy and further reduce relapse risk by impeding the development of bony metastases.

The last one is a multi-stage multi-arm randomized controlled trial planned to look at the efficacy of new treatments such as zoledronic acid used in combination with hormone treatment in patients with prostate cancer. Such combinations may increase the time during which cancer is not growing, ultimately resulting in increased survival [53].

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Chapter 12
New Targeted Therapies for Bone Metastases

Allan Lipton, Luis Costa, Paul Sieber, William C. Dougall, and Ada Braun

Abstract A number of targeted agents under investigation or in development have shown promise in the treatment or prevention of bone metastases. Among them is denosumab (XGEVA, Amgen Inc.), a fully human monoclonal antibody targeting the RANK ligand (RANKL) pathway that was approved on 18 November 2010 in the United States (Amgen XGEVA [denosumab] prescribing information, 2012). Denosumab has been proven superior to zoledronic acid in preserving skeletal function and integrity by preventing skeletal complications among patients with bone metastases from solid tumors. Denosumab has demonstrated prolongation of bone metastasis-free survival in men with castration-resistant prostate cancer and is being investigated for this outcome in women with early-stage breast cancer. Another study is prospectively evaluating a potential prolongation of overall survival with denosumab in patients with metastatic lung cancer. Also currently in development are numerous targeted agents that impact the function of the various growth factors released from the bone matrix that stimulate tumor growth, bone destruction, and lead to bone metastases.

Keywords Bone metastases • Osteoclast • Osteoblast • RANK

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12.1 Introduction

12.1.1 Bone Remodeling and the RANK Ligand Pathway

Interaction between RANK ligand (RANKL) and the RANK receptor is key in regulating osteoclast-mediated bone resorption [2]. RANKL is a TNF ligand superfamily member that specifically binds to its cognate receptor, RANK, and this interaction has been shown to be essential for the formation, activation and function of osteoclasts. The critical role of this precise interaction between RANKL, RANK, and osteoprotegerin (OPG), a decoy receptor for RANK, in normal bone remodeling led to the hypothesis that dysregulation of this pathway may contribute to the development of bone metastases [3].

12.1.2 The Pathogenesis of Osteoclastic and Osteoblastic Bone Metastases

In bone metastases, tumor cells interact with the bone matrix to induce osteoclastic activity, which is clearly linked to the bone destruction that occurs in bone metastases. Since pathologically-induced osteoclastic bone resorption can release factors within the bone microenvironment which contribute to skeletal tumor establishment and progression as a consequence of bone matrix turnover, the osteoclasts are a target for the treatment or prevention of bone metastases. Tumor-derived factors that cause activation of osteoclasts vary by tumor type and may include parathyroid-hormone-related peptide (PTH-rP), interleukin-6 (IL-6), tumor necrosis factor (TNF), and macrophage colony-stimulating factor (M-CSF). These factors increase expression of RANKL, which acts on osteoclast precursors to induce osteoclast formation, function, and survival, thereby increasing bone resorption.

Bone resorption in turn results in the release of growth factors from the bone matrix, such as transforming growth factor-β (TGFβ), insulin-like growth factors (IGFs), fibroblast growth factors (FGFs), platelet-derived growth factor (PDGF), and bone morphogenetic proteins (BMPs), which stimulate tumor growth through binding to receptors on the surface of the tumor cells. This reciprocal relationship between tumor cells and osteoclasts results in the so-called "vicious cycle" of tumor growth and cancer-induced bone destruction [4].

RANKL is therefore a key mediator in bone metastases. Production of RANKL by cells of the osteoblast lineage and/or bone stromal cells is stimulated by PTHrP secreted by tumor cells [4]. OPG production by osteoblasts can also be down-regulated within the tumor-bone microenvironment by factors such as PTHrP, thus shifting the balance further towards greater RANKL availability, which stimulates osteoclastogenesis [5]. Other factors produced and secreted by tumor cells (IL-6, prostaglandin E_2, TNF, and M-CSF) also increase the expression of RANKL [4]. Regardless of its source, increased expression of RANKL in the tumor environment

leads to increased production, activation, and survival of osteoclasts, and resulting osteolytic lesions [6].

In osteoblastic metastases, humoral factors such as PTHrP and IL-6 are also released and stimulate osteoclastic recruitment and differentiation [7]. Invading cancer cells such as prostate or renal cell carcinoma cells produce soluble paracrine factors (i.e., TGFβ, IGF, and BMPs) that cause excessive osteoblast activation. Production of endothelin-1 (ET-1) by tumor cells appears to play a central role in stimulating osteoblast activity that results in abnormal bone formation [8]. Osteoblastic activation further leads to the release of unidentified osteoblastic growth factors that stimulate tumor cell growth, contributing to a perpetual cycle of cancer-induced bone destruction, tumor cell expansion, and abnormal bone formation.

The dual role of both osteoclastic and osteoblastic activity and the multitude of signaling factors involved in the formation of bone metastases provide a number of potential targets for the prevention and treatment of metastatic bone disease in various malignancies.

12.2 RANK Ligand (RANKL)

Denosumab is a fully human monoclonal antibody that binds to and inhibits RANKL from binding RANK, thereby inhibiting osteoclast formation, function, and survival. RANKL regulates osteoclast differentiation and activation [9]. The role of RANKL in the formation of bone metastases has been characterized in a number of preclinical studies. In bone metastasis models representing established bone metastases caused by diverse tumor types (e.g. breast cancer, prostate cancer, lung cancer, colon cancer) RANKL inhibition effectively blocked tumor-induced bone lesions. Furthermore, the ability of early administration of RANKL inhibitors to block *de novo* bone metastases has provided evidence that RANKL (and osteoclast activity) may contribute to establishment of bone metastases and early metastatic outgrowth in skeleton. An in vivo study in mice bearing prostate cancer tumors showed that treatment with the RANKL antagonist OPG decreased tumor burden and bone lesion formation [10]. Additional evidence for the role of RANKL in bone metastases came from another study in a mouse model of breast cancer that showed bone metastases could be prevented, which was associated with increased survival [11].

RANK expression is not limited to osteoclasts and has also been observed in some tumor cells; RANKL has been shown to stimulate the metastatic activity of RANK-expressing tumor cells [3]. For instance, RANK expression increases tumor cell migration and pulmonary metastases in a breast cancer model [12]. An in vitro study of human prostate cancer cell lines confirmed that RANKL activates both osteoclasts and RANK-positive prostate cancer cells; this study also provided critical evidence that blocking the interaction of RANKL and RANK hindered the development of prostate cancer bone metastases [13]. These preclinical studies indicate that RANKL inhibition can reduce the establishment and progression of bone metastases potentially via two distinct mechanisms, firstly, in the bone via the

well-established ability of RANKL inhibition to block osteoclasts and secondly, via direct effects on RANK-expressing tumor cells.

After phase 1 and 2 trials in humans, denosumab demonstrated superior efficacy in phase 3 trials compared with zoledronic acid across multiple solid tumor types in delaying time to and reducing the risk of a first skeletal-related event once cancer had metastasized to bone, and is currently approved for the prevention of skeletal-related events in patients with bone metastases from solid tumors [1].

Three large, randomized, double-blind, double-dummy phase 3 trials evaluated the efficacy and safety of denosumab compared with zoledronic acid in patients with advanced breast cancer (N = 2,046), castration-resistant prostate cancer (N = 1,901), and other solid tumors or multiple myeloma (N = 1,776) [14–16]. Patient level data from these three identically designed trials were pooled (N = 5,723) and analyzed. Denosumab was superior to zoledronic acid in delaying time to first on-study skeletal-related event, with a hazard ratio (95 % CI; *P value*) of 0.83 (0.76–0.90; $P < 0.001$) for both non-inferiority and superiority tests. The median delay in time to first skeletal-related event was 8.21 months for patients treated with denosumab (27.66 months) compared with patients treated with zoledronic acid (19.45 months). A similar significant delay in time to first and subsequent skeletal-related events was observed in patients with multiple events, with a rate ratio (95 % CI; *P value*) of 0.82 (0.75–0.89; $P < 0.001$). The total number of skeletal-related events was fewer in patients treated with denosumab (1,360 events) vs zoledronic acid (1,628 events). Adverse event and serious adverse event rates were similar overall between treatment groups, with differences observed (denosumab vs zoledronic acid) for renal adverse events (9.2 % vs 11.8 %), acute-phase reactions (8.7 % vs 20.2 %), and hypocalcemia (9.6 % vs 5.0 %) [17].

Furthermore, a noteworthy phase 3, double-blinded, double-dummy, placebo-controlled trial evaluated denosumab for the prevention of bone metastases in 1,432 men with nonmetastatic castration-resistant prostate cancer at high risk of bone metastases. This study found that denosumab significantly ($p = 0.028$) increased bone metastasis-free survival (BMFS) and significantly ($p = 0.032$) delayed the median time to first bone metastasis [18]. Greater efficacy was noted in men at highest risk of developing bone metastases, with shorter baseline PSA doubling time (PSADT), with an increase in BMFS by a median of 7.2 months ($p = 0.006$) for men with PSADT $\leq$ 6 months [19]. Overall survival was the same between treatment groups (43.9 vs 44.8 months; $p = 0.91$). Adverse event rates were similar between patients treated with denosumab vs patients treated with placebo, with the exceptions of osteonecrosis of the jaw (5 % vs 0 %) and hypocalcemia (2 % vs <1 %) [18].

Another pivotal study currently underway compares denosumab with placebo as adjuvant treatment for women with early-stage breast cancer at high risk of disease recurrence (the D-CARE study). RANKL has recently emerged as a key paracrine mediator of hormone signaling in breast cancer, and therefore denosumab therapy may prove to be a viable therapeutic approach for the treatment of this disease [20]. Enrollment of 4,500 patients into the D-CARE study was completed in late 2012, and the total blinded treatment duration is planned for approximately 6 years and 5 months from first patient enrollment. Key endpoints include bone metastasis-free survival, disease-free survival, overall survival, and patient-reported outcomes [21].

12.3 Growth Factors Released from the Bone Matrix

12.3.1 Transforming Growth Factor-β (TGFβ)

TGFβ is a growth factor that is a potential therapeutic target for the prevention of bone metastases due to its regulatory role in cell proliferation, differentiation, apoptosis, and gene expression [22]. TGFβ expression is elevated in several cancers [23], and acts through linking serine/threonine kinase type I and II receptors to initiate signaling [24].

Anti-TGFβ monoclonal antibodies in a renal cell carcinoma xenograft model showed anti-angiogenic activity and anti-proliferative activity [25]. A recombinant chimeric fusion protein that contains the extracellular domain of the TGFβ type II receptor and IL-2 recently exhibited potent anti-tumor activity in a mouse model [26]. Inhibiting TGFβ type I and II receptors has also shown promise in suppressing pancreatic cancer metastases [27]. Another study in a mouse metastatic basal-like breast cancer model has shown that inhibiting TGFβ impacts both bone and lung metastases [28].

Numerous TGFβ signaling antagonists are currently in various stages of development, including SKF104365 (GSK), LY364947/HTS466284 (Lilly/Biogen Idec), LY580276 (Lilly), SB431542 (GSK), and SB505124 (GSK) [29–32].

12.3.2 Platelet-Derived Growth Factor (PDGF)

PDGF overexpression has been characterized in numerous cancers, such as gastric, lung, breast, and prostate, and has been associated with angiogenesis and metastatic processes, including the formation of bone metastases when upregulated in prostate cancer [33–36].

Imatinib mesylate is a potent inhibitor of PDGF receptor (PDGFR) phosphorylation that has been shown in a mouse model to suppress bone metastases secondary to breast cancer [37]. Another study in men with castration-resistant prostate cancer with bone metastases found that the addition of imatinib mesylate to docetaxel resulted in excess grade 3 toxicities that included fatigue and gastrointestinal disorders, resulting in early termination of the study [38]. Further studies exploring the impact of imatinib mesylate therapy on bone metastases are warranted.

12.4 Osteoclast Intracellular Signaling Inhibition

Src signaling pathways in osteoclasts are involved with cellular motility and morphology, including ruffled border formation, actin ring formation, and integrin-mediated activities, as well as RANKL-mediated activities.

12.4.1 Saracatinib

Saracatinib, also known as AZD0530 (AstraZeneca), is an orally bioavailable Src inhibitor that has been shown to reduce osteoclastic bone resorption in a randomized, placebo-controlled multiple-ascending-dose study in 59 healthy men [39]. Saracatinib was subsequently found to significantly decrease bone resorption markers in a phase 1 study in advanced solid tumor malignancies [40]. Phase 2 clinical trials further exploring saracatinib monotherapy in recurrent/metastatic squamous cell carcinoma of the head and neck [41], hormone receptor-negative metastatic breast cancer [42], locally advanced gastric or gastro-esophageal junction adenocarcinoma [43], have failed to show a benefit of saracatinib therapy in these patient populations. A recent phase 1 study of saracatinib and paclitaxel with or without carboplatin in various solid tumors showed acceptable toxicity in most patients and may warrant further investigation of this combination in larger studies [44].

12.4.2 Dasatinib

Dasatinib is another orally bioavailable Src inhibitor that has demonstrated in vitro inhibition of signaling pathways that lead to cell adhesion, migration, invasion, and angiogenesis, critical functions of the metastatic process in prostate cancer cells [45, 46]. Dasatinib has also been shown to inhibit metastases in thyroid cancer both *in vitro* and *in vivo* using an experimental metastasis model [47]. A phase 2 study demonstrated that dasatinib decreased bone turnover in patients with metastatic castration-resistant prostate cancer [48]. The combination of dasatinib with docetaxel showed promise in a small single-arm phase 1/2 study in patients with castration-resistant prostate cancer [49], with an objective tumor response rate higher than expected with docetaxel alone; however, these results were not confirmed in the phase 3 READY trial which recently reported that the addition of dasatinib to docetaxel did not improve overall survival in 1,522 patients with metastatic castration-resistant prostate cancer [50].

12.5 Osteoclast Enzymatic Activity Inhibitors

12.5.1 Serine Protease Inhibitors

Cathepsins are cysteine proteases that increase progression and metastases in numerous cancers [51]. Cathepsin K is a cysteine protease, without which tumor progression in bone is impaired [52]. Odanacatib (MK0822) is a potent cathepsin K inhibitor that reduces bone resorption in postmenopausal women [53] that may be an efficacious therapy for bone metastases. Recent evidence from a preclinical

mouse model of breast cancer has shown that inhibition of cathepsin B may limit bone metastases [54]. In the clinic, two phase 3 trials of odanacatib in patients with breast cancer and prostate cancer were planned but closed before enrollment was initiated for administrative reasons [55, 56].

12.6 Endothelin Receptor Antagonists

Atrasentan, a highly selective endothelin-A receptor antagonist that blocks prostate cancer-induced osteoblastic response in bone, has been evaluated in three large phase 3 trials: as a single agent in men with nonmetastatic prostate cancer, and alone or in combination with docetaxel in men with metastatic disease. Atrasentan did not prolong time to disease progression versus placebo ($p=0.288$) in a blinded, controlled study of 941 men with nonmetastatic hormone-refractory prostate cancer [57]. Atrasentan monotherapy also did not reduce the risk of disease progression relative to placebo (HR [95 % CI] = 0.89 [0.76–1.04]; $p=0.136$) in a blinded study of 809 men with metastatic hormone-refractory disease, despite some reductions in bone alkaline phosphatase (BAP) and prostate-specific antigen (PSA) in exploratory analyses, and the study was terminated early [58]. Most recently, atrasentan in combination with docetaxel did not show a benefit compared with docetaxel alone in 1,038 patients with castration-resistant prostate cancer and bone metastases, prompting the early termination of this study [59].

Another drug in this class, zibotentan (ZD4054), has not shown an improvement in disease outcomes in a phase 3, randomized, placebo-controlled study in men with castration-resistant prostate cancer metastatic to bone [60]. Subsequently, an early efficacy review was undertaken for another phase 3 monotherapy study in patients with non-metastatic disease, leading to early stopping of that trial, as it was determined that zibotentan alone was unlikely to achieve the co-primary efficacy endpoints (progression free survival and overall survival) [61]. The last phase 3 study of zibotentan which was conducted in combination with docetaxel for the treatment of metastatic hormone-resistant disease found no improvement in overall survival with the addition of zibotentan, leading to the discontinuation of the drug's development in prostate cancer [62, 63]. Thus, unless specific biomarkers can identify a population that may benefit, endothelin modulators may have limited future use in these indications.

12.7 Angiogenesis and Bone Metastases

Vascular endothelial growth factor (VEGF) directly enhances osteoclastic bone resorption and survival of mature osteoclasts [64]. VEGF receptors (Flk-1, Flt-1) are detectable in osteoclasts, which induce tyrosine phosphorylation of proteins in osteoclasts [64]. Human breast cancer cells in bone express VEGF-A, B, and C, and inhibition of angiogenesis may prevent bone metastases in certain types of cancer, although this has not been shown in clinical trials to date.

12.7.1 MET/VEGFR2 Inhibition

Cabozantinib is a small molecule tyrosine kinase inhibitor that has activity across multiple receptor kinases, with particular potency toward MET and VEGF receptor 2 [65]. A recent phase 2, nonrandomized study of cabozantinib in pretreated metastatic castration-resistant prostate cancer patients with bone metastases showed high rates of bone scan response and decreases in bone turnover markers [66]. In this study, concurrent bone-directed therapies such as zoledronic acid, denosumab, and radionuclides were used in 45 %, 41 % and 6 % of patients, respectively. Cabozantinib has also shown activity on bone lesions from multiple solid tumor types, including metastatic breast cancer [67], melanoma [68], renal cell carcinoma [69], and non-small cell lung cancer [70], and was approved by the US FDA for the treatment of metastatic medullary thyroid cancer in November 2012 [71].

12.7.2 mTOR Inhibition

Everolimus is an inhibitor of the mammalian target of rapamycin (mTOR) with demonstrated antitumor activity in a variety of solid tumor malignancies [72, 73]. Inhibition of mTOR can also decrease bone resorption by affecting osteoclast maturation and promoting osteoclast apoptosis [74]. Everolimus was recently shown to decrease bone turnover and breast cancer disease progression in bone [75]. Another recent study in patients with breast cancer and bone metastases showed longer time to progression in patients receiving everolimus [76].

12.8 Conclusions

The elucidation of the vicious cycle of bone metastasis in preclinical models has led to many potential targets to explore in clinical studies. However, a need remains to confirm the presence, and role, of these new targets in human bone metastases though additional translational research.

Targeting the RANKL/RANK pathway with denosumab has proven to be an effective treatment for both the prevention of bone metastases in patients with prostate cancer at high risk, as well as for the prevention of potentially debilitating complications once cancer has metastasized to bone in patients with solid tumors. Superiority of denosumab to the prior standard of care, zoledronic acid, was demonstrated across three large, randomized double-blind phase 3 clinical trials in this setting, and resulted in the approval of denosumab in 2010. The ongoing phase 3 study of denosumab compared with placebo in the adjuvant breast cancer setting will further test the ability of denosumab to improve bone metastasis-free survival and other disease outcomes for women with stage II or III disease.

Among the molecules in development for future treatment of metastatic bone disease, the MET/VEGFR2 inhibitor cabozantinib has generated promising results across a variety of tumor types. As additional results from ongoing trials become available, treatment regimens for patients may need to be modified and optimized.

Due to the importance of RANKL in the cascade of events leading to metastatic bone disease, it is unlikely that one agent will emerge as a replacement for denosumab in the setting of metastatic bone disease. It is, however, conceivable that future treatments will involve combination therapies to produce additive effects. Combinations of pharmaceutical agents with radiopharmaceuticals, such as radium 223, or denosumab, as well as combinations with novel agents such as denosumab or cabozantinib might be highly effective in treating patients with cancer-induced bone disease, and may warrant exploration in prospective clinical trials.

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Chapter 13
Systemic Therapy of Bone Metastases

Konstantinos Kamposioras and Evangelos Briasoulis

Abstract A few solid tumors have the propensity to bone and they can form two distinct types of bone lesions, which depend on whether osteoclastic (breast and thyroid cancer) or osteoblastic (prostate cancer) activity prevails. Regardless the types of bone lesion, bone metastazing cancers usually behave indolently and share in common significant sensitivity hormone therapies. The efficacy of chemotherapy is limited, and it depends on the tumor type. In general bone marrow-sparing strategies as are weekly schedules and metronomic chemotherapy appears to be the most appropriate therapeutic approach for patients with bone metastases. Hormonotherapy of hormone-sensitive bone metastases is typically shown effective over protracted periods of time and it usually outperforms chemotherapy in benefiting these patients. Therefore hormonotherapy should be considered as an upfront treatment option for patients with such cancers. Cancer research is currently investigating the molecular mechanisms, which underlie the apparent close ties of hormonal driven cancers and the microenvironment of bone. Improvements in the biological understanding are hoped to boost clinical research into developing most optimal hormonal management of hormone sensitive bone metastases.

Keywords Prostate cancer • Breast cancer • Bone metastases • Hormonotherapy • Therapeutic castration

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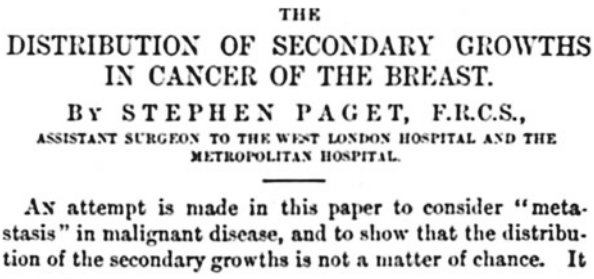
13.1 Introduction

Hormone-dependent tumors have a proclivity to metastasize to bone. Those tumors are the estrogen-receptor (ER) positive breast and the prostate cancer which constitute major causes of cancer related deaths worldwide and also the differentiated cancer of thyroid [1–6]. The osseous tropism of breast cancer was initially recognized late in the nineteenth century when the surgeon Stephen Paget having autopsied 735 fatal cases of breast cancer, argued in his seminal article published in 1889 in the Lancet (Fig. 13.1) that "in a cancer of the breast the bones suffer in a special way, which cannot be explained by any theory of embolism alone . . . the same thing is seen much more clearly in those cases of cancer of the thyroid body where secondary deposition occurs in the bones with astonishing frequency". In attempt to explain his observations Paget introduced the "seed and soil" theory quoting an earlier "organ predisposition" idea of Austrian doctor Ernst Fuchs which he had proposed by studying metastatic spread of choroid melanomas [7, 8].

Many investigators have attempted throughout the years to decode the molecular mechanisms, which underlie the apparent close ties of hormonal driven cancers and the microenvironment of bone. Yet, we still lack molecular biochemical data sufficient to formulate a clear "seed" and "soil" understanding of this biological phenomenon [9–11]. However, from a clinical stand point, most oncologists feel more at-ease when confront patients with bone metastases of hormone-dependent tumors than others with visceral metastases from several solid tumors, because in the first case metastases can be controlled over prolonged time with simple, subtoxic hormonal medications [12–14].

13.2 Types of Bone Metastases

Tumors can cause two distinct, although overlapping types of skeletal lesions when they metastasize to bone. Both types of bone lesions are consequences of disturbance of the normal continuous remodelling of bone which depends on whether osteoclastic or osteoblastic activity prevails [15–19]. Breast and thyroid cancers



THE

DISTRIBUTION OF SECONDARY GROWTHS IN CANCER OF THE BREAST.

BY STEPHEN PAGET, F.R.C.S.,

ASSISTANT SURGEON TO THE WEST LONDON HOSPITAL AND THE METROPOLITAN HOSPITAL.

AN attempt is made in this paper to consider "metastasis" in malignant disease, and to show that the distribution of the secondary growths is not a matter of chance. It

Fig. 13.1 A clip of S. Paget's seminal article of the "seed and soil" theory [7]

produce predominately osteolytic type of bone metastases while prostate cancer is typically associated with the development of osteoblastic metastases [2, 20–24]. However, osteoblastic metastases may also occur infrequently in breast cancer and osteolytic in prostate cancer, while approximately 15 % have mixed type osseous metastases [25–28].

13.3 Occurrence of Breast and Prostate Bone Metastases

It is estimated that approximately 50–70 % of women with advanced breast cancer have skeletal metastases [29]. In illustrating figures, in the year 2012, 40,000 women are expected to die of metastatic breast cancer in the United States. Since two-thirds of with patients with metastatic breast cancer have bone metastases and also two-thirds of breast cancers express estrogen receptors we can estimate that approximately 20,000 of breast cancer patients may develop hormone sensitive bone metastases each year in the US [6, 30–33]. With regard to prostate cancer patients, approximately 30 % have bone metastases already at the time of diagnosis and near all 28,000 patients who are estimated to die of prostate cancer in the year 2012 in the US, will die with bone metastases [30, 33, 34].

13.4 Hormonotherapy

13.4.1 Rationale

Metastatic in bone hormone-receptor positive breast cancer and also prostate cancer, although incurable, they usually respond well to hormonal therapies and run indolently with reported median survival of treated patients 4–6 years [35–38]. Moreover it is acknowledged that hormonotherapy strategies outperform chemotherapy in benefiting patients with bone metastases [12, 39–41].

13.4.2 Assessing Response to Therapy: Limitations

Reported results of several clinical trials which evaluated in the past the antitumor activity of therapies against bone metastases, should be considered with some scepticism because of methodological issues in this clinical setting [39, 42, 43]. In such studies, the evaluation of response of bone metastases to treatment has typically relied on subjective endpoints such as pain relief and quality of life and on evaluable although not measurable data such as recalcification of previously lytic lesions or reduction of “hot spots” on scintigraphy [39].

Difficulties in response assessment of bone metastases pertain mostly to the breast cancer. Reports from phase II and phase III trials of endocrine therapy have repeatedly provided estimates of the activity of endocrine therapies of osseous metastases in breast carcinoma, but unfortunately, they commonly failed to report the response duration in bone or the survival in patients with bone dominant metastases [44]. This problem has found a solution in the case of prostate cancer with the wide adoption of the PSA response evaluation criteria proposed by Bubley et al., in 1999 [45].

13.5 Chemotherapy

Given the fact that mostly hormonosensitive cancers tend to form bone metastases, clinical evidence is limited, regarding superiority of certain chemotherapy agents over others. Generally speaking, the selection of chemotherapy depends on the tumor type and bone marrow-sparing low dose weekly schedules are preferred in most cases [46–49]. In this direction, the concept of metronomic chemotherapy appears to be the most appropriate therapeutic approach for patients with bone metastases [50]. In addition the combination of low dose chemotherapy with radiopharmaceuticals emerges as a viable option [51].

13.6 Breast Cancer

13.6.1 Early Studies

Endocrine therapy was first introduced into the clinics as a therapeutic option for metastatic breast cancer when Sir Beatson reported in 1896 that oophorectomy could induce tumor regression in breast cancer patients [52]. Oophorectomy was understood to work therapeutically in these cases through reduction of estrogen levels. Later on, in the middle of the twentieth century clinical investigators undertook the first systemic approaches to study and compare surgical and pharmaceutical endocrine therapy and first results appeared promising.

In surgical approaches, Pearson and Ray reported a 28 % response rate in 53 patients and Fracchia et al., 33 % in 141 breast cancer patients, all with bone metastases, who were treated with hypophysectomy [53, 54]. Moreover, Fracchia et al., describing the results of adrenalectomy as a therapeutic intervention in patients with advanced breast cancer reported an interesting 36 % response rate in a cohort of 500 of whom 329 patients had bone metastases [55].

When the first therapeutic compounds emerged into clinics, they were first compared with established at that time surgical endocrine interventions. Nemoto et al., reported that 5 out of 12 breast cancer patients with bone metastases responded to

tamoxifen (42 %) compared with 7 out of 11 who responded to adrenalectomy (64 %) [56]. Moreover Santen et al., in another clinical trial in which 96 postmenopausal women or medical therapy with an adrenal inhibitor, aminoglutethimide (AG), plus replacement hydrocortisone, they found that 17 of 34 breast patients with bone metastases responded to aminoglutethimide compared with 8 out of 22 to adrenalectomy [57].

Two randomised studies that compared estrogens and androgens appear to be also of historical interest. Kennedy reported 3 out of 12 bone responses to diethylstilboestrol compared with 2 out of 15 to testosterone, [58] and Goldenberg et al. reported that 2 out of 8 breast cancer patients with bone metastases responded to diethylstilboestrol compared with 4 out of 10 who responded to fluoxymesterone [59].

It should be mentioned that because the assessment of expression of hormonal receptors was very limited before the 1980s, the results of trials conducted before 1980 were rarely analyzed by considering the expression of estrogen receptors in tumor cells [60–62].

13.6.2 Initial Hormonotherapy

Today, it is advised that hormonotherapy of breast cancer bone metastases should solely be considered for women with estrogen-receptor–positive tumors [63].

Tamoxifen, a Selective Estrogen Receptor Modulator (SERM) which blocks the binding of estrogen to its receptor by competitive antagonism, has been the first and continues to be the recommended hormonal therapy for postmenopausal women with metastatic ER-positive tumors [64]. However, although this drug has been used for more than 30 years, there have not been specific data on skeletal response rates [65]. Noteworthy, in one of the first studies Lerner et al., reported that 7 of 18 patients with bone metastases responded to tamoxifen. The investigators of that study drew attention to an observed correlation between response and positive estrogen-receptor assay and acknowledged a value in this test as a means to select patients for tamoxifen treatment [66].

Second to tamoxifen, progestins and inhibitors of the aromatization of androgens were also proven active against metastatic breast cancer, but a series of relatively small trials failed to demonstrate significant differences in favour of any agent when used as initial hormonal therapy, especially for patients with bone metastase [67–70]. Characteristically, Hortobagyi et al., reported 9 responses in a cohort of 18 patients with bone metastases who were treated with medroxyprogesterone acetate, van Veelen et al., reported a 40 % response rate for medroxyprogesterone acetate (MPA) and 23 % for tamoxifen in 25 and 31 patients respectively, and Muss et al., reported a 33 % response rate to oral high dose MPA compared with a 13 % response rate for tamoxifen in breast cancer patients with bone metastases [71–73].

Aromatase inhibitors are a class of drugs which block aromatase the enzyme that catalyzes the last steps of estrogen biosynthesis, by increasing the aromaticity of androgens through successive hydroxylations of the A ring [74]. These drugs have a

potency to suppress effectively peripheral aromatase activity and the biosynthesis of residual estrogens from extra-ovarian produced androgenic substrates in postmenopausal women [75–77]. Today, a third generation of aromatase inhibitors/inactivators (AI) are pushing aside tamoxifen as first line treatment in postmenopausal women with metastatic ER-positive breast cancer [78]. The superiority of AIs over tamoxifen as first line hormonotherapy in postmenopausal patients was clearly evidenced in a large study (907 women, median follow-up 18 months), in which letrozole resulted in more tumor regressions and was associated with a longer time to disease progression than tamoxifen (9.4 vs. 6.0 months; $p = 0.0001$) [79]. The observed benefit was statistically significant irrespectively of previous adjuvant use of tamoxifen and the site of disease [80]. Nonetheless the first evidence of clinical value of third-generation aromatase inhibitors became known when a series of trials demonstrated that AI given as second-line therapy after tamoxifen surpassed in efficacy megestrol acetate, even though responses of bone metastases were not shown significantly different [81, 82]. Lately, a metaanalysis which considered 25 randomized trials with 8,504 patients mostly with hormone-receptor–positive tumors showed that third generation aromatase inhibitors and inactivators were superior to tamoxifen and progestins as first-line treatment for advanced disease [83].

Regarding activity against bone metastases, it seems that examestane is superior to tamoxifen yielding higher response rate in the osseous only disease (48 vs. 14 %) and in the bone and soft tissue disease (42 vs. 36 %, respectively) [84]. The role of Fulvestrant in first line therapy has been tested lately in Phase III trials, either alone or in combination with anastrazole. It should be noted that although Fulvestrant seems to be as effective as tamoxifen or anastrazole in first line treatment its role as alternative hormone therapy has to be further elucidated. On the other hand, in the SWOG S0226 trial the combination of anastrozole and fulvestrant was superior to anastrozole alone or sequential anastrozole and fulvestrant for the treatment of ER-positive metastatic breast cancer. Nevertheless, this was not confirmed in the FACT study [88]. In the combination studies bone metastasis was referred up to 20 % of cases and the two interventions were equivalent as to bone response [85–88].

13.6.3 Hormonotherapy of Relapsed Bone Metastases

The options for second line hormonotherapy may vary broadly, depending on the choice and effectiveness of first line therapy.

Progestins have been used for years as second-line therapeutic option, considered by many as standard therapy in patients who had relapsed to tamoxifen [89]. However data on bone metastases are sparse and inconsistent with considerable variation of response rates reported in clinical studies, which reached a 21 % in early 1980s. Smith et al., for example reported 40 responses in a cohort of 192 breast cancer patients with bone metastases [90, 91].

The first generation inhibitor of the aromatization of adrenal androgens aminoglutethimide has been studied in patients with metastatic breast cancer who had relapsed

after a first line endocrine therapy, usually tamoxifen, but not specifically in regard to bone metastases [92]. Interestingly, in two randomised studies the response rates were in favour of aminoglutethimide when it was compared with tamoxifen. Lipton et al., found a trend towards better activity of aminoglutethimide in women with bone metastases [9 of 27 Complete Response (CR) plus Partial Response (PR) (33 %)] when compared with tamoxifen [4 of 27 (15 %)] [93]. Similarly Smith et al., reported that aminoglutethimide achieved better response rates in bone metastases (35 %) than tamoxifen (17 %) [94]. More recently, new generation aromatase inhibitors were compared with megestrol acetate in randomized trials as second-line hormonal therapy in patients with metastatic breast carcinoma refractory to tamoxifen. Buzdar et al. reported separate trials which compared anastrozole and fadrozole against megestrol acetate (MGA) but both failed to show any superiority for the aromatase inhibitors with respect to the response rate of bone metastases [81, 95]. However, in the Thurlimann et al., study a substantial higher rate of progression in bones in the formestane (51/68) than in the MGA arm (25/53) was observed [96].

A third line hormonotherapy option has recently become available for metastatic in bone breast cancer. This is fulvestrant, a new type of estrogen receptor antagonist which downregulates the ER and is devoid of agonist actions. Fulvestrant has been shown active in patients with metastatic ER + tumors having received prior hormonotherapy with AI and also tamoxifen [97]. Moreover it has been found equally active and well-tolerated with nonsteroidal aromatase inhibitor examestane in a randomized trial of 693 postmenopausal women with ER + advanced/metastatic breast cancer progressing or recurring after nonsteroidal AI. Interestingly 563 patients with bone metastases were included in that trial [98]. It also seems to be effective after multiple lines of therapy with clinical benefit reaching up to 25 % with bone only metastasis [99].

Another interesting approach in highly refractory metastatic breast cancer is high dose estrogen, based on the hypothesis that tumor cells chronically deprived of estrogen with aromatase inhibitors show increased sensitivity to estradiol. In a retrospective review this approach could offer a significant clinical benefit in patients with bone metastases as they could be treated with estrogens for more than 6 months [100].

13.6.4 Hormonotherapy for Bone Confined Metastatic Breast Cancer

Bone-confined metastatic breast cancer has been recognized as a distinct clinical entity. Bone-only metastasis has been reported to occur in 4–37 % of women with metastatic breast cancer [101] and in the vast majority this is hormone receptor positive [102]. We have shown that if metastatic disease remains confined to bone for a minimum of 24 months it will probably follow indolent clinical course for which it is prudent to use gentle therapeutic approaches and mostly remain adherent to hormonotherapy [37]. In this clinical setting we demonstrated that 80 % of patients

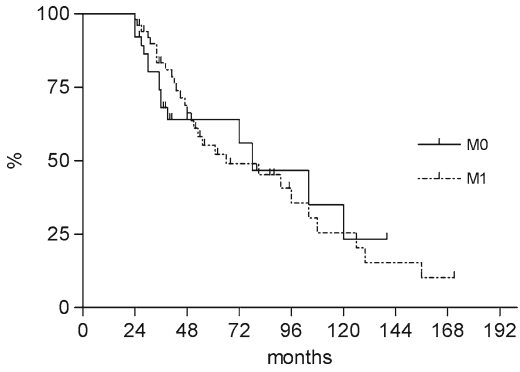


Fig. 13.2 Survival of patients with bone-confined metastatic breast carcinoma (n 104) after the diagnosis of skeletal metastases. M1 (*dashed line*): patients with bony metastases present at the time of diagnosis; M0 (*solid line*): patients with bony metastases that occurred during follow-up [37]

responded to first line hormonal therapy with tamoxifen and a 44 % responded also to second line hormonotherapy [any of medroxyprogesterone, aromatase inhibitors and triptorelin, a gonadotropin releasing hormone agonist] Fig. 13.2. Approximately two thirds in this cohort patients had also received systemic bisphosphonates [37]. Similar data of hormonal efficacy in this clinical setting had also been reported by Sherry et al. In their study a 87 % of treated patients responded to the first hormonal therapy with a median duration of response 10 months, 76 % responded to a second line treatment with median duration of response 12 months, and another 60 % responded also to the third line hormonal therapy [36]. Moreover, Nikura et al., showed that combination therapy of chemotherapy and hormone therapy was not superior to hormone therapy alone for Progression Free Survival (PFS) and Overall Survival (OS) in multivariate analysis in the subset of population with HER2- disease. However they could further identify a more indolent profile, consisting of good performance status (ECOG 0 or 1), single metastatic site, metastasis at presentation and asymptomatic bone disease, that could predict a longer PFS and OS and could potentially treated with hormone therapy [102].

The indolent course of this metastatic in bone disease taken together with the prolonged life expectancy in these patients allows clinicians to utilize multiple lines of hormonotherapy in combination with bisphosphonates before considering a shift to chemotherapy in the interest of protecting the quality of life of patients (Fig. 13.3).

13.6.5 Hormonotherapy Combinations

A number of investigators have shown that the addition of corticosteroids can increase the antitumor effects of endocrine therapies against metastatic breast cancer. Characteristically Rubens et al., reported a higher overall response rate, response duration, and survival when prednisolone was added to ovarian irradiation or tamoxifen in the treatment of 194 women with advanced breast carcinoma [103]. Apart from the combination with corticosteroids all other possible combinations

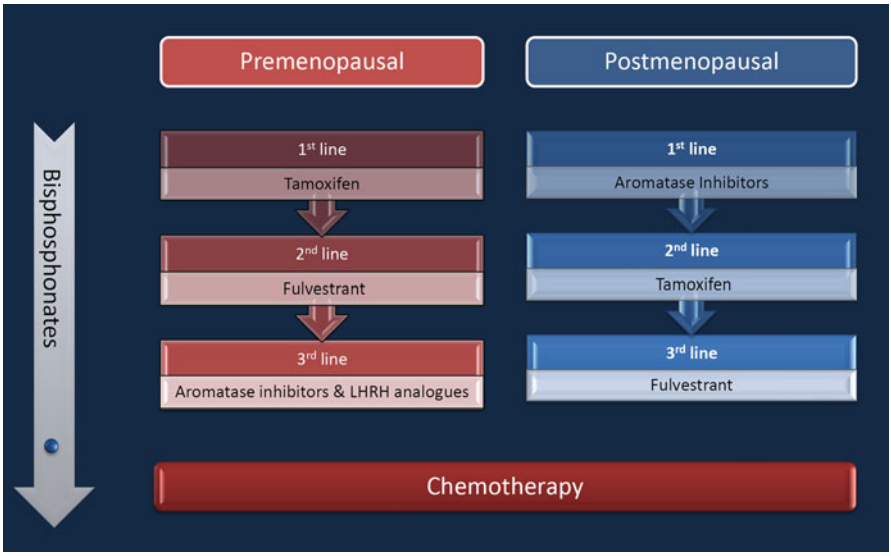


Fig. 13.3 Suggested hormonotherapy algorithm for premenopausal and postmenopausal patients with bone-only breast cancer metastases. Bisphosphonates apply to both clinical settings

of hormonal therapies failed to improve the treatment outcome over single agent therapies [104–107]. For instance, Mouridsen et al. showed that the addition of MPA did not improve antitumor activity of tamoxifen in terms of response rate at different sites of metastases, including bone [108].

It is certain that endocrine therapy with either aromatase inhibitors or selective estrogen-receptor modulators will finally lead to endocrine resistance and disease progression in all thus treated patients. Today clinical and translational research focuses on the development of optimal combinations between aromatase inhibitors and inhibitors of the human epidermal and insulin-like growth-factor receptor pathways which are upregulated in hormone-resistant breast cancers. Preliminary data from phase II studies of such combination therapies are encouraging [109].

The combination of hormonotherapy with bisphosphonates is currently recognized as a valid therapeutic option which was recently introduced in the therapy of breast cancer bone metastases [110]. Following the demonstration of significant reductions in pain and skeletal morbidity compared with placebo with zoledronic acid breast cancer patients with bone metastases is advisable to receive bisphosphonates in combination with anticancer treatment [111, 112]. The clinical significance of this therapeutic practice was initially revealed in a randomized trial in which 371 breast carcinoma patients with osteolytic bone metastases on endocrine therapy were given either pamidronate 90 mg as a 2-h infusion monthly for 2 years or a placebo infusion. That study demonstrated that the addition of bisphosphonates to endocrine therapy produced a sustained reduction in skeletal complications [113]. An additional benefit effect of bisphosphonates is that can offset the induced by the aromatase inhibitors bone loss [114, 115].

13.7 Prostate Cancer

Prostate cancer is the second most frequently diagnosed cancer and the third most common cause of cancer related deaths among men in the western-type economically developed world with medical and social consequences comparable to those of breast cancer in women [116].

Key features of this cancer are its hormone-dependency and typical association with bone metastases [117]. Prostate cancer is unique among solid tumors in that it threats patients' survival and quality of life through bone rather than visceral metastatic involvement. Nearly all treatments of metastatic prostate cancer are directed towards osseous metastatic disease with the aim to prevent their complications or palliate bone symptoms [118–120]. Untreated patients confront an array of potential sequelae that include bone pain, fractures, hematologic consequences of packed marrow, and neurologic impairment resulting from cranial metastases or cord compression [121, 122]. However, in prostate cancer patients with bone metastases, hormonotherapy has the potency to effectively palliate symptoms and even provide survival benefits [3, 123].

13.7.1 Initial Hormonotherapy

Prostate cancer progression is driven by functional androgen receptor signaling. Therefore treatment of metastatic disease has logically been focused on androgen deprivation since Huggins and Hodges published their Noble Prize-winning paper 60 years ago in which they demonstrated the high sensitivity of prostate cancer to androgens. Ever since, hormonotherapy remains the mainstay of systemic therapy of metastatic prostate cancer despite transient duration of responses [124, 125]. The target for endocrine treatment of prostate cancer is to deprive cancer cells of androgens. As shown by Kyprianou at al., apoptotic regression of androgen-dependent prostate cancer cells can be induced by any procedure that reduces intracellular concentration of dihydrotestosterone by 80 % or more [126].

From a clinical point, it should be noted that it is not imperative to start hormonotherapy immediately upon diagnosis of bone metastases in all patients with prostate cancer. The American Society of Clinical Oncology (ASCO) suggests that hormonotherapy for metastatic in bone prostate cancer can be delayed in low risk patients until the development of symptoms because in a number of old patients the disease may follow a very indolent course [118].

13.7.2 Castration

Castration, the time-honoured frontline treatment for metastatic prostate cancer, is a clinical condition defined by testosterone levels below 50 ng/ml in men. This threshold level has recently redefined to <20 ng/ml [127]. The first methods of therapeutic

castrating interventions were bilateral orchiectomy which was permanent and pharmaceutical with diethylstilbestrol which was reversible. Estrogens were thought to suppress Luteinising Hormone [LH] from the anterior pituitary and lower the production of testosterone by the Leydig cells. However, estrogens are no longer considered as a valid therapeutic option in metastatic prostate cancer because of significant thromboembolic and cardiovascular toxicity [125, 128, 129].

ASCO at present recommends bilateral orchiectomy as an acceptable first-line therapy, although it seems that a majority of men would rather opt the potentially reversible medical castration with Luteinizing Hormone–Releasing Hormone (LHRH)[1] agonists [118, 130–133].

Currently potent LHRH agonists with a 100-fold greater receptor affinity and reduced susceptibility to enzymatic degradation compared with the naturally occurring LHRH, have revolutionised the treatment of patients with advanced prostate carcinoma. These drugs are administered by injection at intervals of 1–3 months. Current studies demonstrate that only about 5 % of patients treated with LHRH agonists fail to achieve suppression of testosterone below the level 50 ng/ml [134]. However medical doctors must be aware that LHRH agonists can induce initially a tumour flare effect by inducing a transient increase in LH production and thereof increase of testosterone levels in plasma which usually lasts 1–2 weeks [135]. Therefore patients who commence on LHRH therapy should be warned for the possibility of transiently increased bone pains. Moreover increased medical vigilance is required in patients at risk of metastatic compression of the spinal cord or ureteric obstruction [136]. In such cases either surgical castration should be considered as the treatment of choice or patients should be offered introduction therapy with an antiandrogen for a minimum of 5 days prior to injection of the LHRH agonist with the aim to prevent the flare effects of transient increase of LH and testosterone [137].

There are several LHRH agonists available for clinical use today, including goserelin, leuprorelin, buserelin and tritorelin, but they have not been tested against each other in randomised controlled trials in the setting of metastatic in bone prostate cancer [138, 139].

LHRH antagonists which lack the undesirable flare effects are now being developed as a next generation castration medicines for prostate cancer [140]. These drugs have now entered clinical investigation [141]. After the voluntary withdrawal of abarelix form the USA market in 2005 due to hypersensitivity reactions the pure GnRH antagonist degarelix proved to be as effective as leuprolide at maintaining low testosterone levels over a 1-year treatment period in a randomized phase III trial in which 610 men with prostate cancer were randomly assigned to degarelix (240 mg for 1 month, followed by monthly maintenance with doses of either 80 mg [n = 207] or 160 mg [n = 201]) or to leuprolide (7.5 mg per month) [142]. Degarelix was licensed in the USA and Europe in 2008 as a first-line hormonal therapy for advanced prostate cancer. Degarelix induced testosterone and PSA suppression significantly faster than leuprolide, while this GnRH antagonist achieved a greater suppression of serum alkaline phosphatase suggesting that it might prolong control

[1] Also called gonadotropin-releasing hormone, GnRH

of skeletal metastases in metastatic disease compared with GnRH agonists; something that has not yet proved clinically [143].

13.7.3 Antiandrogens

Antiandrogens, or androgen antagonists, are pharmaceutical compounds which are capable to inhibit the biologic effects of endogenous circulating androgens by competing with them and preventing acquisition of a transcriptionally active conformation of the androgen receptors [144, 145]. It is recommended that nonsteroidal monotherapy can be considered as alternative to castration for the therapy of metastatic prostate cancer, especially in patients who are willing to retain sexual interest and function [118, 146]. Among antiandrogen drugs, the most comprehensively studied one which in addition achieved median survival of treated patients similar to that of castration, is bicalutamide [147, 148]. Steroidal antiandrogens, of which cyproterone acetate is the main representative, have been abandoned as a therapeutic option in metastatic prostate cancer due to toxicity concerns [118, 149].

13.7.4 Combined Androgen Blockade

Surgical of medical castration has been used for years as a standalone androgen-deprivation therapy for metastatic prostate cancer [150, 151]. However, in early 1980s it was found that approximately 50 % of androgens remain in the prostatic tissue following medical or surgical castration, and that adrenal dehydroepiandrosterone [DHEA] plays a major role of as a source of the androgens synthesized locally in the prostate and other peripheral target tissues [152, 153]. Based on these observations, the combined androgen blockade (CAB) therapeutic strategy was developed whereby the androgens of both testicular and adrenal origins were blocked simultaneously at start of treatment with the combination of either orchiectomy or an LHRH agonist and a pure antiandrogen [153, 154]. Recently, a randomized clinical trial and an individual patient data meta-analysis demonstrated that non-steroid antiandrogens can improve survival when added to medical or surgical castration, but with a cost of poorer quality of life. The above data, despite some limitations, provide a Level I evidence in support that combined androgen blockade should be considered as upfront hormonal therapy for patients with prostate cancer bone metastases [155–158].

13.7.5 Intermittent Androgen Blockade

The therapeutic concept of intermittent therapeutic blockade of androgen [IAB] is principally based on experimental studies showing that continuous exposure to reduced androgens can promote prostate tumorigenesis by promoting selection of molecular events which can lead to more aggressive, hormone-refractory tumors.

Moreover IAB, aims also to ameliorate negative treatment effects on the quality of life of patients [159].

However this therapeutic strategy, although it has been proven feasible, it is considered experimental because the available data are so far inconclusive to support clinical recommendations [160, 161]. Definite answers are expected to show up from currently running phase III randomized clinical trials which compare intermittent versus continuous combined androgen-deprivation treatment (ADT). Until then the use of intermittent androgen blockade should be considered only in the context of clinical trials [118].

13.7.6 Second Line Hormonotherapy

Endocrine therapy of metastatic in bone prostate cancer is by definition palliative and not curative. Even though ADT can prolong median survival in prostate cancer patients with bone metastases and benefit a 10 % of them with a 10 years symptomless period, the great majority will eventually experience disease recurrence [162]. Progression to androgen-independent status is expected after a median time of 18 months from hormone deprivation [163–165]. However, available research data indicate that relapsed prostate cancers remain potentially sensitive to intracellular androgens and meaningful responses can further be achieved with novel therapeutic approaches [166–168].

Recent advances in the understanding of the biology of prostate cancer have opened new insights into the issue of resistance-associated mechanisms of castration-recurrent prostate cancer. First, it has been found that the levels of tissue androgens remain capable of activating the androgen receptors which may additionally upregulate to hyperactive status in hormone-refractory phenotype [169–174]. Secondly, adrenal glands secrete hundredfold higher than testosterone levels of the inactive precursor steroids DHEA, its sulfate DHEAS and also androstenedione (4-dione), which are converted into potent androgens in peripheral tissues, including the prostate [175]. Finally, it has been shown that the active androgens made locally in the prostate can exert their action by interacting with the androgen receptor in the same cells where their synthesis takes place without being released the active androgen in the circulation (intracrine function). It is suggested that novel approaches targeting complete suppression of systemic and intracrine contributions to the prostatic androgen microenvironment are required to achieve optimal clinical efficacy in the therapy of metastatic prostate cancer [176–179].

13.7.7 Hormone Therapy Post Chemotherapy Failure

Understanding in depth the biology of castration resistant prostate cancer (CRPC) has highlighted that CRPC is highly hormone dependent. Up-regulation of androgen biosynthesis enzymes, overexpression of androgen receptors, and androgen-receptor mutations leading to androgen-receptor binding by additional ligands that would

not stimulate the wild-type receptor, alterations in androgen uptake by prostate cancer cells seem to be some of the driving forces of the "hormone refractory" prostate cancer [180, 181].

Abiraterone acetate is a potent, selective, irreversible inhibitor of (CYP17), a critical enzyme in testosterone synthesis, thereby blocking androgen synthesis by the adrenal glands and testes and within the prostate tumor. Abiraterone has been proved to increase overall survival in combination with prednisone as compared with the placebo–prednisone group (15.8 months vs. 11.2 months; hazard ratio, 0.74; $p < 0.001$) [182]. In addition there was an improvement in the time of developing a skeletal event (9.9 vs. 4.9 months) [183]. A novel mechanism to explain this improvement can be attributed to the ability of abiraterone to achieve a sustained suppression of testosterone bone marrow aspirate to less than picograms-per-milliliter levels, as this was sophisticated highlighted in patients who underwent bone marrow biopsies [184].

Another oral anti androgen agent recently proved to be efficacious in men with metastatic castration resistant prostate cancer after chemotherapy is enzalutamide (formerly called MDV3100) which acts by inhibiting the signaling of androgen-receptor. In the Affirm study, overall survival was increased by almost 5 months; 18.4 in the enzalutamide versus 13.6 months in the placebo group while the time to the first skeletal-related event was also improved(16.7 vs. 13.3 months; hazard ratio, 0.69; $p < 0.001$). A skeletal-related event was defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. The toxicity was tolerable with fatigue, diarrhoea, and hot flashes being reported more frequently in the enzalutamide group [185].

13.7.8 Hormonotherapy Combinations

Similarly to bone metastases of breast cancer, glucocorticoids appear to be the best drug-partners to androgen-deprivation hormonal therapy in prostate cancer [186]. Glucocorticoids have been proven active as single agents and also capable to suppress androgen-independent prostate cancer growth possibly through inhibition of tumor-associated angiogenesis by decreasing VEGF and IL-8 production directly through glucocorticoid receptors [186, 187].

However, the use of bisphosphonates in the treatment of metastatic prostate cancer remains questionable. Hormonotherapy of metastatic prostate cancer is known to induce bone loss which ranges from 0.6 % to 9.6 % in 1 year after the initiation of androgen depletion therapy [188]. Moreover experiments in mouse models point out that increased bone resorption due to androgen deprivation may facilitate the development and progression of bone metastases [189]. Despite of that, we still lack consensus on the routine use of bisphosphonates in these patients, although it has been shown that these drugs can prevent therapy-related bone loss in hypogonadal men with prostate cancer [190–192]. However, although not officially recommended, bisphosphonates might be individually considered for the treatment of refractory

bone pain and the prevention of skeletal events [193, 194]. Recent data support that zoledronic acid administered annually can effectively prevent bone loss in hypogonadal men with metastatic prostate cancer [195].

13.7.9 Novel Agents and Future Perspectives

It is obvious that the new era for the treatment of CRPC has just begun. Not only abiraterone and enzalutamide seem to be active but a plethora of novel agents are already in phase III clinical trials. TAK-700 (Orteronel) is a reversible CYP17 inhibitor with preferential inhibition of 17,20-lyase over 17-hydroxylase activity, which may in theory reduce the need for corticosteroid supplementation, as secondary mineralocorticoid excess induced by CYP17 inhibition may be more dependent on 17-hydroxylase. Orteronel is currently compared with placebo in two randomized phase III studies in both chemotherapy-naıve and docetaxel-refractory metastatic CRPC, respectively (clinicaltrials.gov ID: NCT01193244 and NCT01193257). TOK-001 is another CYP17 inhibitor that can also down-regulate and antagonize the androgen receptor (AR), which is in early development (clinicaltrials.gov ID: NCT00959959).

On the other hand many questions have been generated after the proved efficacy of GnRH antagonists and the new antiandrogens. Optimal timing and sequencing as well as which should be the standard treatment approach need to be re-evaluated. The use of GnRH antagonist or agonist for initial therapy has to be clarified. The sequence or combination of the new antiandrogens with GnRH analogues has also to be elucidated. The role of abiraterone and enzalutamide in chemo naïve CRPC patients will be highlighted from the currently running phase III trials comparing these agents with placebo, but the direct comparison with chemotherapy will be missing for many years more. In vitro experiments suggest abiraterone exposure could reverse resistance secondary to activation of AR by residual ligands or coadministered drugs, providing a strong rationale for clinical evaluation of combined CYP17A1 inhibition and AR antagonism [196]. Moreover, abiraterone was proved to be effective in pain palliation after the administration of docetaxel and enzalutamide although pain related symptoms were not clearly defined [197]. Further on, whether CYP17 inhibition should be maintained following disease progression, just as standard ADT is continued in the setting of CRPC, is open to investigation. Finally the effect of the different approaches on the bone metastatic niche needs to be further explored.

13.8 Differentiated Thyroid Cancer

Differentiated Thyroid Cancer (DTC), the most common malignancy of the endocrine system, besides its carcinogenesis initiation factors, is highly dependable on the pituitary thyroid-stimulating hormone (TSH) for its increase and progression [198].

The incidence rate of DTC has been continuously increasing over the last two decades, yet it remains relatively uncommon and highly treatable [199, 200]. Among the differentiated histotypes, it is follicular carcinoma which shows a tendency to develop remote metastases in lung and bone, hitherto at low rates [201, 202]. Moreover a small proportion of DTC patients are diagnosed on the basis of the detection of bone metastases [203]. In a large retrospective series the incidence of synchronous and metachronous bone metastases was at the range of 2 % for either, while the mean interval to bone metastases from the initial diagnosis was 5 years [204]. It is estimated that the 4–12 % of patients with DTC will develop bone metastases, rendering a dismal prognostic entity; disease specific survival after bone metastasis 36 % at 5 years and 10 % at 10 years. The tendency of DTC to form bone metastases and its increasing incidence has lately renewed the interest in diagnosing and investigating the physiology of bone metastases from thyroid cancer [205–207].

TSH-suppressive hormonal therapy with thyroxin constitutes a life-long therapeutic strategy in the case of differentiated thyroid cancers because of the known endocrine dependency of these tumors [208, 209]. Thyroxine starts following postoperative radioactive iodine (RAI) ablation as a replacement therapy with the aim to suppress TSH which is considered an important growth factor for DTC [210–213]. Current data show that treatment of bone metastases from DTC is usually not curative but palliative [202, 214]. Nevertheless, RAI therapy may cure up to 17 % of differentiated thyroid carcinoma patients with BM taking up RAI and < 7 % of all differentiated thyroid carcinomapatients with BM [215]. Bone metastases that demonstrate uptake of I^{131} must be treated with recombinant human TSH (rhTSH) aided therapeutic radioiodide [216–218] while TSH ablative hormonotherapy by thyroxine should be considered in cases not sensitive to I^{131} [219]. Although bone metastasis is a strong sign of poor prognosis, early detection and administration of appropriate therapy using radioactive iodine seems likely to improve the survival rate and quality of life in patients with bone metastasis from differentiated thyroid carcinoma. In this contest, medical doctors must be aware that patients with massive bone metastases of follicular thyroid carcinoma and treated with thyroxine are at risk of thyrotoxicosis which can be caused by hyperconversion of administered thyroxine to T3 in the tumor tissue [220].

13.9 Concluding Remarks

Hormone-dependent tumors primarily the estrogen-receptor positive breast and the prostate cancer that make a major cancer burden worldwide, and also thyroid cancer, have a well recognized tendency to metastasize to bone. When metastasize in bone, these tumors produce two distinct, although somehow overlapping types of skeletal lesions which are understood as consequences of disturbance of the normal continuous remodelling of bone. The type of bone lesions depends on whether osteoclastic or osteoblastic activity prevails. Breast and thyroid cancers produce

predominately osteolytic type of bone metastases while prostate cancer is typically associated with the development of osteoblastic metastases.

Clinical experience with hormonotherapy of bone metastases is well established despite inherent difficulties in assessing objective response of bone metastases. In general, oncologists feel comfortable when they confront patients with bone metastases of hormone-dependent tumors because these tumors can be controlled over prolonged periods of time with simple, subtoxic hormonal manipulations/medications. Moreover, it is widely acknowledged that hormonotherapy strategies outperform chemotherapy in benefiting patients with bone metastases.

Cancer research is currently attempting to decode the molecular mechanisms which underlie the apparent close ties of hormonal driven cancers and the microenvironment of bone. Improvements in the biological understanding and gene profiling are hoped to boost clinical research into developing optimal hormonal management of hormone sensitive bone metastases.

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Chapter 14
High-Intensity Focussed Ultrasound and Radio-Frequency Ablation for Bone Metastasis Treatment

Sheliza Halani, Jennifer Coccagna, Edward Chow, Kullervo Hynynen, and Gregory J. Czarnota

Abstract Bone is one of the most common target organs for cancer metastases which can frequently result in fractured or cracked bones and spinal cord compression. Here we review recent information regarding the use of high-intensity focussed ultrasound (HIFU) and other forms of thermal ablation for the pain palliation of bone metastases. High-intensity focussed ultrasound is a non-invasive and effective method for pain palliation and does not have cumulative toxicity effects when used. Similarly, radiofrequency-ablation effectively treats bone metastasis pain but is limited to the placement of hardware for radiofrequency targeting. The effectiveness of thermally ablative techniques is generally limited by the maximum volume that can be ablated and the precision of image-guidance, and it has been concluded that ablative techniques may produce synergistic effects if used in conjunction with standard forms of care. Included is a discussion of the development of HIFU, its

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mechanism of operation, recent clinical studies using image-guided HIFU, the limitations of HIFU, and a comparison to other ablative techniques such as radiofrequency ablation and cryotherapy. These innovative technologies are reaching clinical adoption as new methods for the treatment of bony metastases.

Keywords Coagulative necrosis • Acoustic streaming • Thermal ablation • Radiation force • Microbubbles

14.1 Introduction

Metastasis is one of the complications of cancer that has increased the need for effective forms of palliative treatment. In particular, with better local control of disease, the number of cases of bone metastases has risen, resulting in many negative side effects and impairments for patients. Bone metastases are discovered frequently, occurring in up to 70 % of patients with advanced prostate or breast cancer [1]. Among patients with bone metastases, 50–75 % experience severe pain [2]. Development of bone metastases along the spine is common, frequently resulting in spinal cord compression, vertebral compression fractures, and complications associated with the proper functioning of the nervous system. Malignant spinal cord compression can create sensory deficits, loss of mobility and paralysis [2]. Given this, there is a high demand to safely relieve the symptoms of bone metastases in patients as well as increase their survival rate and quality of life.

Various treatment modalities have been used in the palliation of bone metastases including radiotherapy, surgical resection, chemotherapy, vertebroplasty, kyphoplasty, or a combination of these approaches. However, it is not always possible to treat all patients with these approaches and alternate modalities must be considered. High-intensity focussed ultrasound (HIFU) is a technique that relies on the same principles as diagnostic ultrasound [3], but has been adapted for use in the palliative treatment of metastases. This modality leaves tumour-surrounding, healthy cells undamaged and minimizes side effects associated with treatment. Moreover, it is non-invasive, functions without ionizing radiation, has a relatively short procedure time, and can be more

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easily and willingly repeated than other treatments [4]. In 1942, high-intensity ultrasound beams were used in the first therapeutic trial but the technology did not progress much further due to a lack of real-time imaging as well as some physical barriers [3]. Recently, the field has greatly progressed with the development of systems such as Magnetic Resonance-guided HIFU (MRgFUS) and Ultrasound-guided HIFU (USgFUS), and these techniques have become practical modalities used to ablate tissues in solid tumours while simultaneously acquiring procedural measurements.

14.2 Development of HIFU

The development of HIFU began in the mid-twentieth century with the use of high-intensity ultrasound beams for treatment of neurological disorders in humans. Since then, HIFU has proven to be very effective in thermal ablation of solid tumours in the breast and prostate gland, and has continued to show promising results in the management of secondary tumours.

14.2.1 First Users of Ultrasound Therapy

It was known in the 1800s that the concept of piezoelectricity meant that charge could be generated when pressure was applied to a material. Transducers ultimately used in ultrasound imaging relied on reverse piezoelectricity and made use of the conversion between electrical energy and mechanical energy [5], permitting echo waves from responding tissues to provide diagnostic information. In 1938, Raimar Pohlman, who had developed an imaging method using acoustic lenses, demonstrated a therapeutic effect on human tissues using ultrasonic waves transmitted through acoustic lenses [5]. This was subsequently used to treat inflammatory conditions. These ultrasound waves, in the frequency region of 20 kHz to 2 MHz, were studied in 1942 to develop a technique known as focussed ultrasound [3]. Studied by John G. Lynn and Tracy J. Putnam in 37 animal models, high-frequency and short wavelength waves permitted the successful transfer of high doses of ultrasonic energy to brain areas with negligible damage to non-targeted tissue [5]. Interest in this continued when William and Francis Fry furthered this study in primate models by using a system of four transducers that delivered high-intensity focussed acoustic waves to confined tumour areas in brain ganglia. They noted a significant and lasting elevation of temperature in target tissues, with a minimal rise in temperature in surrounding cells [5]. This specificity proved to be one of the greatest advantages to ultrasound therapy and provided the motivation for further continued development.

Symptoms of neurological disorders, such as Parkinson's disease, have been treated using high-intensity focussed ultrasound. However, visualization of brain tissue and image-guidance of therapy was critical in order to ascertain the appropriate

clinical follow-up in patients, particularly when studying brain cortical regions beyond the cranium. A B-mode image-guided system was developed in the 1970s which allowed for two-dimensional visualization of ablation in cranial regions [5]. Since then, HIFU techniques were augmented in the 1990s with the combination of rapidly induced hyperthermia in tumour regions and image-guidance using advanced scanning techniques such as Magnetic Resonance Imaging (MRI) and Computed Tomo-graphy (CT). Image-guided investigations will be discussed further in Sect. 14.5.

14.2.2 Primary Tumour Ablation

A large number of clinical studies on primary solid tumours have conclusively demonstrated that HIFU ablation serves as a valid therapeutic option. Therapeutic trials have been completed on tumours in regions such as the breast, prostate gland, pancreas and liver, and studying these can have implications on our understanding of potential uses for HIFU in the treatment of metastatic sites.

One study treated over 1,000 patients in China with solid carcinomas using the HIFU system Chongqing Haifu [6]. The solid carcinomas included liver cancer, breast cancer, kidney cancer, pancreatic cancer and other primary malignancies. Feng et al. reported that within 1–2 weeks post-treatment, a distinct boundary was detectable in patients between the targeted and destroyed regions and viable tissue. The treated tissue included the tumour lesion, as well as a small 1.5–2.2 cm margin around the cancerous site. The visibility in follow-up images of a sharp boundary between damaged and viable cells has been a means of detecting the success of ablation. In another study using HIFU for treatment of hepatocellular carcinoma (HCC) after partial rib resection in 16 patients, complete tumour necrosis was achieved in 70 % of the lesions after the first HIFU treatment [7]. In the remaining lesions, HIFU treatment was performed a second time and complete tumour necrosis was visible in all tumours. Again, in a study of US-guided HIFU treatments in patients with advanced pancreatic cancer, eight patients' pain symptoms were completely stopped with either one or two treatment sessions [8]. The possibility of retreatment and the capability of one to two treatments to achieve clinical goals make this a feasible alternative to other modalities. Finally, in a clinical study described by Zheng et al. on HIFU as a safe therapy for HCC adjacent to major hepatic veins, all 39 patients achieved complete tumour necrosis despite the close proximity of the lesions to major hepatic blood vessels. In follow-ups 24 ± 17 months after treatment, no major blood vessel injury was noted [9]. Models studying acoustics and thermal energy in fluids have indicated that this could be due to convective heat transfer and dissipation of heat through blood flow away from the vessel wall [10]. The low vulnerability of blood vessels to HIFU treatment has allowed for its use near such. These advantages have justified the expansion of HIFU ablation for pain palliation of metastatic tumours.

14.3 Mechanism Description of HIFU

There are various technological changes that have been made recently to enhance ultrasound equipment in order to facilitate modern image-guided therapy. Standard hardware and software components are described in this section as well as the physical changes seen in tumour composition after treatment.

14.3.1 Hardware and Software Components

Equipment for HIFU requires a signal generator, a power amplifier and a transducer [11]. HIFU transducers vary geometrically and electronically. Transducers can be concave and self-focussing or can be flat with an acoustic lens on top. Transducers can also be manipulated electronically and can be configured by having multiple piston transducers on a spherically focussed bowl [3]. When multiple transducers are used, the relative phases of transducer elements are different; this system is known as a phased-array transducer. This permits the acoustic beams to be guided in different directions due to their varying phases, which also can correct for some of the problems associated with lenses such as spherical aberration and distortion at the focal point. The signal generator creates the frequency and initial amplitude of the signal, which is then amplified [11]. The transducer vibrates as a result of the produced electric field and generates ultrasonic, high-frequency beams that converge with a fixed focus at the site of the lesion [3]. Transducer focal lengths can range with common focal lengths of 90, 130 and 160 cm [12], and treatment areas are around 3 mm wide and 10–12 mm long [13]. While many conventional transducers are physically moved against the area of treatment, phased-array ultrasonic treatment modalities are electronically controlled and do not require physical sweeping of the transducer [3].

The transducers and imaging systems are connected to a computer for tumour targeting and positioning guidance. Thermal maps and dose maps are created, which permit real-time visualization and feedback. When temperatures or doses reach certain limits, this is visible on the monitoring system and heating can be stopped [14].

14.3.2 Principle of Operation

HIFU creates a quick rise in temperature when acoustic power is delivered [10]. The intensity of HIFU ranges from 100 to 10,000 W/cm^2 with compression pressures as high as 70 MPa and rarefaction pressures around 2 MPa [3]. The transducer permits, with electronic steering, the distribution of the energy over the external surface of the region of interest, but focuses the energy over a small area at the focal point so that tissue between the transducer and focal point remains undamaged [15].

Two major forms of tumour tissue damage can occur during treatment. The destruction of tissue and vasculature at the focal point and not in nearby regions is ideal, especially when treating regions of the body near the spinal cord. When tissue temperatures rapidly rise within seconds in the focal region, the destruction of the vasculature and cellular integrity occurs and necrotic lesions form; this results in irreversible cell death. The energy deposition is high enough to also cause protein denaturation, which can usually occur at temperatures higher than 43 °C [11]. Typically, during HIFU, temperatures above 56 °C for 1 s or temperatures of 65–100 °C for 0.5–1 s result in coagulative necrosis [16].

High-intensity focussed ultrasound can significantly disrupt the vascular elasticity and fibrin in tumour regions and can also result in mechanical effects such as acoustic cavitation [3]. Acoustic cavitation causes necrosis through a different means. Nonlinear, high-amplitude pressure oscillations occur when the acoustic power is deposited. This creates gas bubbles that contract and expand rapidly, resulting in localized heat formation and tissue damage [11]. The oscillation of these gas bubbles can also generate an effect known as microstreaming, in which viscous tissue fluid moves rapidly. Friction generated by these viscous layers moving past each other leads to further heating and can potentially damage cell membranes [17]. This form of cell death is less predictable and more unstable than that above.

14.4 Assessment of Clinical Studies

Bone is one of the most common target organs for cancer metastases, followed by lung and liver as metastatic sites [18]. Bone metastases frequently results in sclerotic or fractured bones, or asymmetrical vertebral body collapse [19]. It can lead to hypercalcemia—the release of calcium into the blood stream—if bone resorption occurs. When bone metastases affect the bone marrow, blood cell levels may become abnormal. This can lead to anemia due to loss of red blood cells, frequent infections during periods of low white blood cells, or unusual bleeding patterns due to a lack of platelets. One of the most prominent symptoms is malignant spinal cord compression, which occurs when the tumour squeezes the spinal cord [20]. Among the 500,000 people in the United States who die from cancer annually, 12,700 will suffer from malignant spinal cord compression [2]. Malignant spinal cord compression can result in motor weakness (76–78 % of patients), autonomic dysfunction (40–64 %), or sensory loss (51–80 %) [21] and can cause neck and back pain, numbness, or difficulties with walking and posture [20]. Cauda equina syndrome can be another outcome as nerves at the end of the spinal cord are compromised due to spinal cord compression. The following discussion quantifies and analyzes the use of HIFU ablation for spine and bone metastases by comparing three clinical studies.

Liberman et al. studied patients with bone metastases using MRgFUS [22]. Thirty-six procedures were completed on 31 patients; 11 out of the 31 patients' primary tumours were breast tumours and 18 out of the 31 metastatic sites were in the iliac bone, the uppermost pelvic bone. Spinal anesthesia was used during the

procedure and the ultrasound transducer was a phased-array system. Mean treatment times were 66 min, ranging from 22 to 162 min. The average energy per sonication was 1,135 J, ranging from 440 to 1,890 J, with the number of sonications averaging 17.3 (range 8–32). Results of the study concluded that patients showed a decline in pain sensations, with a visual analog scale mean baseline score of 5.9 at the beginning of the study, a mean of 3.8 3 days after treatment, and a mean of 1.8 3 months after the study ($p<0.003$). It was also noted that 67 % of patients reduced their opioid medication intake. This study suggests that the pain improvement could be due to denervation of local bone and a consequent reduction in pain sensation caused by heat denaturation of the periosteal layer, in addition to the reduction of pain-causing pressure by ablation of tumour tissue. This was suggested since bone absorption of acoustic energy is up to 50 times greater than soft tissue tumours. The lower thermal conductivity and higher absorption rate of bone permit the use of lower energy levels and destroys less periosteum. Twenty-five of the 31 patients participated in a follow-up assessment 3 months later and of these, 50 % reported a VAS score of 0, indicating that there was an equal partial and complete response in these patients. However, with a larger patient group and a longer follow-up time, further analysis could be completed with regard to pain palliation. While the source of the pain could be derived from various origins as the patients were ill with several metastases, the study was useful in determining whether or not some pain palliation can be possible from focussed ultrasound surgery.

A study reported by Li et al. compared the use of HIFU in 25 patients with malignant bone tumours at either primary or metastatic sites. The treatment was guided by B-mode ultrasonography and testing was conducted using biomarkers, contrast-enhanced MRI and PET-CT, both before and after HIFU treatment, using 99mTc-methane-diphosphonate (99mTc-MDP). Out of the 25 patients, five underwent two HIFU sessions each and two patients underwent three HIFU sessions each. The primary tumours (osteosarcomas) were situated at the femur, tibia, humerus, scapula, pubis and rib. The metastatic bone tumours had varying primary tumour sites such as hepatic sarcomas, lung sarcomas and colorectal sarcomas. The tumour blood vessels targeted had a diameter of less than 200 μm and the metastatic bone tumours had an average volume of 277.23 cm^3. Mean treatment time was 231 +/− 173 min, with a range from 28 to 648 min. In patients with primary bone tumours, 4–6 weeks of chemotherapy was administered prior to receiving HIFU treatment and 10–20 days following HIFU treatment patients received an additional 2–4 weeks of chemotherapy (intravenous methotrexate/vincristine, doxorubicin, and cisplatin). Adjuvant chemotherapy was given to patients with metastatic bone tumours if deemed necessary. Table 14.1 summarizes the findings.

Significant conclusions can be drawn from comparing the results of HIFU treatment on these primary and metastatic bone tumours. These findings indicate that patient ratings of pain significantly decreased after treatment and the majority of patients had either a complete or partial response as opposed to a moderate response, stable or progressive disease. It is noteworthy to point out that the overall response rate was 9.6 % higher when treating with HIFU on primary bone tumours than on metastatic bone tumours. Moreover, the 0 % survival rate 3 and 5 years

Table 14.1 Evaluation of HIFU on primary and metastatic bone tumours. Types of responses, long-term survival rates, and pain ratings on the VAS scale are documented (Modified from Li et al. [18] Complete response: tumours completely necrotic for >4 weeks; Partial response: tumour necrosis >50 % or decrease in lesion multiplication diameters >50 % and continued for >4 weeks; Moderate response: tumours >50 % necrotic or tumours decreased >25 %; Stable disease: decrease or increase in tumours <25 %; Progressive disease: new lesions developed or tumour increased >25 %)

	HIFU on primary bone tumours	HIFU on metastatic bone tumours
Response	Complete response: 6 (46.2 %)	Complete response: 5 (41.7 %)
	Partial response: 5 (38.4 %)	Partial response: 4 (33.3 %)
	Moderate response: 1 (7.8 %)	Moderate response: 1 (8.3 %)
	Stable disease: 0 (0 %)	Stable disease: 1 (8.3 %)
	Progressive disease: 1	Progressive disease: 1
	Overall response rate: 84.6 %	Overall response rate: 75.0 %
Survival	1-year: 100 %	1-year: 83.3 %
	2-year: 84.6 %	2-year: 16.7 %
	3-year: 69.2 %	3-year: 0 %
	5-year: 38.5 %	5-year: 0 %
Verbal Rating Score (VRS) for Pain assessment	Before treatment: 1.85 ± 0.69	Before treatment: 1.75 ± 0.97
	After treatment: 0.08 ± 0.28	After treatment: 0.17 ± 0.39
	$p < 0.01$	$p < 0.04$

following treatment to metastatic bone tumours differs, as expected, from the 69.2 % and 38.5 % 3 and 5 years after treatment, respectively, on primary bone tumours. With these treatments four of the metastatic patients developed a low-grade fever of around 37.5–38.4 °C, however, their body temperatures returned to normal within 3–5 days. In addition, 1–5 days following HIFU therapy, targeted areas showed swelling which disappeared entirely within 1 week after treatment. Prior to HIFU treatment, six patients were noted to have venous skin enlargement, but examination following treatment revealed that four patients were entirely asymptomatic, one patient displayed a decrease in swelling and one patient's symptoms remained unchanged. Four to six weeks after HIFU, responsive primary and metastatic tumours were cold lesions (on radionuclide scans) and displayed reduced contrast agent uptake.

In these treatments, the high absorption of tumour-laden bone and the lower chance of retransmission of acoustic energy results in a high efficiency in converting HIFU acoustic energy into heat. The uniform distribution of therapeutic dose created by HIFU and its ability to treat various tumour shapes expands its possibility to create necrosis in many different tumours. Overall, the use of HIFU on metastatic bone tumours did display improved symptoms and limb function. This study showed that the use of HIFU and chemotherapy might be synergistic, and similar to the first study, suggests that possible denervation at the periosteum contributed to the results, as well as reduction in tumour mass and spinal pressure.

A study documented by Gianfelice et al. used MRgFUS on 11 patients with a total of 12 metastatic lesions [23]. Here, patients had previously undergone chemotherapy

and radiation therapy, and the received HIFU treatment for pain and symptom reduction. In these patients with bone metastases, primary tumours existed in the breast, kidney, lung and liver, with breast tumour sites in 5 out of the 11 patients. Bone lesions treated included the ilium, scapula, clavicle and ischium, with 7 of the 12 lesions within the ilium. The number of sonications ranged from 12 to 18 and treatment time ranged from 28 to 103 min. Using a visual analog score pain scale, the mean score of 6.0 before treatment was reduced to a mean of 0.5 3 months after treatment, which is a decrease of 92 % ($p<0.01$). Pain was clearly reduced at 14 days and pain medication usage also declined. Seven patients no longer required use of analgesics, and the remaining four patients had a 50 % or greater reduction in analgesic use.

No serious adverse effects related to treatment were observed. All osteolytic lesions demonstrated some thinning of the nearby bone cortex, but no patients were noted to have severe cortical destruction. There was some necrosis noted in the medullary component of bones, which were attributed to the thinning of overlying bone, consequently decreasing its absorption and permitting the transmission of thermal energy to the inner bone. In order to assess the effect of repeat treatment, one individual underwent two separate HIFU treatments many days apart, and another had two adjacent metastatic sites treated in the same HIFU session. Repeat treatment showed no increase in morbidity or cumulative effects. It is important to note during procedures whether lesions are osteolytic or osteoblastic as this factor significantly contributes to the analysis of any post-treatment bone sclerosis and thus, the efficacy of HIFU.

Taken together, these studies contribute to the validation of HIFU as a non-invasive method of tumour ablation. Mean-treatment time was longer in the ultrasound-guided study than in either of the magnetic resonance-guided studies, and the lower end of these treatment ranges approximates the treatment time for radiotherapy [24]. The second study demonstrates that HIFU promotes longer survival in patients with primary malignant bone tumours as opposed to those with metastatic bone tumours, which should be taken into account when treating patients with differing stages of cancer. Studies of surgical resection show that this course of treatment better promotes long-term survival than HIFU in patients with bony metastases [25]. Although preservation of the integrity of the nervous system is one of the objectives when treating metastases, studies indicate that local denervation of the bone periosteum can reduce pain sensation. This contributes to greater pain palliation with HIFU as peristeal denervation occurs in conjunction with coagulative necrosis of the tumour region. Malignant bone tumours radically alter the integrity of cortical bone and result in differences between the acoustic characteristics of normal bone and tumour-affected bone, which must be taken into account when treating these tumours with modalities such as HIFU.

14.5 Image-Guided HIFU

Image-guidance is a critical component to treatments, at all stages of a patient's HIFU procedure. Real-time feedback is essential during sonications and the specifications of sonications can only be realized during patient-specific treatment with image-guidance

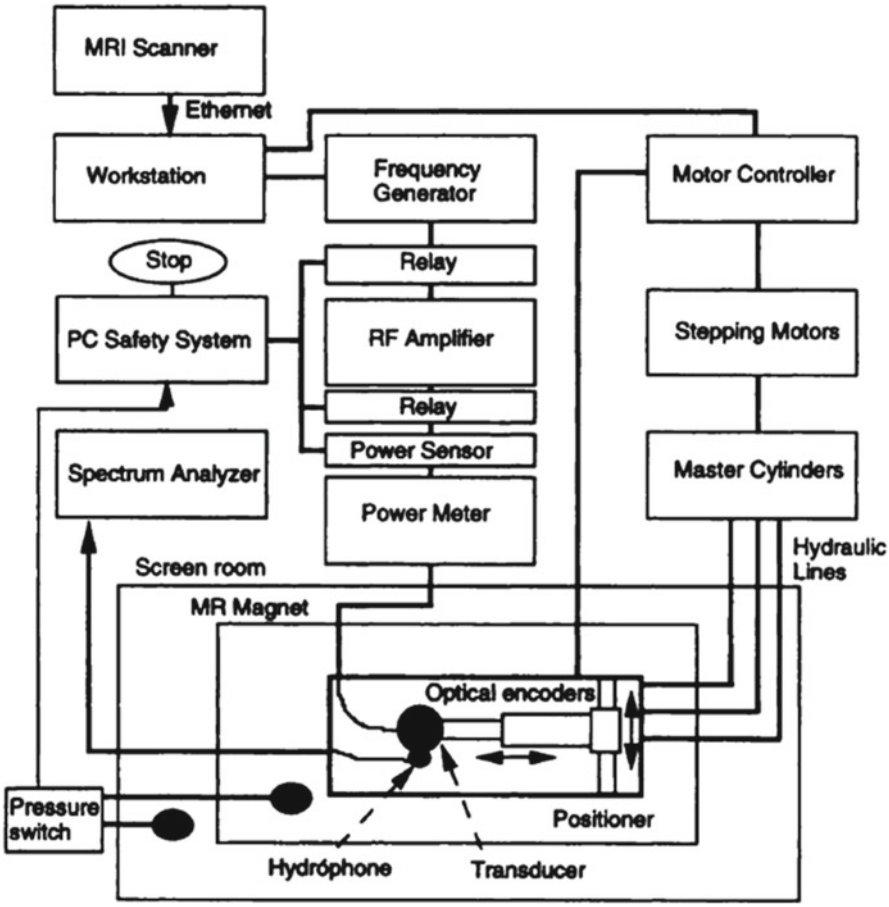

Fig. 14.1 Interaction of software and hardware components in an MR-guided HIFU system [61]

for genemetric and temperature-controlled feedback. Specifically, imaging is necessary pre-treatment for tumour evaluation and protocol planning, immediately before treatment for patient and system positioning, during treatment to monitor thermal effects, and post-treatment to evaluate the success of the treatment. This section outlines advantages and disadvantages of MR- and US-guided HIFU (Fig. 14.1).

14.5.1 Magnetic Resonance Imaging (MRI) Guidance

Imaging with MRI provides high anatomical resolution and high sensitivity in tumour delineation which allows for accurate treatment planning [26]. Magnetic resonance imaging –compatible ultrasound therapy transducers can be embedded in the patient MRI-tables to facilitate the use of the MR system. Transducers are often

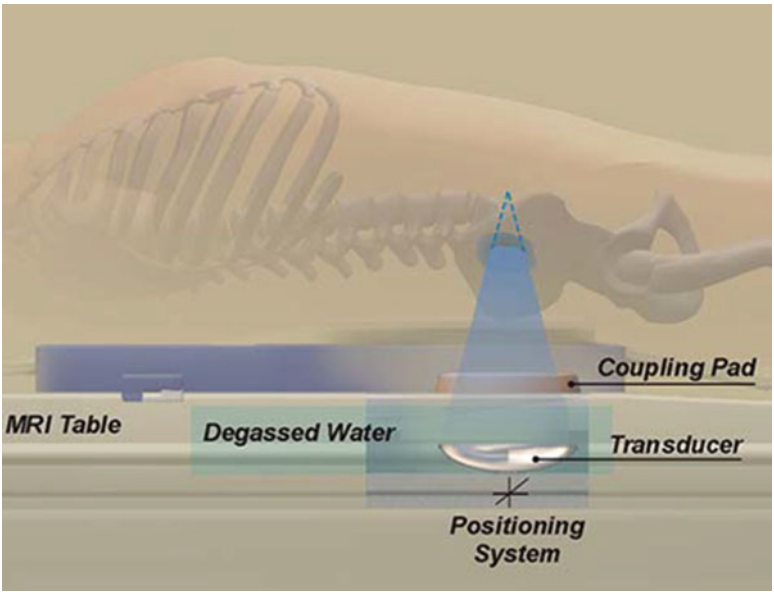

Fig. 14.2 MRgFUS system showing the transducer and the positioning system and the ultrasonic energy converging at the focal point. The transducer is embedded in the patient table to facilitate the use of MRI [22]

situated in water baths and coupled to patients via gel pads in order to eliminate the interference of the acoustic energy with air and increase the signal-to-noise ratio [23]. Transducers in MR-guided systems use piezo-composite materials to ensure MR compatibility with the magnetic field generated within the bore [27]. During MRgFUS procedures, transducer positioning is computer-controlled and is accomplished using a hydraulic system [28]. Linear actuators are hydraulically-driven and short pulses of pressure create motion that is step-wise and allows for precise transducer positioning [28]. MR images are taken during each sonication, which is a few seconds in duration, and then temperature and spatial maps are created and displayed. Processing of images, transferring of data, and the development of quantitative measurements often take about 10 s [28] (Fig. 14.2).

Guidance with MRI allows for beam path visualization as well as tumour targeting in the sagittal, axial and coronal planes [29]. Transient tissue temperature can be measured using MRI due to the relationship between applied power and the proton resonant frequency (PRF) [30]. Health care professionals using MRI-guidance with HIFU have been able to detect damage past the targeted tissue due to both linear (frictional) ablation and unstable, non-linear forms of ablation (cavitation and streaming) and to adjust treatment accordingly [31]. This can be imposed on anatomical MRI images to detect regions where cell temperatures have reached toxic levels and to assess tissue damage thresholds [26]. Magnetic resonance imaging can also effectively display the boundary between untreated regions and those with coagulation necrosis [12]. Although MR systems are expensive and the initial

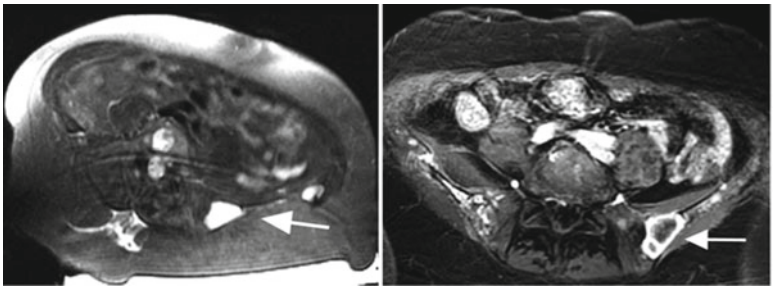

Fig. 14.3 A patient from the study done by Gianfelice et al. [23] contrast-enhanced T1-weighted MR images pre-treatment (*left*) and post-treatment (*right*) show the medullary component of the osteolytic metastasis of the *left* iliac bone and the necrotic lesion

apparatus can cost upwards of 1 million dollars [23], they provide immediate feedback during treatment permitting temperature and dose monitoring. Thermometry with magnetic resonance detects soft tissue temperatures around the targeted site, but the temperature of bone cannot be detected due to the lack of a PRF shift that is temperature-sensitive [22].

For the purposes of treatment, MRgFUS permits the shape of the focal volume to be modulated using spatial and temporal control [31]. Recent studies have shown an improvement in necrotic tumour volume by image-guided FUS as well as less energy propagation far from the target site, in comparison to regular sonications, with the energy level the same in both cases [31]. Magnetic responance-guidance allows for controlled, localized damage when treating tumours in close proximity structures that absorb large quantities of acoustic energy.

In the Liberman et al. study using MRgFUS on bony metastases[22], the phased-array Exablate® 2000 system by InSightec Ltd. (Haifa, Israel) was used in conjunction with a 1.5 T MRI scanner (General Electric, U.S.A.). Pretreatment MRI images were used to identify the targeted region. When patients were positioned on the tables, the position and sonication pathway were checked using T2-weighted (water-suppressed) fast spin-echo MR images. Patient treatment plans were personalized to eliminate damage to surrounding, non-targeted tissues. At the end of each treatment, T1-weighted (fat-suppressed) contrast-enhanced MR images were taken to ensure tumour ablation and minimal damage to surrounding tissues. Three months following treatment, T1- and T2-weighted MR images were repeated, showing no signs of long-lasting damage to the surrounding tissues. The successful results were confirmed in CT images taken 3 months later, which showed some calcification near the targeted tissues.

Gianfelice et al. reported the use of MRgFUS for painful bone metastases [23]. Unenhanced T1-weighted MR imaging and gadolinium enhanced T1-weighted MR imaging were completed prior to treatment (Fig. 14.3). Researchers said that this was completed to ensure that patients could be treated with MRgFUS and to create a baseline image when comparing treatment images. Images that were T2-weighted were taken on the treatment day, and T1-weighted imaging was completed

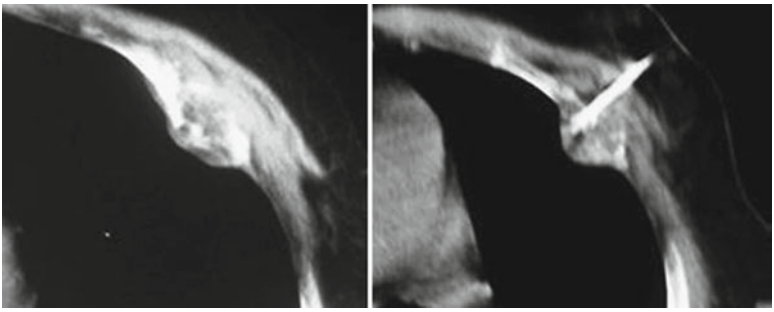

Fig. 14.4 CT scan image showing the needle electrode placement into a metastatic tumour site at the rib. [45]

1–3 months following treatment. These images demonstrated an average decrease of 49.8 % in tumour volume, from 33.3 cm^3 to 16.6 cm^3. Imaging completed 3 months after treatment on nine of the 11 patients indicated a tumour increase in one patient (14 %), no change observed in two patients (0 %), and a decrease in tumour size in six patients by an average of 44 %, compared to the 1-month study. Unenhanced CT-imaging in nine patients confirmed that five patients (56 %) had increased bone density at the site of their osteolytic metastases. In general, the constant use of MRI is not harmful to patients and provides results that are useful in studying tumour volume at all stages of treatment, delineating between cases with successful and unsuccessful ablation procedures.

14.5.2 Ultrasound (US) Guidance

Ultrasound-guided HIFU systems, such as Ablatherm and Sonablate devices, use ultrasonic transducers for both imaging and treatment. When soft tissues are heated, the resulting echo pulses of acoustic energy travel back to the transducer and are used for detection of tissue response. Hyper-echoes are detected in B-mode ultrasonography [14]. They are believed to be created either when tissues boil due to cavitation or from bubbles generated during cavitation at the focal point [29]. In addition, since HIFU destroys tumour cells and vasculature, forms of ultrasound such as Doppler ultrasound can be used to detect changes in blood flow (perfusion) that occur during tissue damage subsequent to HIFU treatment. This cannot be done with other forms of imaging such as MRI or CT [32] (Fig. 14.4).

Other versions of image guidance such as USgFUS are still under development as they do not directly provide information about thermometry or elastography. Pulse-echo ultrasonic guidance is not always useful for imaging thermal damage because the ultrasonic backscattering coefficients of the ablated and non-ablated regions are not significantly different [10]. Some studies have attempted to use microwave-induced thermoacoustic tomography (TAT), which uses non-ionizing radiation to

study the energy deposition in soft tissues. This imaging modality ideally produces images with high resolution due to the short wavelength of thermoacoustic waves as well as good contrast because of the differences in microwave absorption rates in various tissues [10]. Ultrasound-guided systems are relatively inexpensive compared to MR-guided systems and create high-resolution images, however they are still being modified as they do not confer all the advantages of other imaging modalities.

In a recent review [33], researchers compared studies in Chinese databases using USgFUS and MRgFUS on various benign and malignant tumours including bone metastatic sites. They concentrated on adverse events resulting from treatment and the extent to which these events depended on the site of the tumour and the system being used. Device-related side effects were not noted in the palliative treatment of bone metastasis with MRgFU. They noted that 21 % (46/224) of the patients with bone tumours that had received USgFUS had suffered adverse events, the most common being skin burns, fractures and nerve injuries ($p = 0.0003$). However, researchers attributed this to the location of the disease and the vulnerability of sensitive structures near the region of interest. More research is needed to determine the applicability of USgFUS to bone metastases.

14.6 Limitations and Risks Associated With HIFU

Some limitations associated with HIFU are related to the ability of various tissue types and organs to absorb acoustic energy. Acoustic energy cannot propagate through air- or gas-filled organs such as the bowel or lungs. Appropriate beam path planning and determination of an acoustic window is necessary in order to visualize the way in which acoustic energy will reach targeted tissues without suffering interference from other structures. Furthermore, patients can be anesthetized or given breath-hold devices so that organs do not move during treatment and alter the beam path [34], although anesthesia often increases the length of hospital stays [31]. Bone, cartilage, and other calcified tissues absorb large amounts of ultrasonic energy [31], thus appropriate thermal dose calculations must be made when studying the focal regions of targeted tissues for different patients [26].

One study developed a numerical model to conclusively demonstrate that due to convective cooling and acoustic streaming, the temperature buildup near large blood vessels can be smaller than that expected. Large blood vessels reduce the temperature at their boundaries and thus affect the lesion size and the volumetric shape of tissue affected by ultrasonic energy [35]. These factors must be taken into account when calculating expected results from thermal ablation.

As discussed in the clinical studies summarized earlier, patients are susceptible to certain side effects from HIFU treatment. A study conducted of patients who had undergone HIFU to bone tumours noted various side effects experienced as a result of the treatment including skin burns, local nerve injuries, fractures, infections, epiphyseal separation, alkaline phosphatase (ALP) elevation, hemoglobinuria or ruptures [33]. In a separate study by Li et al. [18], 12 patients were noted to have

suffered from first-degree burns which faded within 2 weeks; two patients reported second-degree burns which faded without scarring within 4 weeks after treatment, and; three patients were without sensation in the limb affected with osteosarcoma during HIFU treatment, but regained feeling following treatment. In addition, some patients experienced short-lasting fevers.

14.7 Comparison to Other Ablative Treatment Modalities

High-intensity focussed ultrasound has apparent advantages over some of the commonly used treatment modalities for bone metastases. HIFU is not limited by cumulative effects or tumour-resistance as is external beam radiation therapy (EBRT). Although EBRT is the standard of care, it delivers ionizing radiation to a patient with inevitable cumulative dose effects. Some tumours are radio-resistant, which is why EBRT has a success rate of 70–80 % [36]. Radiation has also been shown to induce nausea and vomiting in some patients [2].

Surgical interventions have been used in patients; however, invasive methods put the patients at risk of developing infections and are limited in their application for bony metastases. Other ablative techniques aside from HIFU have advantages and disadvantages that closely reflect those of HIFU. In order to permit comparison, this section discusses clinical studies in which radiofrequency ablation, cryotherapy, laser-induced interstitial thermotherapy and microwave ablation have been used for pain palliation for bone metastases.

14.7.1 Radiofrequency Ablation

Radiofrequency ablation (RFA) is a minimally invasive ablative technique used to eliminate cancerous cells. In percutaneous RFA, a needle electrode is inserted into the tumour and high-frequency, alternating electrical currents are passed through the electrode which generates heat and destroys the cancerous cells at the region of interest. Needle electrodes can be single electrodes or hollow electrodes that contain multiple retractable electrodes for treatment [37]. Target temperatures are around 100 °C and ablations last between 5 and 15 min [38]. Water-cooling systems are sometimes added to needle electrodes and thermocouples are used to monitor temperatures adjacent to lesion sites. RFA is completed with the assistance of MRI, US, CT or other forms of guidance but depends on electrode insertion. Table 14.2 and the following discussion explain the results and significance of clinical studies performed to assess the use of RFA on bone metastases.

In a study conducted by Kashima et al. [39], internally-cooled electrodes were used and real-time CT fluoroscopy was used to place needle electrodes in patients. If the maximum tumour diameter was greater than 3 cm, cement was placed near the lesion site to prevent fractures. The technical success of this trial, defined by the

Table 14.2 Summary of studies assessed that use RFA for pain palliation of bony metastases (Modified from [38–40, 42, 44, 45])

Study group	Bone metastases	Concurrent therapies	Pain palliation	Other commentary
Kashima et al. [39]	40 patients, 54 total bone metastases Mean maximum tumour diameter 4.8 ± 2.3 cm (1.0–12.0 cm)	Radiotherapy prior to RFA Cement placed if diameter >3 cm	VAS Baseline: 6.1 ± 1.5 Post-treatment: 1.8 ± 1.7 ($p < 0.001$)	Survival post-treatment 1-year: 34.2 % 2-year: 19.9 % 3-year: 10.0 %
Goetz et al. [38]	43 patients	74 % had received prior radiation 91 % previously taken opioids 70 % took opioids during RFA	41/43 (95 %) reported 2-unit drop on pain scale Mean worst pain of 7.9 (pre), 3.0 (12 weeks post $p < 0.0001$), 1.4 (24 weeks post $p = 0.0005$)	Median number of ablations per lesion was 3.0 (1–14) Average time per ablation was 11.7 min (1.1–52.5 min)
Belfiore et al. [42]	12 patients, 13 osteolytic metastatic lesions	One patient received cementoplasty post-RFA	BPI mean pain scores 1-year post-RFA Worst: 7.7 to 3.1 Avg.: 5.0 to 1.8	
Grönemeyer et al. [44]	10 patients, 21 unresectable, osteolytic spinal metastases	Four patients needed vertebroplasties (3–5.5 mL of polymethyl methacrylate)	VAS pain scale, 9/10 reported pain relief; 74.4 % average pain reduction Back-pain related disability reduced by average 27 %	CT- and fluoroscopic-guidance
Thanos et al. [45]	30 patients, total 34 osseous metastases Lesions 1–14 cm diameter; Mean of 3.9 ± 2.6 cm		19 out of 30 reported early pain reduction within first 24 h after treatment	Bone scintigraphy and spiral-CT for guidance
Callstrom et al. [40]	12 patients, 1 osteolytic metastasis each Lesions 1–11 cm	Prior radiation therapy and chemotherapy had failed	Mean worst pain pre-treatment 8.0, 3.1 4 weeks post-RFA ($p = 0.001$) Mean pain interference in activities: 6.6–2.7 4 weeks post-RFA ($p = 0.002$)	

correct placement of the needle electrode in the target tumour and successful completion of planned ablation, was 100 %. The 3-year survival rates and median survival lengths were low: 10 % and 17 months in the 12 patients with complete tumour ablation and 0 % and 6.5 months in 28 patients with incomplete tumour ablation ($p<0.04$). Kashima et al. suggested that prognosis depends greatly on the number of bone metastasis sites as well as the stage of cancer. Many of these patients suffered from advanced cancer and 57 % of deaths of this patient population resulted from intrahepatic lesions. Transient nerve injury was only noted in one patient out of 40 (2.5 %) and this was improved after 1 week, however, metastases continued to invade the patient's spinal cord. These researchers concluded that RFA is a safe therapeutic technique, but suggested that RFA is limited in its ability to ablate large tumour sizes and should perhaps be used as a part of a multidisciplinary approach. Callstrom et al. [40] agreed with this, suggesting that anti-osteoclast agents, bisphosphonates, chemotherapeutic agents or radiotherapy can have synergistic effects when used simultaneously with RFA.

In Goetz et al.'s multicenter study [38], researchers noted that one of the limitations of RFA is that the tip of the needle electrodes cannot spread out in osteoblastic metastases, thus metastases with an osteolytic component are best treated with this approach. Single ablations were performed on patients with lesions less than or equal to 3 cm in diameter, whereas multiple ablations were required for patients with lesions between 3 and 5 cm. For lesions greater than 5 cm, and the goal of treatment was to focus on the interface between bone and soft tissue. Opioid usage decreased at weeks 8 and 12 ($p=0.01$), but this was not persistent at 24 weeks. While the RFA pain reduction results are significant, the use of opioids in patients prior to and during treatment suggests that other techniques could be helpful when used in conjunction with RFA treatment. Adverse events including second-degree burns at the electrode grounding pad, transient bowel and bladder incontinence and fracture of acetabulum after RFA at an acetubular lesion were noted in three patients. Another multicenter study [41] which used image-guided RFA of bony metastases also stated that patients with painful metastases in the sacrum or presacral region are limited in their options. Ablation of nerves near these areas must be avoided in order to prevent bowel or bladder incontinence.

Belfiore et al. [42] had selection criterion similar to the RFA trials above, and was used when radiotherapy and common therapeutic methods failed. In their study, nine lesions were treated with a single needle and another four with expandable electrodes. Imaging in 9 out of 12 patients showed large necrotic areas involving the tumour-bone interface, however, not all of these necrotic areas covered the entire osteolytic areas. Whereas two cases were successfully re-treated, three lesions greater than 3 cm in diameter at the humerus, scapula and iliac wing were re-treated at 1 month and did not show satisfactory tumour-bone ablation; RFA could not be used to ablate large lesions and tumour volume changes treatable were constrained by the capability of the RFA electrode. Additionally, in this study, a patient with sacral metastasis from rectal adenocarcinoma was further stabilized by cementoplasty. Toyota et al. [43] also demonstrated satisfactory pain reduction when combining cementoplasty and RFA in 17 patients.

Grönemeyer et al. demonstrated similar results [44]. Neurological function in patients measured on the Frankel scale was maintained in nine patients and improved in one patient. Despite this, four patients needed vertebroplasties and 3–5.5 mL of polymethyl methacrylate was used in these procedures. As well, researchers concluded that RFA treatments needed to be re-started if irritation occurred during heating near the spinal cord or sympathetic nerves. Thanos et al. [45] had no complications in their study; however multi-tined electrodes were used for all lesions. Seven-array, 2–3 cm multitined electrodes were used for lesions smaller than 3 cm and nine-array multitined electrodes were used for larger lesions. Larger lesions required oncologists to either treat with an increased number of electrodes and/or longer periods of time of energy deposition, both of which can result in longer treatment times.

Radiofrequency ablation, similar to HIFU, is valuable in its ability to significantly reduce pain sensations in patients in early and late-stage disease, post-treatment. Treatment with RFA is a repeatable procedure that also allows for tissue diagnosis during treatment [46]. This type of ablation usually reaches tumour sites a few millimeters around the needle electrode, but is not feasible in reaching distal areas [47]. It is limited in the tumour volume it can ablate; microscopic tumours and very large lesions are both difficult to treat with this modality [37]. Oncologists and researchers have created strict guidelines for patient selection of this treatment, requiring that patients undergoing RFA treatment have a pain sensation of greater than or equal to 4 on a 0–10 scale, have one or two focal sites, cannot have osteoblastic metastases, and are usually non-responders to chemotherapy and radiation therapy [38, 44, 45]. Treatment with RFA should not be used if lesions are located within 1 cm of major nerves, the spinal cord, bowel, or bladder [41]. This technique has been generally used for pain palliation in conjunction with vertebroplasties and cementoplasties to further strengthen patient skeletons, and is mainly useful for pain relief after traditional standards of care have not been useful.

14.7.2 Cryotherapy

One of the first uses of cryotherapy for bone tumours was in conjunction with orthopedic surgery to achieve minimal loss of bone and function [48]. Cryotherapy for bone metastases involves the use of a hollow metal probe that is placed through the skin to reach the tumour site. Pressurized gas in the probe is rapidly expanded resulting in cooling to temperatures around −100 °C within a few seconds. Freeze-thaw-freeze cycles are used to ablate tumours at such low temperatures. The frozen area is called an ice ball, and complete cell death can occur within about 3 mm internally to the ice ball margin [41]. Cellular necrosis is said to occur through a variety of possible mechanisms including the formation of intracellular ice crystals, membrane disruption, vasculature failure, protein denaturation, and changes in electrolyte concentration. Thawing further allows ice crystals to combine and disrupt cellular integrity, leading to cell death [48]. Multiple probes can be placed in a parallel arrangement at the tumour periphery in order to completely cover the tissue-bone interface in the case of bone metastases, but this usually increases the procedural time. Cryoablation

Table 14.3 Summary of studies assessed that use cryotherapy for treatment of bone metastases (Modified from [49, 50])

Study group	Metastases	Concurrent therapies	Pain palliation	Other commentary
Tuncali et al. [49]	22 patients, total 27 unresectable metastatic tumours (17 soft-tissue metastases and 10 bone metastases) Mean lesion diameter 5.2 cm	One patient received intramedullary rods 1 week post-cryotherapy	Attained in 17/19 patients treated for pain	MRI-guidance with 0.5 T magnet All lesions adjacent to or surrounding a sensitive structure
Callstrom et al.[50]	14 patients with either 1 or 2 bony metastases 1–11 cm in diameter		Mean worst score 6.7 (pre) and 3.8 (4 weeks post) $p=0.003$ Mean pain interference with daily activities 5.5 (pre) to 3.2 (4 weeks post) $p=0.004$	CT-image guidance

is best performed with a well-insulated probe with a diameter of 11–17 gauge, and recently developed probes contain argon gas for freezing and helium gas for thawing [41]. Saline is sometimes used during treatments in order to prevent skin freezing. Care must be taken to minimize destruction of the bone cortex and periosteum. The following representative studies below used cryotherapy to treat bone metastases.

Tuncali et al. [49] achieved 89 % pain palliation and reported that cryoablation near sensitive structures such as major blood vessels is feasible and must be completed carefully in order to prevent adverse events. In only two patients, cryoablation of spinal and paraspinal metastases caused transient lower extremity tingling, numbness and weakness, which spontaneously resolved within 1 week. Some sensory deficits were noted after two presacral tumour sites were treated and these deficits were attributed to ablation of the sacral plexus branches. The patient in that study who received surgical placement of intramedullary rods was required to do so in order to stabilize bone and prevent fracture, post-treatment. Researchers also noted that MRI guidance was more useful than CT guidance because in CT images both tumour and ice balls are typically hypodense and not easily distinguishable. Guidance with MRI was also claimed to be more useful than ultrasound guidance because ultrasonic images cannot detect the entire circumference of the ice ball in one view, as can MRI. The report by Callstrom et al. [50] discussed their selection criteria and stated that patients chosen for treatment were required to have a 4 or greater on a BPI scale of 0–10 and be non-responders to conventional therapies. Pain palliation was successful, as seen in Table 14.3, and the eight patients who were prescribed

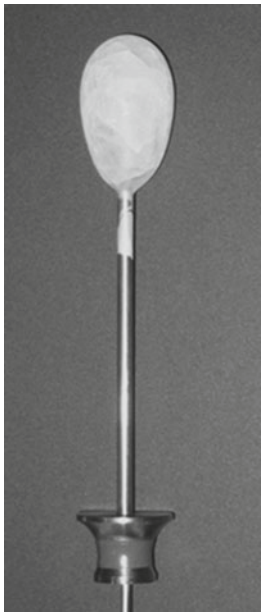

Fig 14.5 13-gauge cryotherapy needle with ice ball at the end [49]

narcotics prior to treatment noted a reduction in medication after cryotherapy. A direct correlation was noted between the number of probes and the size of the lesion; a mean of 2.8 ± 1.6 probes were used per treatment the larger the lesion, the greater number of probes used. Mean treatment time was 139 ± 53 min and with CT-guidance, treatment time was 185 ± 56 min. Callstrom et al. discussed that while the mean treatment time was 46 min longer in order to set up CT-guidance, CT images can be useful in showing the ice ball region and low-attenuating necrotic tissue (Fig. 14.5).

A final study on cryotherapy compared different forms of treatment for renal cell carcinoma with bone metastases. Kollender et al. [51] compared 29 cases of wide surgical excision, 25 cases of marginal excision and adjunctive cryotherapy using liquid nitrogen, and two cases of amputation. In treated patients, 91 % had significant pain relief and no difference in pain control, and function was noted in those with wide surgical excision versus those with marginal excision and cryotherapy. However, four lesions recurred; three within the lesions treated with marginal excision and cryosurgery and only one from a metastatic site treated with wide excision. Despite this, it was stated that cryotherapy is advantageous around weight-bearing joints as joint surfaces are preserved after treatment.

In general, ice balls created during cryotherapy are visible as low-attenuation regions in CT and MR images. Cryotherapy can treat lesions with larger diameters in a single session, such as 8 cm diameter lesions [41], relative to the small diameters treatable by RFA. Radio-frequency ablation and cryotherapy, similar to HIFU, are minimally invasive techniques that are not limited by cumulative dose effects, are useful in pain palliation, and should be considered in combination with other modalities.

14.7.3 Laser-Induced Interstitial Thermotherapy, Microwave Ablation, Alcohol Ablation

In laser-induced interstitial thermotherapy (LITT), the frequently used laser is Nd: YAG (neo-dymium yttrium aluminum garnet), with a wavelength of 1,064-nm, or laser diodes are used with wavelengths of 980 or 805 nm [52]. Necrosis occurs when heating is induced by a coherent, monochromatic Nd: YAG generated light that passes through a fiber-optic tip at the tumour site [53]. Cooled applicators are used as in RFA to prevent carbonization at the probe tip and to expand the diameter of the necrotic lesion [53]. Lasers operate at a power of 5–10 W for 10–15 min [54]. A study by Papini et al. used percutaneous laser ablation to treat two patients with unresectable bony metastases from thyroid carcinoma. One case had tumour 90 % ablated after two sessions of treatment and the other 80 % ablated after two sessions. Increase in performance status, tumour volume decrease 3 months post-treatment, and reduction in analgesics were all noted. Laser-induced interstitial thermotherapy works similarly to other ablative techniques and must be monitored for temperature control, tissue impedance, applicator positioning, and in order to minimize damage to nearby structures [52].

Microwave ablation is another form of percutaneous thermal ablation which uses electromagnetic waves with a frequency of around 1 GHz to create oscillations in water molecules [55]. As the water molecules align their dipole moments with an alternating electric field, tissue temperature rises, resulting in necrosis. Microwave ablation is advantageous over RF ablation because it not does require the use of grounding pads and has higher ablation temperatures and shorter treatment times [55]. Moreover, unwanted heating in major structures with high impedance is reduced because electrical currents are not used.

Percutaneous ethanol ablation is another method of percutaneous tumour ablation whereby needles are inserted into tumours and alcoholization causes dehydration and tissue necrosis. Vascular thrombosis and tissue ischemia also result which contribute to necrosis, and it has been suggested that this can also achieve pain palliation for bone metastases. Nonetheless, alcohol ablation is an unpredictable form of ablation due to a random distribution of ethanol when injected [56].

14.8 Future Directions

High-intensity focussed ultrasound and other thermally ablative techniques used to treat bony metastases represent innovative alternatives to the treatment of skeletal metastases. These techniques have been used primarily in palliative settings to control pain and also attempt to reduce the onset of further tumour growth in patients. Research continues in these fields in the hopes of enhancing both the technological and clinical aspects of thermally ablative modalities.

14.8.1 Technological Improvements

HIFU technology is being refined in its real-time imaging capability for anatomical guidance and thermometry, transducer design, and modes of energy transfer [3]. Adequate treatment monitoring continues to be developed in the areas of thermometry, elastography, and radiation force imaging [14]. Acoustic radiation force impulse (ARFI) imaging provides further information on the mechanical properties of tissue, more so than that provided by US-guidance [14], and may be useful for monitoring HIFU treatments. This modality functions because of the energy deposition in soft tissue when acoustic energy passes through it. This energy creates a transfer of momentum during wave reflection that acts in the direction of ultrasound propagation. The displacement of the soft tissue is known as the radiation force, which presents information to the user about tissue types [17]. *In vitro* animal studies on elastography have been completed and researchers have concluded that elastographic depictions of lesions are useful in studying types of tissue damage and the treated volume [57]. Further research is needed, incorporating both thermometry and elastography measurements in image-guidance.

Precise positioning of transducers and applicator probes is also required in order to adequately target the region of interest. Guidance with CT is often used in ablative techniques to guide percutaneous injection of needle electrodes and probes. Probes are continually becoming smaller and fiber-optic tips are on the order of a few hundred micrometers and are thus difficult to detect with imaging. Fiber stoppers can be used, but technological improvement in this field are currently underway in order to develop better forms of guidance for probe insertion [52]. Transducer technology is being improved upon and a more recently developed transducer type is known as a CMUT, a capacitive micromachined ultrasonic transducer. This type of transducer is created using silicon micro-machinery and changes in capacitance are what create signal transduction and were discussed in a study using MRgFUS, and appeared to allow for fabrication flexibility, diminished acoustic beam loss, and efficient beam transmission. Heating from CMUT's was monitored using MRI and heated a HIFU phantom by 19 °C in 5 mins. This transducer type is relatively new and is being tested on surfaces such as gel phantoms before being tried in clinical settings [58]. Phased-array ultrasonics are also useful in treating different regions of total tumour volumes without having to re-position the transducer, and this can reduce total treatment times. Similarly, transducers with annular arrays and cylindrical 2D arrays have been developed for experimental purposes to further study the alteration of the focal point during treatment without moving the transducer itself [59]. In addition, an *in vitro* and animal study was completed in 2010 to assess the use of a robotic system to setup the ultrasonic transducer to target a focal site [60]. New technologies still need to be tested in clinical settings and devices must gain approval before being introduced for therapeutic use.

14.8.2 Clinical Research

In theory, HIFU treatment of bone metastases promotes prolonged survival by reducing structural damage to the bone cortex and only ablating up until the tissue-bone interface. This minimizes bone destruction in comparison to widely invasive techniques such as surgery, and with minimal damage to the bone surface, HIFU allows for faster bone healing after treatment [36]. In spite of this, long-term survival rates in the studies discussed have been low and are in large part due to the advanced stages of cancer that patients are suffering from. Clinically, ablative techniques are being developed to determine ways to treat multiple metastatic sites but should also find better use as a primary treatment for tumours, minimizing surgery and radiation needed. Considerable work is also being done to determine how the effect of HIFU ablation can be enhanced when used with adjuvant radiation therapy, chemotherapy or cementoplasty [61–71]. The injection of microbubbles is also being studied as a novel way to augment the success of tumour ablation by increasing heating at the focal point [59].

Presently, HIFU, radiofrequency ablation, cryotherapy and other ablative modalities are useful in treating skeletal metastases, but are limited by technological and clinical constraints. These therapies are as useful as the ability of transducers and probes to cause significant thermal effects on tumours and can only be used with adequate guidance. As most of these bony metastatic sites are close to nervous system structures and important vasculature, serious negative repercussions can result if ablative techniques are unsuccessful. Further investigation is needed to deduce whether thermal ablation for the pain palliation of bone metastases produces adequate results on its own or concurrently with more standard forms of care.

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Chapter 15
Neuropathic Bone Metastases

Daniel Roos

Abstract Neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory part of the nervous system. Several validated instruments exist for its diagnosis and for assessment of response to treatment. Neuropathic pain is common in cancer patients, and may occur as a consequence of bone or soft-tissue metastases in the vicinity of nerve(s), although there is debate about the mechanism. There are limited data on the use of radiotherapy to palliate neuropathic pain of malignant origin in general, and due to bone metastases in particular. One randomized trial comparing a single 8 Gy with 20 Gy in five fractions for neuropathic bone pain (Trans Tasman Radiation Oncology Group, TROG 96.05) found no statistically significant difference in outcomes between the arms, and response rates were of similar magnitude to those observed for localized bone pain. However, further research will be required to determine whether higher doses are more effective.

Keywords Bone metastases • Neuropathic pain • Palliative radiotherapy

15.1 Introduction

Metastases in the vicinity of nerves may give rise to neuropathic pain. Neuropathic pain is defined by the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP) as pain arising as a direct consequence of a lesion or disease affecting the somatosensory part of the nervous

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system i.e. afferent, as distinct from efferent motor, or autonomic parts of the nervous system. The level of certainty with which a diagnosis of neuropathic pain can be made is graded as "possible", "probable" or "definite" based upon an algorithm with four criteria (plausible pain distribution, history suggesting a relevant index lesion or disease, sensory signs confined to the corresponding innervation territory, and confirmatory diagnostic tests) [1].

15.1.1 Clinical Features of Neuropathic Pain

Neuropathic pain is described by patients using various terms including burning, searing, tingling, shooting, stabbing or electric shock-like sensations, and may be associated with altered sensation along the course of the affected nerve(s) including paraesthesia, allodynia, hyperalgesia or hyposensitivity. It is experienced in regions innervated by the dermatomes of involved spinal (or cranial) nerves, or portions of these dermatomes innervated by peripheral nerves. Such pain is often described as intractable or opioid resistant and can be very disabling. It needs to be distinguished from "referred pain" from peripheral joints, which is perceived as deep rather than superficial, and is mediated by branches of nerves supplying both the joint and the muscles and bones acting about the joint e.g. hip pain radiating towards the knee [2].

15.1.2 Prevalence of Malignant Neuropathic Pain

The term malignant neuropathic pain here refers to neuropathic pain caused by a metastatic tumor mass arising in bone (neuropathic bone pain, NBP) (Fig. 15.1) or in soft tissue. There has recently been increasing interest in the clinical burden caused by this type of pain. A systematic review of studies published until 2010 concluded that its prevalence in over 11,000 patients with active cancer and who reported pain is conservatively 19 %, but up to 39 % if mixed nociceptive/neuropathic pain is included [3]. In a cross-sectional survey, Kerba et al. reported that 17 % of 98 patients referred to a Canadian comprehensive cancer center for palliation of bone metastases had pain with neuropathic features [4]. Another recent observational study found a 31 % prevalence of neuropathic pain among 1,100 patients with any kind of pain visiting 19 Spanish radiation oncology units. In three quarters of cases, the neuropathic pain was attributed to tumor, and in most of the others to treatment (surgery, radiotherapy or chemotherapy) [5]. Clearly, malignant neuropathic pain is a significant clinical problem, pharmacotherapy for which is addressed in Chap. 8.

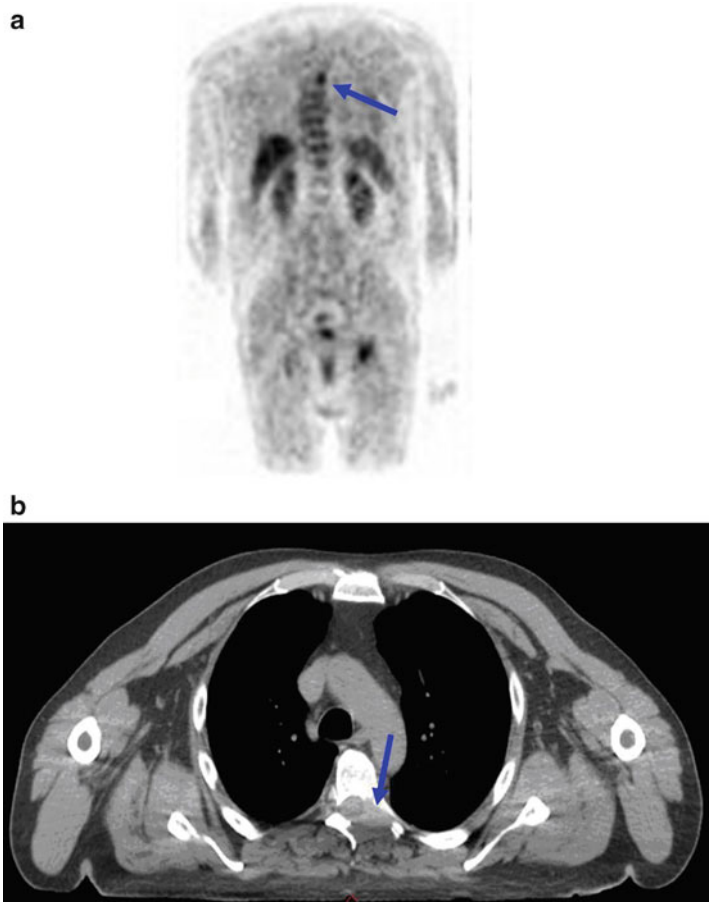

Fig. 15.1 A 60 year old male with known lung cancer developed left sided mid-thoracic back pain and paraesthesiae with dermatomal radiation around the chest wall to a level just below the left nipple. (**a**) Anterior view of a coronal PET section through thoracic spine showing focal uptake in the left side of the vertebral column. (**b**) Axial CT confirming a destructive bone metastasis in the region of the left T5-6 intervertebral foramen involving the exiting T5 nerve root and accounting for the patient's neuropathic bone pain. He was treated with palliative radiotherapy to this site

15.1.3 Pathogenesis of Malignant Neuropathic Pain

There is debate about whether this type of pain is due to mechanical pressure on nerves from the adjacent tumor, whether it is instead due to "chemical" irritation of nerves by cytokines elaborated by either the tumor or by host cells acting pathologically in response to the tumor (e.g. osteoclasts), or perhaps due to a combination

of both factors. The distinction is of more than academic interest. With the first hypothesis, higher doses of radiotherapy (RT) might be more effective in relieving neuropathic pain by inducing greater tumor shrinkage, whereas for the latter hypothesis, lower "anti-inflammatory" doses may suffice (as utilized for plantar fasciitis or thyroid eye disease, for example) [2].

15.2 Clinical Assessment Measures

Assessing the severity of NBP, and the response to treatment, are both complicated by the fact that there will generally be two components to the pain viz. *local* pain at the site of the bone metastasis and *radicular* pain corresponding to the dermatomal innervation territory of the involved nerve(s). It is possible that the two components may differ in severity at presentation, and also that they may respond differently to treatment.

15.2.1 Local Bone Pain

Local bone pain has generally been assessed by categorical pain scales e.g. none, mild, moderate, severe as used by the British Bone Pain Trial Working Party [6, 7] or by a 0–10 score such as the Brief Pain Inventory [8], taking into account concurrent analgesic use. Patients draw the site of pain on a body diagram, to hopefully verify that they are rating the index site rather than other site(s).

15.2.2 Neuropathic Bone Pain

With respect to neuropathic pain, instruments other than the above-mentioned new IASP criteria have been developed for *diagnosis*, including the Self-completed Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) [9]. This validated questionnaire sums the scores of seven symptom items such that a total score $\geq$12/24 suggests pain of predominantly neuropathic origin. However, neither of these were designed to assess *response* to treatment—they are unlikely to be sensitive to change as items are scored dichotomously (present/absent) only. Other pain instruments have been developed for that purpose. These include the Neuropathic Pain Scale (NPS) [10] and the Neuropathic Pain Symptom Inventory (NPSI) [11]. Note that all of these measures were developed from mixed populations with neuropathic pain of predominantly *non*-malignant origin (e.g. diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, trauma) and none have been validated for *malignant* neuropathic pain, per se, although it is plausible that they would be suitable for the latter also.

15.3 Radiotherapy Treatment

Radiotherapy for *local* bone pain has been the subject of numerous randomized trials and several meta-analyses (see Chap. 9). However, in nearly all of these trials, either *neuropathic* bone pain was explicitly (or implicitly) excluded, or those patients with a neuropathic component to their pain were not separately identified. Hence, the proportion of randomized patients who would be considered to have had NBP is unknown. The one possible exception was a British study which reported: "The likelihood and durability of pain relief in 84 [of 761] patients thought to have referred pain at presentation was not significantly different from that of patients without referred pain (data not shown)" [6]. Because these data were extracted retrospectively on the basis of apparently radiating pain drawn on to body diagrams, the proportion of patients with genuine NBP was thus uncertain.

15.3.1 Patterns of Practice

Surveys on patterns of practice for management of bone metastases have shown that radiation oncologists are more reluctant to employ single fraction treatment in the setting of NBP than for localized bone pain [12, 13]. This reluctance presumably relates to the belief that higher doses are needed for metastases directly contacting or compressing nerves. There may also be concerns about impending cord/cauda equina compression in view of proximity to the spinal canal.

15.3.2 The Neuropathic Bone Pain Trial

Only one study has specifically examined RT for NBP, Trans Tasman Radiation Oncology Group, TROG 96.05. At the time this trial was under development, there was no satisfactory working definition of neuropathic pain. The clinically unhelpful IASP definition was "pain initiated or caused by a primary lesion or dysfunction in the nervous system" [14]. For TROG 96.05, NBP was therefore defined empirically as pain or dysaesthesia radiating superficially along the distribution of peripheral nerve(s) compressed or irritated proximally by the presence of a bone metastasis in the vicinity of the nerve(s), often accompanied by sensory changes in the same dermatomal distribution. There needed to be plain x-ray and/or bone scan evidence of osseous metastasis(es) at the index site, although neither CT nor MRI were mandated—this trial was conceived and conducted in the conventional simulation era (without CT planning or routine availability of MRI), consistent with other bone pain studies at that time. It is interesting to note in retrospect, however, that this definition of NBP shared very similar principles to the revised IASP criteria described above, albeit without the formal "certainty" grading of the latter [1]. Similarly, none of the abovementioned neuropathic pain instruments were available at the time, and by default, the British pain chart was used (slightly modified) [6, 7]. There was no

attempt to separately score the severity of the local versus radicular pain components. Complete response was defined as improvement in pain score from severe, moderate or mild to none with no analgesia for the index pain; partial response was improvement in pain score by at least one grade (e.g. severe to moderate) with no increase in analgesia for the index pain. Treatment failure was defined as the first of any of the following events referable to the index site: increase in pain score by at least one grade and/or significant increase in analgesia; re-irradiation; development of clinical spinal cord/cauda equina compression or pathological fracture.

Between 1996 and 2002, 272 patients from Australia, New Zealand and UK were randomized to a single 8 Gy (8/1) versus 20 Gy in five fractions (20/5). The commonest primaries were lung (31 %) and prostate (29 %) and 89 % of patients had spine as the index site. On the basis of extensive quality assurance auditing undertaken throughout the trial in order to assess compliance with the eligibility criteria and treatment protocol, it was concluded that NBP was being correctly identified (only three patients were deemed probably not to have genuine NBP). Major dose violations were uncommon (6 % of cases) [2, 15, 16].

The main outcomes were as follows: There were no statistically significant differences between the arms in intention-to-treat overall response rates within 2 months of commencing treatment (53 % for 8/1 vs. 61 % for 20/5, $p = 0.18$), nor in complete response rates (26 % vs. 27 % respectively, $p = 0.89$), or median time to treatment failure (2.4 months vs. 3.7 months respectively, $p = 0.056$). There were also no statistically significant differences in the rates of re-treatment, cord compression or pathological fracture at the index site by arm [2].

15.3.3 Clinical Implications

That the results were very similar for 8/1 and 20/5 argues against the "tumour shrinkage" hypothesis, mirroring the situation with uncomplicated (local) metastatic bone pain where meta-analyses have confirmed equivalent intention-to-treat response rates of ~60 % for (low dose) single fractions and (higher dose) fractionated schedules (see Chap. 9). On the other hand, because most outcomes were numerically slightly in favour of 20/5, the authors concluded that it may be reasonable in general to recommend 20/5 for NBP. However, for patients with short expected survival (e.g. poor performance status and/or non-breast/prostate primary), the added cost and inconvenience of fractionation may not be offset by clinical benefit. In addition, 8/1 would be a reasonable option in centers with long waiting times for fractionated treatment.

15.3.4 Radiotherapy for Neuropathic Pain of Soft-Tissue Origin

Of course, malignant neuropathic pain does not necessarily have to be associated with *bone* metastases. Common examples include painful brachial plexopathy from

breast cancer metastatic to supra-clavicular nodes, or sacral plexopathy from pre-sacral involvement by rectal cancer. Perineural infiltration from head and neck cutaneous or mucosal primaries can also cause malignant neuropathic pain (trigeminal neuralgia). However, surprisingly at the time of writing, there appear to have been no randomized trials, nor even any systematic study of RT specifically for neuropathic pain in the extra-osseous setting despite the abovementioned high prevalence of malignant neuropathic pain.

15.3.5 Future Directions

Diagnostic criteria, pain instruments, 3-D imaging and RT planning and technology have all moved on considerably since TROG 96.05. However, the question remains as to whether doses higher than 20/5 may be more effective for NBP, and clearly, further randomized data are needed [17].

Experience from a second trial proposed by Canadian researchers in 2011 may inform any future investigation. After a survey of potential international collaborators at the time identified considerable divergence of opinion about the appropriate trial question and format, it was decided to initially evaluate the use of the IASP criteria and S-LANSS to identify eligible patients, and the NPS and NPSI instruments for response assessment (see Sect. 15.2.2). The plan was to then proceed with a randomized Phase II pilot trial using a mixed control arm of 8/1 *or* 20/5 (pre-specified by center) versus 30/10 as the experimental arm. The study would mandate CT or MRI of the index site in order that the anatomical relationship between tumor and involved nerve(s) could be assessed at presentation and follow-up. Subject to viability and results of the pilot, a randomized phase III trial would be undertaken aiming to answer the dose question definitively. Preliminary observations suggested that the above generic neuropathic pain instruments may not translate readily to NBP (personal communication). However, in the meantime, lack of local Canadian infrastructure, competing clinical demands and equivocal international support eventually rendered the project non-viable. It was abandoned in 2013, and the question remains unresolved.

There is also need for prospective evaluation of palliative RT for malignant neuropathic pain of soft-tissue origin.

15.4 Summary

There are very limited data on the role of RT for malignant neuropathic pain. One randomized trial on neuropathic pain due to bone metastases (8/1 vs. 20/5) showed response rates of similar magnitude to those observed for localized bone pain, but leaves open the question of optimal dose fractionation.

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Chapter 16
Spinal Cord and Cauda Equina Compression

Ernesto Maranzano and Fabio Trippa

Abstract Metastatic spinal cord compression (MSCC), diagnosed in 3–7 % of cancer patients, is a dreaded complication of metastatic cancer which must be diagnosed early and treated promptly to avoid progressive pain, paralysis, sensory loss and sphincter dysfunction in the patients. Magnetic resonance imaging is the best tool for diagnosing MSCC. Radiotherapy (RT) remains the treatment of choice in the majority of cases whereas surgery is advised only in selected patients. Hypofractionation schedules are safe and effective in MSCC. Although the most appropriate RT fractionation schedule remains unclear, many studies have shown that the choice of treatments should be matched to the prognosis of affected patient. When diagnosis of MSCC is made, steroids are generally prescribed to control edema and lessen pain. New techniques such as radiosurgery and stereotactic RT may be of benefit in high selected patients, including those with recurrent MSCC.

Keywords Bone metastases • Spinal cord compression • Cauda equina compression • Diagnosis • Surgery • Radiotherapy • Steroids • Stereotactic radiotherapy

16.1 Definition and Incidence

Metastatic spinal cord compression (MSCC) is one of the most dreaded complications of metastatic cancer. Its natural history, if untreated, is progressive pain, paralysis, sensory loss, and sphincter incontinence in patients. Although MSCC can be classified as intramedullary, leptomeningeal and extradural, in clinical practice extradural compression is the most frequent event. Moreover, several studies have shown that

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MSCC occurs at multiple non contiguous levels in 10–38 % of cases and the tumor is usually located in the anterior or antero-lateral spinal canal [1].

The definition of MSCC has changed over the last few decades and has both clinical and radiographic criteria and encompasses the anatomy of the cord as well the cauda equina. The Princess Margaret Hospital of Canada defines MSCC as: "compression of the dural sac (spinal cord and/or cauda equina) and its content by an extradural tumor mass. The minimum evidence for cord compression is indentation of the theca at the level of clinical features (i.e., local or radicular pain, weakness, sensory disturbance, and/or sphincter dysfunction)" [2]. Autopsy studies suggest that approximately one third of patients with solid tumors may have metastases to the spine, but the clinical evidence of MSCC is estimated in 3–7 % of patients. Approximately 50 % of MSCC cases in adults arise from breast, lung, or prostate cancer, but has also been described in patients with lymphoma, melanoma, renal cell carcinoma, thyroid carcinoma, sarcoma, and myeloma. In children the most common tumors are sarcoma, neuroblastoma and lymphoma. The most frequently involved site is the thoracic spine (59–78 %), followed by the lumbar spine (16–33 %) and the cervical spine (4–13 %) [3, 4].

16.2 Physiopathology

In the majority of cases, vertebral body metastases can produce spinal cord or cauda equina compression in two ways. The first results from continued growth and obliteration of the marrow space with expansion into the epidural space, producing impingement on the anterior thecal sac and its surrounding venous plexus. Alternatively, destruction of cortical bone by the tumor can result in vertebral body collapse with posterior displacement of bony fragments into the epidural space and epidural venous plexus. The pathophysiology of MSCC is vascular in nature because the compression of the epidural venous plexus leads to venous stasis, consequent hypoxia, and increased vascular permeability. This edema impairs spinal cord function which results in weakness and sensory impairment. In more advanced stages, the increased interstitial edema combined with progressive direct physical pressure on the spinal cord by the expanding mass, ultimately leads to ischemia of white matter and permanent neurologic loss [5].

16.3 Clinical Presentation

Spinal cord and cauda equina compression, once established, is usually highly symptomatic (Table 16.1). Pain is the most common symptom and accompanies in approximately 95 % of adults and 80 % of children with MSCC, and usually precedes the diagnosis by days to months [6]. Classic pain syndromes that affect patients were: local, mechanical, and radicular.

Table 16.1 Clinical symptoms and signs in spinal cord and cauda equina compression

Symptoms/signs	First symptom (%)	Symptom at diagnosis (%)	Sign at diagnosis (%)
Back pain	96	96	63
Weakness	6	76	87
Anomalies of reflexes	0	0	65
Autonomic dysfunction	0	57	57
Hypoesthesia	1	51	78
Ataxia	2	5	7

Local pain (i.e., back or neck pain) depends on expansion, destruction, or fracture of the involved vertebral elements and radicular pain is caused by compression of the nerve roots or cauda equina. Several characteristics distinguish it from the pain of degenerative joint disease. The first may arise at any level, whereas the second one rarely occurs outside the low cervical or low lumbar spine. It is usually described as a persistent "gnawing" emanating from the region or segment of the spine affected by metastatic disease. It is hypothesized that growth of the metastatic tumor, most commonly located in the posterior vertebral body, leads to periosteal stretching and/or a local inflammatory process that stimulates the pain fibers within the spinal periosteum Recumbence alleviates the pain of degenerative joint disease but frequently aggravates that of MSCC. Usually, this pain respond to steroids administration [7].

Mechanical pain, also known as axial back pain, is aggravated with movement, activity, or simply increasing weight-bearing forces on the spinal segment affected. Metastases that result in vertebral body damage (e.g., deformity, collapse) may result in spinal instability, which likely results in muscle, tendon, ligament and/or joint capsule strain and ensuing symptoms of mechanical pain. Unfortunately, such discomfort is usually refractory to narcotics and steroids [8].

Radicular pain may occur when vertebral metastases compress or irritate a nerve root, yielding pain in the dermatomal distribution of the involved root that is often described as "shooting," or "stabbing." Interestingly, dysesthetic/neuropathic pain may also arise when patients possess intradural extramedullary disease, creating pain that may be described as an "intense burning" sensation [7-9].

Neurological symptoms are common in patients with MSCC and weakness is the second most common symptom at presentation, usually follow the development of local or radicular pain and generally progress to plegia over a period of hours to days [3, 10]. Other symptoms of MSCC are sensory loss and incontinence, which typically develop after the pain.

Urinary retention, a common occurrence in patients who receive narcotics, is an atypical presentation without spinal pain or neurologic signs [1, 3]. Neurological status at the time of diagnosis, particularly motor function, has been shown to correlate with prognosis for these patients, thus reinforcing the concept that early diagnosis and prompt therapy are powerful predictors of outcome. Sensory disturbances such as anesthesia, hyperesthesia, and/or parasthesia typically occur in correlation with motor dysfunction. In this way, patients with radicular pain or weakness may also complain of sensory abnormalities in the same dermatomal distribution, while patients

with myelopathy may elicit a sensory level across the chest or abdomen. Particularly, patients with MSCC of the thoracic cord may present complaining only of discomfort around the chest, described as if they were being restricted by a "tight shirt" or "corset."

16.4 Diagnostic Work-up

Initial evaluation should begin with a detailed medical history, clinical examination, and directed laboratory tests. Assessment and documentation of bowel/bladder function, motor weakness, and sensory deficits are critical. The imaging armamentarium available includes plain radiography (RX), computed tomography (CT), magnetic resonance imaging (MRI), bone scan (BS), single-photon emission CT (SPECT), and positron emission tomography (PET). In the setting of complete subarachnoid block, myelography may increase the risk of neurologic deterioration.

Radiography can be a first tool as a screening test, by revealing lytic or sclerotic areas of bone, and vertebral deformity [11]. Bone destruction and substantial sclerosis are reliable indicators of metastases. However, vertebral body collapse can be associated with non-neoplastic lesions in up to 22 % of cases [17] and in approximately the half of examines these lesions can be missed on RX alone [11].

Computed tomography with 3-dimensional reconstruction provides excellent detail of the bony anatomy of the spine. Also, CT angiography can visualize the vertebral arteries in the foramen transversarium and as they enter the cranium, which assists surgical decision making and patient safety [12]. The angulation, rotation, and overall instability of a fracture, the extent of erosion of the vertebral body, pedicles, and posterior elements, and the degree of osteoblastic canal compromise are well visualized on CT.

Magnetic resonance imaging is considered the gold standard imaging modality for assessing spinal metastatic disease. It is more sensitive than standard radiographs, CT, and BS in detecting metastatic lesions in the spine [13]. Such sensitivity is due to the fact that MRI allows for superior resolution of soft-tissue structures such as intervertebral discs, the spinal cord and nerve roots, meninges, and paraspinal musculature. Moreover, considering that more than 85 % of patients have multiple-level involvement, MRI can show multiple levels of cord impingement in one examination. It is worthy to note that MRI diagnoses MSCC in 32–35 % of patients with back pain, bone metastases, and a normal neurologic examination [14]. In the pre-MRI era, myelography and CT were the imaging modalities of choice for the diagnosis of MSCC, and CT remains the best exam when MRI is not available. MRI has a sensitivity of 93 %, a specificity of 97 %, and an overall diagnostic accuracy of 95 % in detecting MSCC [4]. The advantages of MRI include its noninvasive ability to image soft tissue anatomy in detail, its ability to image multiple levels of cord impingement in one examination, and consequently, its usefulness in planning local treatment.

Nuclear imaging include BS, SPECT, and PET; BS is the oldest technique and almost 50 % of its results are false-negative for bone metastases, particularly in case

of vertebral medullary space involvement [15]. Moreover, BS does not accurately distinguish between pathologic and non-pathologic fractures. The PET is now more commonly used for whole body metastatic surveys and as a staging technique in patients with known systemic cancer. A recent comparison of BS, SPECT, and PET found that PET was as accurate as MRI [16]. However, poor spatial resolution necessitates concomitant use of CT and because of limited availability, resources, and study evidence SPECT and PET are not part of the standard evaluation.

16.5 Prognostic Factors and Survival

Prognosis is above all related to early diagnosis and therapy. Clinical risk factors for patients with suspected MSCC must be specific and sensitive for complete patient management. Back pain, an early and sensitive indicator of MSCC, is a non specific symptom, whereas signs consistent with actual spinal cord injury as weakness, paresis and plegia are more specific, but once they become evident the neurological outcome may be poor regardless of treatment. Many clinical variables are reported as prognostic factors for patients' post treatment ambulatory function and survival, but early diagnosis and prompt therapy are powerful predictors of outcome. In fact, MSCC patients able to walk and with a good sphincter function at the time of diagnosis have a higher probability of remaining ambulant and of a longer survival after treatment [3]. Favourable or radiosensitive cancers (i.e., breast and prostate carcinomas, myeloma and lymphoma) rather than unfavourable or less radiosensitive cancers (i.e., lung, bladder, and kidney carcinomas) are also significantly associated with a better outcome [17]. There could be various reasons to explain the better prognosis related to so called favourable histologies: (i) the better natural history, (ii) the higher response rate in presence of paraparesis or paraplegia and/or sphincter disturbance, (iii) a slower development of motor deficits before radiotherapy (RT), (iv) the longer interval between diagnosis of the primary malignancy and occurrence of MSCC. All these characteristics related to tumors with favourable histology were described as predictive of a better, functional outcome. Although Barcena's review reported location of tumour within the spinal canal, general medical status of the patients, and therapy used, as factors potentially determining functional prognosis in patients with MSCC, no other prospective published trials has shown the importance of these factors [18]. Some authors showed that patients with bone fracture greater than 50 % at the level of spinal cord compression had a poor response to RT compared to patients who had a less than 50 % compression fracture. However, considering that no studies reported the patient pretreatment motor status, no firm conclusions can be drawn [19, 20]. Nevertheless, the presence of vertebral body collapse is not an important prognostic variable if treatment selection is accurate (i.e., surgery before RT when there is bone impingement on the cord or nerve roots, and/or when stabilization is necessary) [19, 20] (Table 16.2).

The speed of neurologic deficit onset can condition functional outcome which is significantly better with slower development of motor dysfunction before RT.

Table 16.2 Prognostic factors of metastatic spinal cord compression

Major:
Early diagnosis and prompt therapy
Minor:
Post-treatment motor function
Tumor histology
Response to steroids
Performance status
Time from diagnosis of the primary tumor to appearance of spinal cord compression
Time from development of motor deficits to treatment

One study evidenced that ambulatory recovery occurred in 86 % and 35 % of patients with a history of >14 days compared with 1–7 days, respectively [20]. Early detection and treatment when the patient is still able to walk result in the highest chance of ambulation. In MSCC the aim of treatment is to improve the patients' quality of life through control of back pain and preservation or recovery of motor and sphincter functions. Although it could be questioned whether local treatment increases patients' survival, there is a tight relationship between survival time and functional status. In fact, MSCC patients who have no motor dysfunction live longer than paraparetic and paraplegic ones, and generally die of systemic tumors rather than local progression at the spine.

Survival after MSCC is principally related to primary tumor type ranging from 17 to 20 months for breast, prostate and myeloma to only 4 months for lung cancer [21]. If untreated, the majority of patients with MSCC become paraplegic with a median survival time of 2–3 months [22].

16.6 Treatment

As already highlighted, treatment success is related to the severity of the epidural disease and to the patient's clinical condition at the time of diagnosis, it is important to confirm diagnosis early and to begin treatment before significant myelopathy develops. Treatment of MSCC can be surgery followed by RT or RT alone. The choice of treatment depends on patient selection according to specific factors reported in Fig. 16.1 and discussed below. When a diagnosis of MSCC is made, the first intervention is generally steroids to control edema and lessen pain.

16.7 Surgery

Surgery plays an important role in selected cases. Patchell et al. published the results of a trial that randomized patients to surgery and post operative RT or RT alone [23]. The study aimed to recruit 200 patients was prematurely closed because an interim

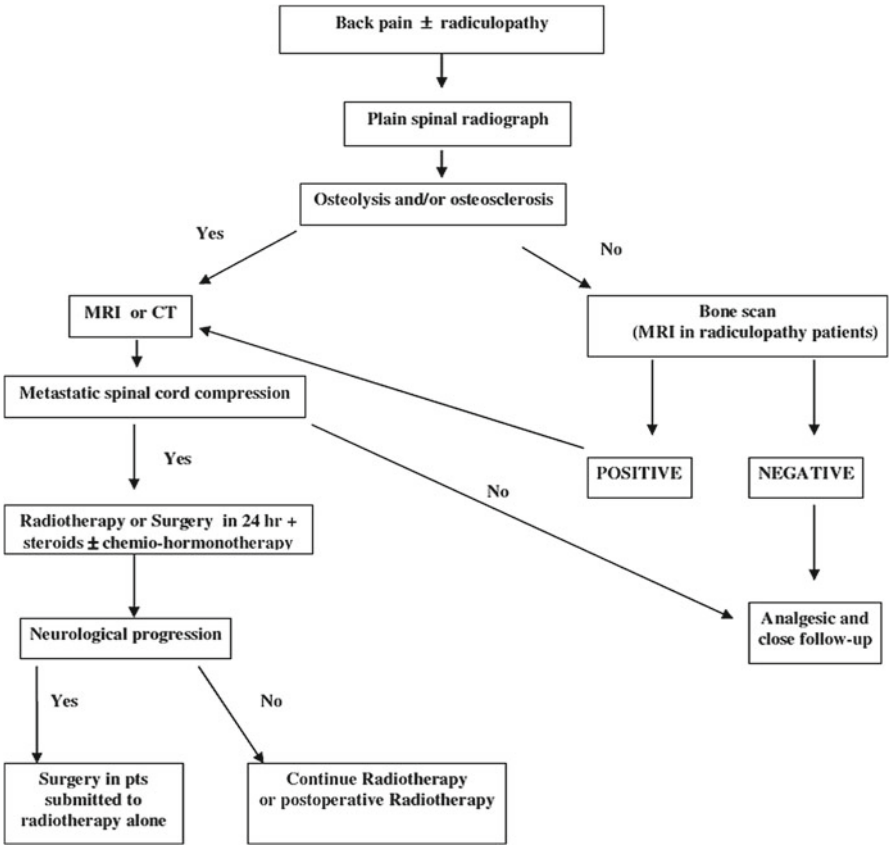

Fig 16.1 Flow chart of early diagnosis and therapy in patients with metastatic spinal cord compression (Legend, *MRI* magnetic resonance imaging, *CT* computed tomography)

analysis showed a significant improvement in ambulatory rate in the combined surgery and RT arm. The published results are therefore based on 101 patients accrued from seven centres over a 10-year period with 70 of the patients recruited from one centre. The study has been criticized because of the poor results in the RT-alone arm which contrast with published RT data and, furthermore, since mechanical causes of cord compression were not stipulated as an exclusion criteria, some patients may have been treated inappropriately with RT alone [2, 24]. A secondary data analysis of this study published in 2009 looked at age stratification and demonstrated a tight interaction between age and treatment effect, such that as age increases, the benefit of surgery is diminished. Statistical analysis showed that there was no difference in outcome between treatments for patients aged 65 years or more [25]. A meta-analysis of surgery versus conventional RT for MSCC published in 2005 identified 4 RT and 24 surgical trials involving 578 and 1,020 patients, respectively. Resected patients obtained a better recover ambulation (85 % vs. 64 %) and pain control (90 % vs. 70 %)

respect to RT alone. No prognostic and predictive factors were adjusted in this analysis [26]. However, the surgical data used in this meta-analysis contain primarily uncontrolled cohort studies and preceded the Patchell et al. publication. Conversely, an analysis performed retrospectively on 122 patients treated with surgery followed by RT matched 11 known prognostic factors to 244 patients submitted to RT alone found that treatment approach had no impact in any of the outcomes examined (i.e., improvement in motor function, post-treatment ambulatory rates, recovery of ambulation among nonambulatory patients, 1-year local control and 1-year overall survival [27].

Recently a systematic review, which analyzed data published from 2004 to 2011, concluded that surgery can be considered for patients with a good prognosis who are medically operable, and technical factors that allow proper fixation/stabilization need to be considered for any surgical technique adopted [28].

Finally, on the basis of the literature evidence, it can be concluded that initial surgical resection followed by RT should be considered for a carefully selected group of patients that are affected by single-level MSCC and neurological deficits and controlled or absent primary and metastatic disease elsewhere. Other possible indications for surgery include stabilization, vertebral body collapse causing bone impingement on the cord or nerve root, compression recurring after RT, and an unknown primary requiring histological confirmation for diagnosis. Nevertheless, when there are diagnostic doubts, CT-guided percutaneous vertebral biopsy can be an alternative to open surgery to avoid surgical side effects, and reduce incisional pain and postoperative recovery period.

Regarding surgical approach, laminectomy should be abandoned and every effort should be made to minimize the surgical toxicity assuring an adequate decompression and a spinal stability. In fact, laminectomy does not remove the tumoral mass and, when there is vertebral body collapse, it may also cause post surgery spinal instability. Generally, RT must be administered 7–10 days after surgery, either after no grossly complete resection or as an adjuvant treatment after a macroscopic radical ablative surgical procedure [1, 28].

16.8 Radiotherapy

Although RT is an effective approach for the majority of MSCC patients, the optimal radiation schedule remains unknown. Except for particular circumstances, the use of conventional fractionated RT (2 Gy per day to a total dose of 30–50 Gy in 3–5 weeks) has been abandoned in favour of RT regimens requiring a smaller number of fractions. Since 2005, two phase III randomized multicentre Italian trials have been published [29, 30]. The first trial compared a short-course regimen (i.e., 8 Gy repeated after 1 week to a total dose of 16 Gy) to a split-course regimen (i.e., 5 Gy × 3, 4 days rest and then 3 Gy × 5) [29]. The second one compared the same short-course regimen to 8 Gy in a single fraction [30]. It is worthy to note that both of these trials were performed on patients with short life expectancy (≤6 months),

and that responders maintained function until death. While both hypofractionated RT regimens adopted resulted effective, the authors concluded that 8-Gy single fraction can be the best option considering that it is well tolerated, effective and convenient in this setting of patients. Published retrospective and prospective non randomized studies support the above randomized data in that no dose-fractionation schedule has demonstrated a higher ambulation rate. However, considering that in some case the long-course RT regimens were associated to an increase of local control duration in MSCC patients, some authors argument in favour of more prolonged RT regimens for patient selected on the basis of a better prognosis [31-33].

Recently, it was published a score predicting post-RT ambulatory status [34]. It was developed based on 2,096 retrospectively evaluated MSCC patients. Tumor type, interval between tumor diagnosis and MSCC, presence of other bone or visceral metastases at the time of RT, pre-treatment ambulatory status, and duration of motor deficits were the six prognostic factors resulting significant for survival and ambulatory function.

Finally, evidence suggests that until further randomised data are available, short-course/single fraction regimens (e.g., 5×4 Gy, 2×8 Gy, or 1×8 Gy) can be used for patients with short life expectancy, while fractionated, higher dose schedules (e.g., 10×3 Gy or greater) should be considered for patients with better prognosis.

Radiotherapy planning is optimal when an MRI is available. With MRI, vertebral and paravertebral involvement can be better defined with respect to all other radiological procedures. Radiation portals should be centered on the site of epidural compression and accurate 3D-conformal RT should be used in the majority of cases. In the 16–25 % of cases who develop recurrent MSCC after RT, 64 % of early recurrences are within two vertebral bodies of the site of initial compression [1]. Therefore, radiation portals should be extended two vertebral bodies above and two vertebral bodies below the site of compression. Adjacent sites of bony involvement and paravertebral masses should also be encompassed in the treatment volume.

16.9 Steroids

Generally, in MSCC patients RT is administered with concomitant steroids to lessen back pain, prevent progressive neurologic symptoms, and reduce RT-induced spinal edema [1]. Steroids should be given immediately when the clinical and radiological diagnosis of MSCC is obtained. Dexamethasone is the most frequently used drug, although the use of methylprednisolone is also reported [35]. The dexamethasone dose ranges from moderate (16 mg/day in 2–4-times daily parenteral or oral divided doses) to high (36–96 mg/day), sometimes preceded by an intravenous bolus of 10–100 mg [1, 35]. Steroids are usually tapered over 2 weeks. No study has been published comparing high- to moderate- dose of dexamethasone. There is only one randomized clinical trial comparing high dose dexamethasone to no drug in 57 patients with MSCC treated with RT [36]. This trial evidenced that high dose dexamethasone significantly improves post treatment ambulation, but associated to

a certain probability (11 %) of high toxicity. A phase II trial showed the feasibility of treating patients with MSCC, no neurologic deficits, or only radiculopathy, and no massive invasion of the spine at MRI or CT with RT (10×3 Gy) without steroids [37]. However, in clinical practice, considering that published studies have shown no difference in outcome between high- and moderate- dose dexamethasone, and the relatively high incidence of side effects from steroids, above all in patients with diabetes mellitus, hypertension, and peptic ulcer a moderate dexamethasone dose of 16–32 mg/day is suggested for symptomatic MSCC patients [38].

16.10 Chemotherapy and Hormone Therapy

For treatment of MSCC, chemotherapy or hormone therapy can be used in combination with RT, or alone in adults who are not surgical or radiation candidates but who have sensitive tumors such as lymphoma, small cell lung carcinoma, myeloma, breast, prostate, or germ cell tumors. In children chemotherapy is the primary treatment for chemo-responsive tumors [1].

16.11 Promise of Newer Technologies

The majority of MSCC patients have low performance status, paraparesis, paraplegia and/or other prognostic factors associated with a short life expectancy. In these cases palliative short course or single fraction RT regimens represent the standard treatment. A more aggressive RT may eventually be justifiable for patients selected according to good performance status, oligometastatic disease and longer life expectancy. In this subset of patients a higher RT dose can be prescribed using special techniques. Linear accelerator technology has evolved with multileaf collimation, intensity modulated irradiation, systems of image guidance, and robotic technology. Radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) have emerged as new treatment options in the multidisciplinary management of metastases located within or adjacent to the vertebrae and spinal cord. They provide attractive options to deliver high dose per fraction radiation, typically in single dose (e.g., 10–16 Gy) or in hypofractionation (e.g., 9 Gy×3 fractions or 6 Gy×5 fraction) [39].

In contrast to other RT techniques, SRS and SBRT allow treatment to the involved vertebrae and spinal cord with a high radiation dose, reducing irradiated volume, and sparing uninvolved segments [39, 40]. The role of SRS and SBRT for epidural decompression in selected groups of MSCC patients is under evaluation together with the potential higher risk of RT-induced myelopathy. These techniques cannot be used as an emergency procedure given the time taken for planning and treatment verification. The need for sophisticated and expensive radiation units, which are offered only in few specialized centres, limits the routine use of SRS and SBRT [41-43].

16.12 Conclusion

Early diagnosis and prompt therapy are powerful predictors of outcome in MSCC. The best diagnostic tool for diagnosis and treatment planning is MRI. Generally, RT is accepted as the first line treatment for the majority of patients with spinal cord and cauda equina compression, and surgery should be considered for a carefully selected group of patients. As suggested by many prospective clinical trials, hypofractionated RT regimen can be considered the regime of choice, while more protracted RT schedules can be used in selected MSCC patients with a predicted long life expectancy. The new technologies of irradiation provide an interesting opportunity for selected patients, though it is much more expensive, and can be administered only in highly specialized radiation centers.

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Chapter 17
Pathological and Impending Fracture

Julian B. Sernik, Albert J.M. Yee, and Markku T. Nousiainen

Abstract Orthopaedic surgery can provide significant palliation to patients with symptoms arising from bony metastatic involvement and prevent pathologic fractures in those at highest risk. This chapter will review the role of surgery in the management of skeletal metastases and discuss factors that should be considered prior to surgery. An overview of current treatment of pathologic fractures and the evaluation of pre-critical bony lesions will be presented. Assessment of the need for potential surgical intervention using published criteria and scoring systems will be reviewed as well as a synopsis of the surgical treatment and management for appendicular and pelvic metastases. Novel approaches to more accurately guide fracture risk prediction radiologically will be presented and the role of emergent surgery discussed.

Keywords Bone metastases • Impending fracture • Fracture • Skeletal related events • Surgery

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17.1 The Role of Surgery in the Management of Bone Metastases

Orthopaedic and spinal surgery can provide significant palliation to patients with symptomatic bony metastases and those at risk for pathologic fracture and debilitating bone pain. The timing of surgical intervention falls within the realm of the art of medicine and involves decision making that relies on the strength of physician-patient relations and informed consent. The limitations of what orthopaedic surgery can achieve under these circumstances needs to be made clear to the patients and their families to arrive at a treatment plan that is both realistic for the surgical team and consistent with the patient's wishes. In this population, patient preferences need to be strongly weighed in the shared decision process. The promise of surgery may erroneously be considered to represent a cure and appropriate education regarding the reasons to consider surgery warrant clarity.

In general, the roles of surgery in the management of bone metastases are to:

1. Relieve pain that is refractory to conventional pharmacologic and local radiation therapies in the treatment of symptomatic bony metastases.
2. Stabilize bony metastases that are at significant risk for pathologic fracture.
3. Stabilize pathologic fractures to decrease pain and increase function.
4. Decompress the spinal canal and stabilize the spine in cases where the metastatic lesion causes spinal cord compression or for vertebral lesions at high risk for compression of the neural elements and subsequent neurologic deterioration.

Knowing the relative indications and contraindications to surgery is paramount in clinical decision making. Whilst there are some clinical and radiographic guidelines that may help in this process, the authors of the chapter wish to stress the importance of the physician-patient discussion as this open dialogue is essential to the success of our medical and surgical therapies. Ultimately, it is the patient's experience of pain relief and quality of life improvement that defines successful palliation.

Metastatic cancer is the most common malignant disease of bone in adults. In the United States alone, approximately 1.2 million new cases of cancer are diagnosed. Of these, up to 50 % have the potential to spread to bone, with prostate, lung, and breast, thyroid and renal cancer being responsible for more than 80 % of cases of metastatic bone disease [1, 2]. Bone metastases often produce significant pain and disability early in the course of disease as a result of pathologic fractures, anemia, and hypercalcemia [3]. Seventy percent of the bone metastases occur in the axial skeleton and 10 % in the appendicular skeleton with preference towards the proximal ends of long bones [4]. The risk of fracture is dependent on anatomical location, geographic size of the lesion, and tumour invasiveness [4, 5]. Forty percent of pathological fractures occur within the proximal femur and it is estimated that approximately 10 % of bone metastases require surgical intervention [6]. Breast carcinoma is the most common cause of pathologic fracture with lesions occurring in up to 35 % of patients with bony metastasis [7], followed by kidney, lung, thyroid and lymphoma [8]. It is important to remember that pathologic fractures may occur due to either osteolytic, mixed, or osteoblastic lesions; in all instances, the

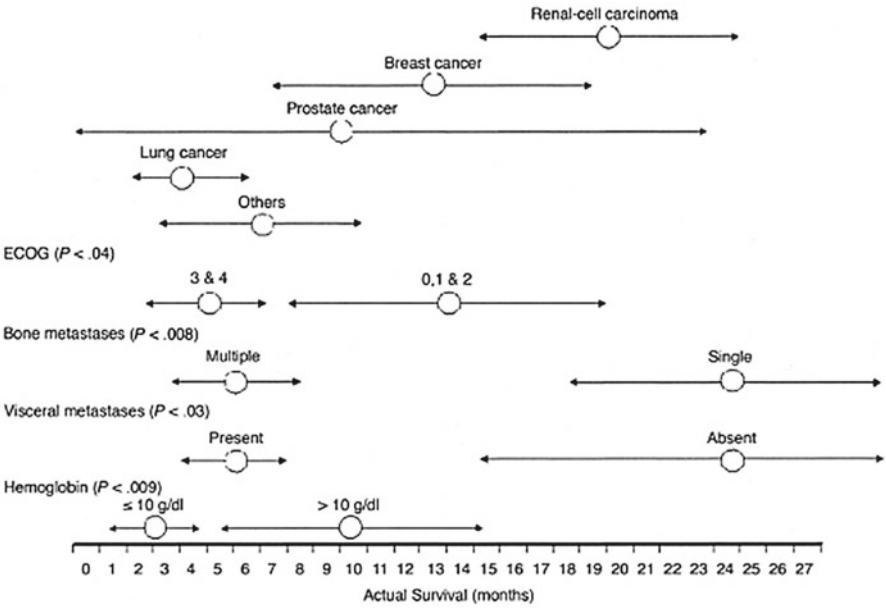

Fig. 17.1 In this sliding scale, the circles represent the medians, and the arrows represent the 95 % CIs in 191 patients treated surgically for metastatic bone disease

structural integrity of the lesion is less than that of normal bone [8]. Lytic lesions tend to result from breast and lung cancer primaries while osteoblastic lesions tend to originate from prostate cancer primaries [9]. Even in blastic prostate bony metastases the annual rate of fracture may be as high as 20 % [10]. For most patients, a pathological fracture heralds the end-stage of their disease. Overall, half will die within 6 months of surgery for pathological fracture or paraplegia and only a few will survive for several years [5].

Many studies have attempted to identify prognostic implications of bony metastasis on survival. In all cases, a bony metastasis worsens the prognosis and a skeletal related event (SRE) worsens it further. An SRE is defined as having either a pathologic fracture, spinal cord compression, bone pain requiring radiation therapy or orthopaedic surgery [11]. Nathan et al. prospectively assessed 191 patients who were surgically treated for pathologic fractures caused by metastatic bone disease and derived a sliding scale for predicting the survival of patients operated on for a pathologic fracture based on type of primary, polyostotic versus monostotic presentation, presence of visceral metastases, Eastern Cooperative Oncology Group (ECOG) performance status and haemoglobin level [12]. The graphic representation of how these factors influence survival can be found in Fig. 17.1. In their study, lung cancer patients fared the worst with a median survival of only 4 months from the time of orthopaedic consult while renal cell carcinoma fared the best with a median survival of 20 months.

Breast cancer is the most commonly diagnosed cancer among women and the second largest cause of cancer related deaths in women [13]. More than half of these women will develop skeletal metastases [14]. In population based analysis of 98,260 cases diagnosed with breast cancer in the United States between 1999 and 2006, the presence of a bony metastasis and a SRE incurred a 6.2 times the risk of death (HR 6.2 95 %CI 5.9–6.5) during the 3.3 year median follow up [13]. Typically osteolytic in nature, the bone metastases now observed in this patient population have evolved towards a more osteolytic/osteoblastic phenotype, as a result of bisphosphonates being a standard of care for the treatment of established bone metastases [1].

Prostate cancer is the most commonly diagnosed malignancy of men in the industrial world [15] and the second leading cause of cancer related deaths in men in the United States [11]. In a population based analysis of 126,978 men diagnosed with prostate cancer between 1999 and 2005 in the U.S., the presence of bony metastasis with a SRE translated to a 10.2 times greater chance of death within the median follow up period of 3.3 years (HR 10.2, 95 % CI = 9.8-10.7) [11].

Lung cancer is the most common cause of cancer-related death world-wide [16]. Patients who develop skeletal metastasis requiring surgery have the worst prognosis of all patients with pathologic fractures [12]. In a study of 98 lung cancer patients requiring surgery for skeletal metastasis, the median survival after surgery was 3 months and the cumulative 1-year survival rate was only 13 %. Those requiring spine surgery fared worse than the remainder of the surgical patients as they survived for only 2 months as compared to 4 months post-operatively [16].

Renal cell carcinoma (RCC) is among the ten most common cancers in both men and women. Approximately one third of patients with newly diagnosed RCC have metastatic disease at the initial presentation with up to half of these affecting the skeleton. For patients with metastases, the 1-year survival rate is approximately 50 % and the 5-year survival rate is only 10 %. Compared to other types of carcinoma frequently affecting bone, the prognosis of RCC is better than for lung cancer, but worse than breast and prostate cancer. The main reason for the poor prognosis is the poor response of RCC metastases to radiation and chemotherapeutic regimens [17]. Some authors have suggested that a curative approach to orthopedic surgery for RCC bony metastasis be taken. One such study compared patients before and after a change in surgical approach from one of palliation to one of wide resection and was able to demonstrate a survival advantage of the later group. This approach suffers from historical control bias and has yet to be validated prospectively [17].

Although not yet externally validated, a system of risk stratification based on five prognostic factors has been developed to predict survival in patients with RCC with bony metastases. The five factors included in this tool are sarcomatoid differentiation, vertebral bone involvement, extraosseous metastasis, increased LDH (>1.5 times upper limit of normal) and increased CRP (>0.3 mg/dl). If a patient has 0–1 risk factors the survival after detection of bony metastasis was 33 months, with two risk factors the survival was 10.5 months and with 3–5 risk factors the survival was only 3.8 months [18].

Bone is the second most common site of metastasis from thyroid cancer, with lung being the most common. Bony metastasis represents a poor prognosis,

especially when other sites of metastasis are also present. The disease-specific survival rate after detection of bony metastasis was 36 % at 5 years and 10 % at 10 years in a retrospective study of 52 patients who underwent treatment for thyroid cancers with bony metastasis at a single site. The authors of the study showed a weak survival benefit to resection of solitary bony metastasis but admitted that the indications for this approach are limited by the frailty of the patients, the likelihood of multiple bony metastasis and the lack of prospective data to support the practice [19].

Bayesian classification is a statistical method that describes relationships between multiple variables and can be used to produce models which may predict outcomes even in the presence of incomplete or discordant data. This technique has been applied to a variety of oncologic outcomes and has recently been applied to prognostication in patients diagnosed with bony metastases. Similar to previous work, the model includes features such as the surgeon's estimate of survival, hemoglobin concentration, and absolute lymphocyte count, presence of a pathologic fracture, ECOG performance status, number of bone metastases, and the pathologic diagnosis. While not externally validated, a predictive model has been developed and may represent the future of prognostication in patients with bony metastases [20].

The treatment of bone metastases involves a multidisciplinary approach. Avoiding the potential complications related to bone metastases is the rationale that often prompts an orthopedic assessment. Assessments are broadly characterized into four groups: impending fractures, pathological fractures, spinal instability and spinal cord/cauda equina compression. Pain is the most common presentation of a patient with a skeletal metastasis, two thirds of which will have a radiographically detectable lesion [21].

The decision making process involves a series of risk/benefit calculations. First, the magnitude of the surgery must be weighed against the patient's physiological capacity to tolerate it. Second, the patient ought to have sufficient life expectancy postoperatively to not only recover from surgery, but to enjoy a reasonable period of time in which to benefit from the superior pain control, functional improvements and overall quality of life that surgery may provide. As such, the ultimate goal of orthopaedic intervention is to provide therapies that improve patient palliation at an acceptable risk. A minimum life expectancy of between 6 weeks and 3 months are advocated prior to considering orthopedic surgical interventions. Life expectancy is difficult to calculate accurately and likely depends on many factors including the cancer primary, the burden of bone metastases, the anatomical location of the metastases, and the presence or absence of a pathological fracture [5, 12, 20, 22–24].

17.2 Assessing the Need of Surgical Interventions by Different Criteria and Scoring Systems

There have been numerous systems developed that may guide clinical decision making regarding orthopaedic or spinal surgery for symptomatic bony metastases. Much of the historic literature in appendicular skeletal metastases has focused on

two-dimension radiographic analysis. With modern generation CT and MRI imaging, three-dimensional renderings of pathologic bony lesions have provided much more detail regarding bony architecture and have the potential to more accurately gauge the risk for pathologic fracture when compared to two orthogonal views on routine plain radiography. This is of particular interest in the spine where vertebral involvement involves a complex of anterior, middle, and posterior vertebral column involvement with inherent issues of neural tissue passage in the spinal canal. The ability to predict a pathologic burst fracture of the spine is more important to the preservation of normal spinal cord function that the potential for a wedge-compression pathologic fracture. Plain radiographs of the spine and bone show only very advanced bony destruction and longitudinal assessments by CT or MR imaging is more routinely practiced in guiding patient care. Translational research opportunities coupling modern imaging with more accurate prediction models of fracture risk is an area that is attaining increasing interest and shows promise in transforming clinical practice and care by providing more accurate assessments of pathologic fracture risk versus conventional clinical assessments based on plain radiographic imaging and surgeon based assessments of 'low, medium, or high' risk [12].

Fidler et al. found that the incidence of long bone fractures was related to the cortical involvement based on plain radiographs [25]. When 25–50 % of the cortex was involved the fracture incidence was 3.7 %; This rose to 61 % and 79 % when 50–75 % and 75 % of the cortex was involved, respectively [25]. Similarly, Mencke proposed prophylactic internal fixation if the ratio of the width of the metastasis to the diameter of the bone exceeds 0.60, if there is ≥13 mm of axial cortical destruction of the femoral neck, if there is ≥30 mm cortical destruction of the femoral shaft, or ≥50 % cortical destruction of the femoral shaft [26]. Mirels devised a clinical scoring system grading the site, the pain, the type of lesion and the amount of cortex affected on a 12-point scale. He proposed any score of 7 or below should be treated by irradiation and any score of 8 or higher should be treated with internal fixation [27, 28]. Damran et al. have shown this score to have a high false negative rate, with a specificity of 35 % and a sensitivity of 95 % [29]. It is important to recognize that the management of impending fractures should never be based on radiographic appearances alone; only those that are symptomatic or are located in high risk anatomic areas such as the proximal femur should be considered for surgical intervention.

17.3 Fracture Risk Assessment

The clinical guidelines designed to predict pathologic fractures appear to be limited by their reliance on plain radiographs. Retrospective radiographic examination studies determined that fracture risk in metastatic lesions of the femur could not be established by measurements from standard radiographs alone [30]. Radiographically lesions are often immeasurable as no clean boundaries exist. Large errors occur when measuring simple defects from plain radiographs; errors in measuring diaphyseal defects of up to 100 % have been found [31]. High percentages of lesions

(16–29 %) are also missed using radiographs alone [32]. Even in long bones, existing clinical guidelines that use some measure of defect geometry to assess fracture risk allow for probabilities of clinical errors as much as 42 % [33]. Visual analyses of CT and plain radiographs have not been successful in estimating strength reductions or load bearing capacity in bony metastases.

17.4 Surgical Treatment of Appendicular and Pelvic Metastases

While most patients with a pathologic bony lesion without a fracture can be managed by systemic and radiation therapy alone, the majority of pathologic fractures are best treated with surgery [8]. Despite the fact that some fractures have the ability to heal on their own, the length of time required for healing is inappropriate for patients with a limited life expectancy. In addition, the time to achieve bony union is increased secondary to the negative local biologic effect of the metastasis [8]. Thus, the indications for surgery include: (1) a life expectancy of greater than or equal to 1 month for fractures of the weight-bearing dome of the acetabulum and a life expectancy of greater than 3 months for a fracture outside the weight-bearing dome of the acetabulum; (2) medical condition amenable to undergoing surgery; (3) remaining bone adequate to support the proposed surgical construct; and (4) ability for surgery to provide patient mobilization and facilitation of general care [6].

Before embarking upon surgery, a firm diagnosis of the metastatic lesion must be made. The diagnosis is made with a thorough history and physical examination, plain radiographs of the entire bone, bone scan, and blood and urine investigations. If the diagnosis is unclear, obtaining a CT or MRI can help differentiate between the etiologies of pathologic fracture and delineate the soft tissue component of the lesion [8]. If the diagnosis is still not identified, then an image guided fine-needle or open incisional biopsy is indicated. Intra-lesional biopsies attained at the time of intramedullary nailing by reaming of long bones are commonly not of diagnostic quality and should not routinely be relied upon for pathologic diagnosis [1, 34].

The most effective surgical means to relieve pain and restore function is with internal fixation or prosthetic replacement. The goals of these procedures are to convert open-segment defects into closed defects, restore bone strength to withstand physiological loads, and allow for immediate weight bearing [8]. This focus is different from the management of non-neoplastic fractures, whose goal is to promote fracture healing. As such, techniques such as prosthetic replacement or stabilization with polymethylmethacrylate bone cement (PMMA) are used in metastatic situations. The general rule is to select a surgical solution that will be robust enough to improve function and relieve pain for the duration of the patient's life in a single surgery.

There is variation in practice internationally with some considering resection of the tumour deposit for the management of oligo-metastatic bone lesions. Intralesional curettage is the predominant technique used in many cases. This may provide temporary local tumour control, slow local progression, allow for better assessment

of remaining bone and permit bone cement to be used to fill the defect. Curettage and cementation may provide improved stability to the fixation construct, and allowing surgical adjuvants such as postoperative radiotherapy to have increased rates of success [8] This technique is particularly appropriate when significant cortical destruction has occurred or a closed reduction is not possible [1]. Closed fracture intramedullary fixation techniques are indicated in situations where the fracture is anticipated to heal with stabilization and adjuvant therapy alone or the fixation itself will outlast the patient's projected survival [1, 8]. Multiple myeloma and breast cancer metastases typically respond to radiotherapy and therefore curettage may not be necessary for these lesions [1]. Although uncommon, the indications for extralesional excision include the involvement of expendable bone with tumours (i.e. fibula, iliac wing, ribs, clavicle, scapula), epiphyseal fractures, a solitary metastasis when there has been a long interval between treatment of the primary tumour and development of the metastasis, or when the patient has a long projected survival, as with renal or thyroid carcinoma [1, 17, 19, 22, 35, 36].

Adjuvants to surgery include angiography, cryosurgery, chemotherapy, radiofrequency ablation, microwave ablation, and radiotherapy. Angiography should be used preoperatively to embolize hypervascular tumours such as renal and thyroid carcinomas, so as to minimize intraoperative bleeding. Residual local tumour can be treated with systemic chemotherapy, if sensitive. Postoperative local radiation remains the principal surgical adjuvant for the vast majority of cases. It is delivered to the whole surgical field and extends the full length of the bone so as to suppress tumour growth and maintain structural integrity to the remaining bone to avoid a future pathologic fracture [8]. It is important to note that if radiation is used in the management of a lesion without surgical stabilization, there is an increased risk of pathologic fracture in the peri-radiation period [8]. The induced hyperemic response at the periphery of the tumour weakens the adjacent bone and increases the risk of spontaneous fracture. If not stabilised with surgery, the bone should be protected by splints and/or weight bearing restrictions where appropriate until its structural integrity has been restored through healing.

Fractures involving the three different regions of bones, epiphysis, metaphysis, and diaphysis, are managed with different forms of fixation. Epiphyseal fractures are best treated with resection and endoprosthetic implantation. Long-stemmed prostheses are used so as to prevent future pathologic fractures from occurring at distal sites secondary to disease progression or adjuvant radiotherapy. This tactic provides immediate bony stability and enables full weight bearing, rapidly restoring patient function [8]. In the proximal femur, hemiarthroplasty is indicated if there is no degenerative change or the hip and no evidence of metastatic disease in the acetabulum [22]. A total hip arthroplasty is performed if there is acetabular destruction [22]. Hip arthroplasty reconstruction of metastatic disease can often be a more complex procedure than arthroplasty performed for primary osteoarthritis. Because humeral head fractures are associated with extensive destruction of the rotator cuff soft tissues or associated tuberosities, the traditional aim of surgical management has been to regain shoulder stability and relieve pain with hemiarthroplasty recognizing that rotator cuff function may be limited [37]. Reverse total shoulder

arthroplasty has shown some promise with respect to maintaining shoulder function in the context of wide resection for metastatic bone disease involving the proximal humerus [38, 39].

Metaphyseal fractures can be managed in a variety of ways. Load-sharing devices, such as intramedullary nails, are the implants of choice in the majority of metaphyseal fractures. Because they can span the entire bone, reduced rates of fixation failure and future fracture proximal or distal to the implant are seen [40]. Some animal models have demonstrated lower intramedullary pressures and reduced pulmonary debris with negative pressure systems that evacuate the contents of the canal during reaming and this technique may prove a safe option in metastatic long bone lesions requiring intramedullary nails [40]. Reaming is advisable since a nail of wider diameter may provide better stability, less pain, and may reduce the risk of implant breakage or nonunion. Nevertheless, nails can fail if the fracture does not heal. Thus, intramedullary nails are contraindicated in situations where metaphyseal fragments cannot be adequately stabilized with the proposed construct, where it is assumed that stabilized bone will not heal, and when densely sclerotic lesions are present (making nailing difficult) [8]. In these instances, implantation of a prosthetic replacement or fixation with plates and screws and PMMA insertion is indicated. Prosthetic replacement can be challenging as adequate attachment of important soft tissue attachments such as the greater and lesser trochanter of the femur or the greater and lesser tuberosity of the humerus, may be difficult due to tumour involvement.

Diaphyseal fractures are ideally managed with tumour curettage, bone cementing, and insertion of an intramedullary device. If proximal and distal interlocking screws cannot provide adequate stability, or if the intramedullary canal is too small to accept a nail (as may occur in the case of certain humeral shaft fractures), plate fixation and cementing may be considered [37]. If a diaphyseal lesion is associated with an epiphyseal or metaphyseal lesion, a cemented long-stemmed prosthesis is used.

The most common long bone to sustain a pathologic fracture is the femur. The majority of fractures in the femur involve the proximal portion; 50 % of these are in the femoral neck, 30 % are in the subtrochanteric region, and 15 % are in the intertrochanteric region [6]. The ideal management of femoral neck fractures involves either hemi- or total hip arthroplasty. Inter- or subtrochanteric fractures are best managed by intramedullary nailing with a reconstruction nail (which permits screw fixation into the femoral head and neck) [6, 36]. In lesions where extensive osteolysis is encountered and irradiation is planned in the postoperative course of treatment, augmentation with PMMA may be necessary [37]. In lesions that have been irradiated prior to the fracture and there is no plan for postoperative irradiation, primary bone grafting can be considered [37].

Other treatment options, such as external fixation, cast/brace immobilization, and amputation, may also be used to manage certain pathologic fractures. External fixation and cast/brace immobilization are indicated when (1) extensive disease precludes effective internal fixation; (2) the patient is pre-terminal; or (3) patient's medical status prohibits surgery. Amputations are effective in managing (1) extremity lesions that cannot be reconstructed; (2) ulcerated or infected lesions; (3) cases with

Table 17.1 Summary of surgical options for management of metastatic lesions to appendicular bone

Bone—location	Surgical management
Clavicle	Rare
Scapula	Rare
Glenoid	Resection/reconstruction
Proximal humerus—epiphysis	Long-stemmed hemiarthroplasty
Proximal humerus—proximal third	Long-stemmed hemiarthroplasty *or* allograft/hemiarthroplasty composite reconstruction
Humerus—diaphysis	Locked intramedullary nailing *or* internal fixation with PMMA (if extensive bone loss after curettage) *or* intercalary spacer (if large segmental defect, failed fixation)
Distal humerus	Bicondylar plate fixation *or* endoprosthetic reconstruction *or* flexible intramedullary nails (if lesion above epicondyles)
Forearm	Internal fixation with PMMA *or* flexible rods
Hand	Intralesional surgery with curettage and PMMA *or* amputation (if distal and extensive)
Supracondylar femur	Internal fixation with PMMA *or*distal femoral replacement
Proximal tibia	Internal fixation with PMMA *or* proximal tibia replacement
Tibia—diaphysis	Locked intramedullary nailing *or* internal fixation with PMMA (if extensive bone loss after curettage)
Tibia—distal	Internal fixation with PMMA
Foot	Intralesional surgery with curettage and PMMA *or* amputation (if distal and extensive)

Table 17.2 Predicting the risk of pathologic fracture. Prophylactic fixation is recommended with a score of at least nine points (Adapted from [16, 28])

Feature	Points		
–	1	2	3
Size	<1/3	1/3–2/3	>2/3
Site	Upper extremity	Lower extremity	Pertrochanteric femur
Pain	Mild	Moderate	Mechanical
Radiographic image	Blastic	Mixed	Lytic

intractable pain; and/or (4) cases where rehabilitation after reconstructive surgery is too time consuming, such as with the foot. See Table 17.1 for a summary of methods of treatment for metastatic lesions to bones of the upper and lower extremities.

The indications for surgical treatment of impending fractures remain controversial. Although multiple authors such as Harrington, Mirels, and Healey have provided criteria predictive of pathologic fracture, these are neither highly sensitive nor specific (see Table 17.2 for a summary of Mirels' scoring system). Nevertheless, operating on impending fractures is indicated if the surgery will minimize pain or when the treatment for the impending fracture is significantly safer or more effective than surgery that would be performed once the bone has fractured completely. Patient outcomes are improved when prophylactic surgical intervention is chosen

instead of managing a fracture once it occurs; shorter hospitalization, earlier home discharge, earlier return to premorbid function, improved survival, and fewer hardware complications are amongst the benefits incurred [41].

17.4.1 Pelvis and Acetabulum

Improvements in systemic oncological treatment have led to prolonged survival of patients and an increase in the number of patients with destructive lesions of the pelvis. Diffuse involvement of the pelvis, particularly the periacetabular area, is of significant concern, as it can lead to mechanical instability that may cause severe pain and functional disability [42, 43].

17.4.1.1 Non-surgical Treatment

Pathologic pelvic fractures outside the area of the acetabulum rarely require surgical stabilization and reconstruction [43]. In consultation with medical and radiation oncologists, analgesics, bisphosphonates, radiation, hormone, and chemotherapy should be considered if bone destruction is limited and the patient has not received prior treatment [43]. Lesions not involving the weight-bearing area of the acetabulum can be treated with modification of weight-bearing and external beam radiation [43]. Structurally significant lesions of the ischium, pubis, or sacroiliac area are rare and are usually managed effectively with radiation alone. Avulsion fractures of the anterior superior and inferior spines, iliac crest, and superior and inferior rami are common and are treated non-operatively [44, 45]. In addition, patients with extensive bony lesions, advanced disease, or poor functional status may not benefit from surgical intervention. If the tumour is responsive to non-surgical treatment (i.e. early myeloma or lymphoma), extensive bone destruction may be surgically managed during or after medical and radiation treatment [44].

17.4.1.2 Surgical Treatment

Despite the successes of non-operative care, bony destruction or disabling symptoms may continue. Surgical management is considered if (1) acute symptoms do note abate after a period of protected weight-bearing, use of analgesics, and anti-neoplastic treatment; (2) restoration of satisfactory function with control of pain is not achieved within 1-3 months following radiation therapy; (3) a pathologic fracture develops in the acetabulum or ipsilateral femur; or (4) there is an impending fracture of the ipsilateral femur [43, 46]. Although the surgical management of a patient with periacetabular metastasis can be a major surgical procedure with a significant risk of complications, surgery has become more successful with the evolution of joint replacement procedures and prosthetic components. Several studies

Table 17.3 Harrington classification of acetabular defects from metastatic disease (Adapted from [51, 53])

Class	Features
1	*Minor defect*: superior and medial walls intact; lateral cortices intact
2	*Major defect*: deficient medial wall
3	*Massive defect*: deficient lateral cortices and superior dome
4	Resection required for cure

have shown that surgery provides pain relief, improves function, and maintains and restores mobility to those with periacetabular metastases [47–49].

Proper pre-operative planning includes obtaining appropriate diagnostic imaging studies to accurately assess the location of the tumour. This requires a combination of plain radiographs (Judet views determine the extent of columnar involvement) and computed tomography (CT). CT is especially useful in determining the integrity of the medial wall, acetabular dome, and any associated soft tissue component of the tumour.

Classification of acetabular defects is based on the location of the fracture, the extent of osteolysis associated with the tumour or irradiation, and surgical issues relating to achieving stable implant fixation [43]. Harrington's classic classification system describes the extent of acetabular involvement with particular attention to which areas of the acetabular walls are deficient (see Table 17.3) [37]. Levy et al. described a similar classification system and suggested that as most lesions involve mixed segments, acetabular destruction should be classified as minor, major, and massive [50].

As with the appendicular skeleton, cases involving metastatic renal and thyroid carcinoma and multiple myeloma require preoperative angiography and embolization in order to minimize intraoperative blood loss and allow for a more controlled reconstruction. Pre-operative angiography and embolization should also be considered in other tumours when extensive osteolysis exists without a clearly defined margin or when there is evidence of an extra-cortical soft tissue mass [51]. When a sharp, sclerotic tumour margin is apparent on plain radiographs, the metastatic lesion is likely to be slowly progressive and not as vascular [51].

The choice of reconstruction is based upon the existing structural damage to the acetabulum and by following the aforementioned general principles of the surgical treatment of metastatic bone disease, which include gross tumour removal, filling the bone defect, and bypassing the defect with a prosthetic component [8, 43]. According to Harrington's classification, patients with class I deficiency (lateral cortices and lateral and medial walls intact) can be treated with routine total hip arthroplasty with cementing of both the acetabular and femoral component. Mesh may be used to support the medial wall of the acetabulum and to prevent migration of PMMA into the pelvis. Long-stemmed femoral components are used to stabilize the femur because of the possibility of additional metastatic foci in the proximal two-thirds of the femur. Traditionally, cementing of the acetabulum and femur was regarded as necessary since conventional total hip arthroplasty was thought to fail

due to insufficient surrounding bone, leading to loosening and migration [37]. More recently, highly porous metal cups have been successfully used for class I defects after pre-operative radiation. [52].

Patients with class II lesions (medial wall deficient) typically present with protrusion of the femoral head through the medial acetabular wall (secondary to the tumour or post-irradiation osteonecrosis). Surgical management of this situation involves the use of acetabular cups designed to resist protrusion by transferring weight bearing stresses across the deficient medial wall to the anterior and posterior columns. After tumour excision, the resultant bone deficiency is cemented (or bone grafted if the patient has a good prognosis) [43]. An anti-protrusio cage is then firmly placed onto the intact rims prior to having a cemented polyethylene cup inserted into it. Screws affixing the ring or cage to bone/cement provide additional stability. A long-stemmed, cemented femoral component is implanted as with a class I deficiency.

Class III lesions (medial, lateral, and superior walls deficient) are the most challenging lesions to manage. As there is no intact bone on which to lay an anti-protrusio cage and the bony deficiency cannot be successfully supplemented by using PMMA alone or by placing the acetabular cup in a more proximal position, a more elaborate reconstruction is indicated. This involves placing several large Steinmann pins across the deficient area from the iliac wing into the low anterior and/or posterior column. Cement is injected into the deficient areas of bone around the Steinmann pins, which behave as reinforcement bars. An anti-protrusio cage is placed upon this construct and a polyethylene cup is cemented into place. Mesh along the medial wall prevents extravasation of PMMA into the pelvis.

Management of class IV lesions (resection required for cure) is rare. Most lesions requiring this treatment involve solitary metastatic hypernephromas, unifocal lymphomas, or thyroid carcinomas that continue to be symptomatic despite prior radio- and chemotherapy. The principles of reconstruction apply the same techniques as with class III lesions. Adequate resection of tumour should not be compromised in an effort to make pelvic reconstruction easier; it may be necessary to perform an internal hemipelvectomy alone [37].

In cases that require either partial or near-complete hemipelvectomy for tumour control, several reconstructive options exist. These include the use of hemipelvic allograft, autograft (if tumour lysis has not weakened the bone to the point that it can no longer support weight, it is possible to autoclave the bony segment and use it to reconstruct the pelvic ring) [37], or custom-made pelvic endoprostheses in association with total hip arthroplasty [53]. Alternatively, saddle prosthesis can be implanted [54]. All options provide adequate functional outcomes despite the major surgery required.

Surgical approaches for metastatic reconstruction involve either a Kocher-Langenbeck or lateral transgluteal hip approach. The lateral one or two windows of the ilioinguinal approach are used in addition when tumour within the acetabular dome requires further exposure and Steinmann pins need to be inserted into the ilium/anterior column. After tumour removal, bleeding is controlled with sponges soaked in adrenaline and thrombin. In situations where bleeding occurs despite

previous embolization, rapid curettage followed by packing with Gelfoam® or polymethylmethacrylate (PMMA) can minimize blood loss [43].

Review of the outcomes of patients that undergo acetabular and femoral reconstruction indicates that the majority experience a marked improvement in pain and ability to ambulate. Although the risk of incurring a surgical complication can be significant (including perioperative death, dislocation, infection, nerve palsy, deep venous thrombosis, and reconstruction failure), these procedures do provide an improvement in the quality of life in patients who have a poor long-term survival secondary to their disease [8, 46, 48, 49, 51, 55].

17.4.1.3 Minimally Invasive Techniques

Innovative minimally invasive techniques such as percutaneous radiofrequency ablation, osteoplasty, and cryosurgery are evolving. The main advantage these techniques have over surgery is that they are less morbid—surgical exposure, blood loss, and surgical times are minimized.

Radiofrequency ablation (RFA) is useful as it can be performed with regional anesthesia, can treat patients not considered suitable for surgery, and is effective in treating painful metastases after radiation therapy. Newer advances in RFA include bone specific device designs. The main limitation of conventional local external beam radiation therapy (XRT) has been the detrimental effects on the normal tissue surrounding the tumour. In the spine for example, radiation given at a sufficient dose, may induce myelopathy. Modern advances in local radiation therapy include strategies such as radiosurgery, or stereotactic body radiation therapy (SBRT) that selectively deliver a much higher radiation dose to the tumour while reducing the dose to surrounding tissue [56]. These advances may increase the applicability of radiation therapy to tumors in the spine that have traditionally been regarded as poor candidates for XRT. Cryosurgery, using liquid nitrogen to induce tissue necrosis, provides excellent local control in numerous benign-aggressive and malignant bone tumours with minimal bone and functional loss [57]. Liquid nitrogen is used with caution, as the morbidity of skin necrosis, infection, temporary neuropraxia, fracture, and damage to underlying cartilage does exist [57].

Percutaneous osteoplasty such as vertebroplasty and kyphoplasty™, involve the injection of PMMA, calcium sulfate copolymers, or polymer resins with ceramic particles. These techniques have been found to be effective in providing pain relief by stabilizing bony defects [43]. The main indications for acetabuloplasty include pain, impending fractures, and the need for bone reinforcement. Contraindications include articular cortical destruction of the acetabular roof more than 5 mm in diameter and soft tissue involvement more than three times the area of bone destruction [58]. To avoid local progression, radiotherapy is recommended after the procedure [43]. Complications from osteoplasty include intraarticular and soft tissue PMMA leakage, fever, renal insufficiency, thrombophlebitis, hypotension, pulmonary embolism, and cardiac arrest [43].

17.5 Emergency Surgery

This is often required for symptomatic pathologic fractures that profoundly impacts ambulatory capacity. As such, pathologic fractures in weight bearing long bones and pathologic burst fractures in the spine with progressive spinal cord compression and neurologic impairment often warrants surgical consultation. Pathological fractures in upper extremity long bones may be of lesser importance as it pertains to ambulatory capacity unless in the presence of multiple bony disease with existing impairment to lower extremity function. The role of spinal surgery for metastatic spinal cord compression warrants discussion. Surgery is often indicated for one of two goals: to stabilize the spine and to decompress the neural elements. Extensive bony metastatic involvement of the spine, particularly at a level with both significant anterior and posterior involvement can result in spinal instability with micromotion that causes recalcitrant axial based pain that often can render a patient non-ambulatory due to axial pain. This may occur in the absence of significant spinal canal compromise or neurologic symptoms/signs. Patchell et al. validated the effectiveness of surgery and radiation therapy to treat metastatic epidural spinal cord compression. A significantly greater ability to ambulate was observed in patients who were treated by surgery and radiation therapy when compared to radiation therapy alone [59]. The presence or absence of neurologic impairment and the rate of neurologic deterioration appear important prognostic factors in considering potential success of decompressive surgery in reversing neurologic impairment that has occurred. When neurologic deterioration is rapid or when significant neurologic impairment has existed beyond 48 h, the ability of surgery to reverse the condition is guarded and better arguments of surgery in affording stability need to be considered in the context of patient symptoms.

The decision for emergency surgery also warrants consideration of patient clinical condition. The ability to tolerate a general anaesthetic the ability to withstand the usual stresses of surgery in the context of post surgical infection and overall patient conditioning are all issues that warrant pre-surgical assessment. With appropriate pre-operative counselling, the surgical management of patients with symptomatic bony metastases can lead to significant improvements in the quality of life in this patient population [60].

17.6 Conclusion

The surgical management of skeletal metastases offers significant palliative value in terms of function, quality of life and pain relief for selected patients. A working knowledge of the role surgery plays in the management of skeletal metastases is vital for physicians caring for these patients. A systematic and multi-disciplinary approach combined with sound communication skills can establish appropriate goals and attain them under otherwise difficult circumstances.

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Chapter 18
Reirradiation

Peter Hoskin

Abstract Radiotherapy for metastatic bone pain and metastatic spinal cord compression has a high rate of success but in a proportion of patients there will be recurrence of symptoms requiring retreatment. This can be undertaken safely after initial use of external beam and radioisotope therapy for metastatic bone pain with similar rates of success to those seen after primary treatment. Retreatment for metastatic cord compression must respect spinal cord tolerance doses and stereotactic techniques may have an important role.

Keywords Bone metastases • Radiotherapy • Reirradiation • Bone pain • External beam • Radioisotopes • Spinal cord compression

18.1 Introduction

The role of radiotherapy for the treatment of metastatic bone pain is well established.

The standard approach will involve external beam radiotherapy although radioisotope treatment is another alternative which has an important place in the management of more widespread symptoms. The management of bone metastasis has become increasingly complex with the development of new systemic agents both targeting the tumour cell and the bone homeostasis. It is therefore unusual that a patient with bone metastases will be treated only with radiotherapy but with a combination of other agents such as chemotherapy, hormone therapy, biological agents, bisphosphonates or RANK-L antagonists. The net result of this is that

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patients presenting with metastases of the common tumours to bone have a much longer life expectancy than in the past. Recent studies show a mean life expectancy of patients presenting with bone metastases of around 3 years with a range that exceeds 10 years. Re-treatment is an important issue for many of these patients in whom initial therapy may last for many months or even several years, but persisting bone metastases eventually result in recurrent bone pain. Similarly other manifestations of bone pathology such as spinal canal compression may return in patients who survive a sufficient time. One study in spinal canal compression has shown that in patients surviving 2 years or more, there was a 45 % risk of developing a further episode of cord compression at the same or new site, with a median time to progression of 236 days [1]. Re-irradiation in this setting is therefore also of considerable importance.

18.2 External Beam Radiotherapy

A number of guidelines and meta-analyses have been now published evaluating the efficacy of external beam radiotherapy for metastatic bone pain. These show a consistent picture with pain relief developing within the first 4–6 weeks after radiotherapy and successful amelioration of pain in 60–70 % of those treated. No advantage in initial response has been shown for any particular dose fractionation schedule. There is however another consistent observation from the randomised controlled trials that have evaluated different fractionation schedules in that a number of patients having single doses will subsequently have re-treatment. This is shown in Fig. 18.1, taken from the most recent systematic review [2]. The overall risk ratio for re-treatment at 2.58 reflects a probability of patients having further radiotherapy of between 20 % and 25 %. The situation in a randomised trial is of course often very different to that in the clinic. The trial protocols did not stipulate specific criteria for re-treatment, and as a result there may be other factors which have influenced the overall probability of retreatment including physician preference for their original randomisation schedule. The time frame of re-treatment is shown in Fig. 18.2 [3], and can be seen to be a continuous event over the first 12 months from treatment. In the UK bone pain trial which reported re-treatment in some detail, there was no difference between pain level or analgesic use at the time of re-treatment between those re-treated and those not re-treated which would strongly support the view that this was not a major criteria, however, the Dutch bone pain trial which also evaluated re-treatment in considerable detail [4] found a higher number of non responders in the single fraction group at the time of re-treatment compared to the multiple fraction group (42 % vs. 33 %) although there were more patients with progression in the multi-fraction group (50 %) compared to the single fraction group (32 %) In that database other characteristics which predisposed for re-treatment were a higher incidence in male patients, primary lung tumours and better performance status.

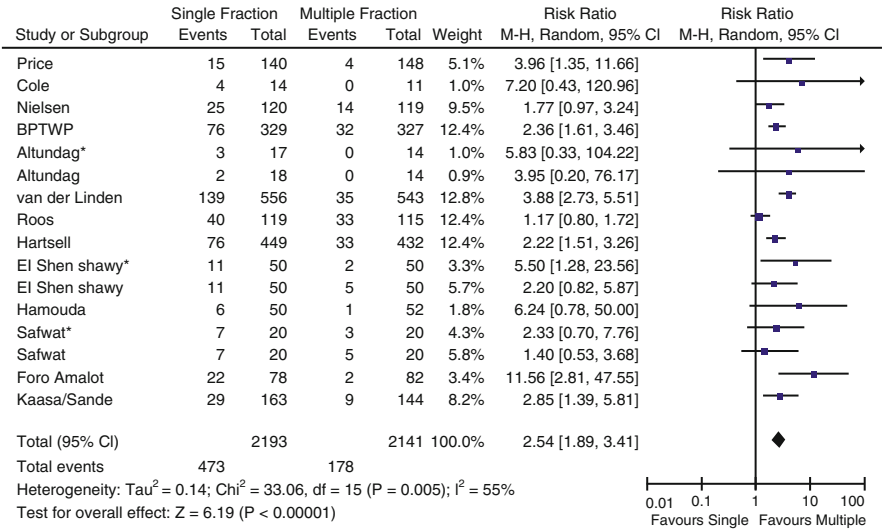

Fig. 18.1 Incidence of reirradiation after external beam radiotherapy in relation to initial dose fractionation received (From Ref. [2]. With permission)

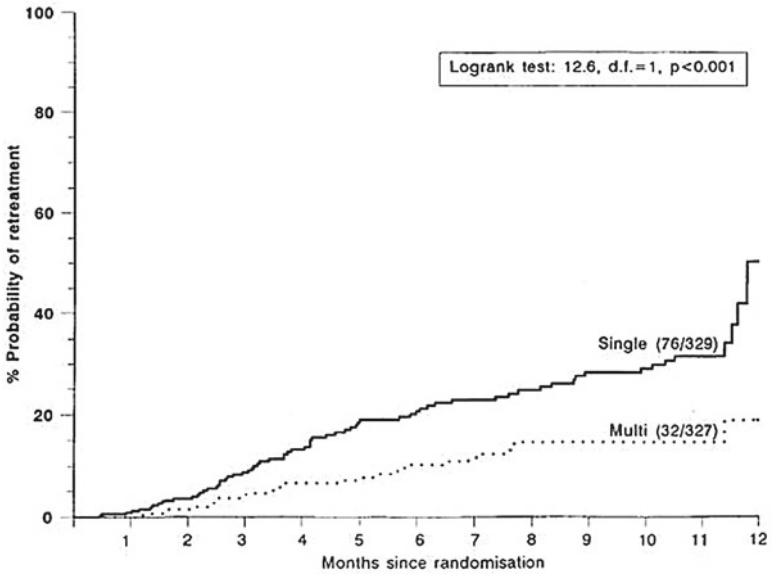

Fig. 18.2 Pattern of reirradiation with external beam radiotherapy (From Ref. [3]. With permission)

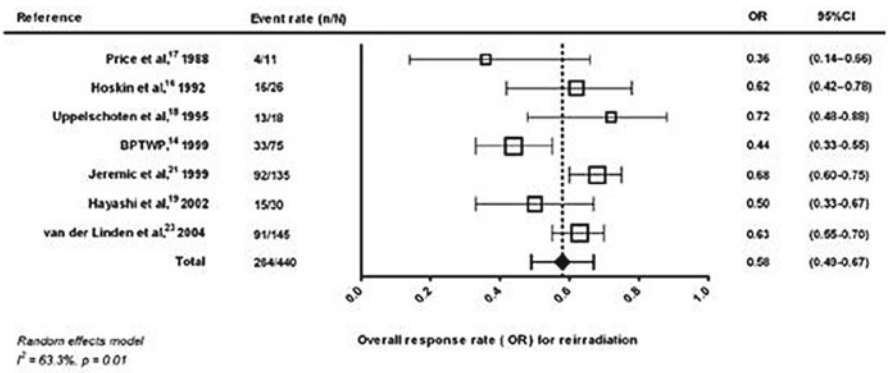

Fig. 18.3 Response rate for reirradiation (From Ref. [6]. With permission)

The efficacy of re-irradiation of bone metastasis has also been the subject of a systematic review and meta-analysis [5]. Three different scenarios for re-irradiation were identified, those patients with no pain relief or pain progression after initial radiotherapy, those with a partial response seeking a better level of pain control, and those achieving initial partial or complete response with subsequent relapse. It was noted that although pain relapse occurs in around 50 % of initial responders within 1 year from treatment, the number of patients undergoing re-irradiation is less than this with a range between 8 % and 42 % in the papers studied. A total of ten papers were included in this qualitative review with seven of these being subject to a quantitative meta-analysis. The overall response rate for re-irradiation was 58 % with a range of partial response rates from 28 % to 45 % and complete response rates from 16 % to 28 %. The time to response after re-irradiation ranged from 3 to 5 weeks with a duration of remission from 15 to 22 weeks. Results for overall response rate in the seven studies subject to meta-analysis are shown in Fig. 18.3. The overall conclusion from this overview was that re-irradiation is effective for around 60 % of patients. It was not possible from this data to define the category of patient in terms of their initial response which would benefit most. The detailed analysis of the Dutch bone pain trial which was included in the meta-analysis found an overall response rate of 63 % which when broken down was 66 % in single fraction patients and 46 % in multiple fraction patients, a difference that was not statistically significant. Similarly the duration of response was longer in initial single fraction patients at 16 weeks compared to only 8 weeks in multiple fraction patients. There was no consistent relation between initial response and likelihood of response to re-treatment, an observation that has been found in other series looking at this issue. Thus, it does appear that patients failing to respond to their first treatment may still respond to re-irradiation and this should not be denied on the basis of a poor initial response. No clear relation to other demographic characteristics has been consistently identified although the Dutch study does suggest that breast cancer patients have a high response probability and prostate cancer patients a low response rate.

The dose delivered in the re-treatment cohorts varies widely from additional single doses to multi-fraction schedules. It is not possible from the data to make any specific recommendation, all schedules appearing equally efficacious. This is the subject of a prospective randomised trial which compares a single dose of 8 Gy with 20 Gy in five fractions. This trial has recently completely accrual and the results are eagerly awaited.

The mechanism by which re-treatment is effective following irradiation is uncertain. This reflects the general lack of accurate information on the overall mechanism of action of radiotherapy in relieving bone pain. Putative mechanisms include tumour cell kill, but probably not tumour shrinkage, reduced production of pain mediating cytokines or altered pain fibre neurotransmission. It seems likely that the same mechanism would be effective with re-irradiation although this does not explain the efficacy of re-irradiation in the patient with primary refractory pain, unless in some patients there really is a dose response and a threshold for one or more of the effects of bone pain has to be reached before pain relief is achieved.

18.3 Radioisotope Therapy

Where there is scattered bone pain, radioisotopes are a very effective treatment option. A number of agents are available including strontium-89, rhenium-186 and -189 and samarium-153. Whilst the efficacy and primary treatment has been well established in phase three studies, published data on re-treatment is sparse [6]. The studies of these agents in general have allowed entry of patients having had previous radiotherapy for bone pain up to 6 weeks or so prior to administration of the radioisotope, the only exclusion criteria being previous hemibody irradiation. They do not stipulate whether previously irradiated sites are still painful at the time of radioisotope administration or whether they specifically responded to the radioisotope treatment.

Similarly there is little data available to guide the use of re-treatment with radioisotopes although anecdotally this is effective. One of the early studies [7] reports on 24 out of 119 patients initially treated with strontium who were re-treated for recurrence of pain. In this group, 18 received two injections of strontium-89, five received three injections and one received four injections. The paper states that the results were in general comparable to that seen after the first treatment and the effect on platelet count which is the main toxicity after strontium treatment was no greater following re-treatments. Other authors have reported that radioisotopes can be given safely to re-treat patients on multiple occasions [8] and recommend a minimum time between re-treatment of 10–12 weeks for strontium and 6–10 weeks for other radioisotopes in order to allow for bone marrow recovery. Another series of 76 patients with prostate or breast cancer reports on 16 patients who were re-treated receiving two or three doses of strontium. The mean interval between doses was 7 months, and clinical response after the second dose was good in 63 % with similar responses after a third dose in three patients. Anecdotally, re-treatment on up to ten occasions has been reported [9]. The overall picture therefore is that re-treatment is

well established with most published experience with strontium. A time lapse of 10–12 weeks to allow for bone marrow recovery is recommended and similar responses to that at time of initial exposure can be expected.

18.4 Spinal Metastases and Spinal Canal Compression

Re-treatment of spinal canal compression is a bigger problem than that of uncomplicated bone metastases because issues related to spinal cord tolerance must be considered. With this in mind, there is considerable interest emerging in the role of complex focal radiotherapy techniques such helical tomotherapy, VMAT and stereotactic radiotherapy in this setting. One report of 62 patients who received re-irradiation for in field recurrence of metastatic spinal cord compression after either a single dose of 8 Gy or 20 Gy in five fractions initially describes improvement of motor function in 25 patients, stable disease in 28, and deterioration in only nine. No radiation myelopathy was observed after doses of 8 Gy single dose, 15 Gy in five fractions or 20 Gy in four fractions with treatment [10]. A further report of 54 patients who received a median dose of 30 Gy initially received re-irradiation for recurrent spinal cord compression with a median additional dose of 24.25 Gy. Seventy four percent were ambulatory at the time re-irradiation and at the end of re-irradiation this was 78 %. Again no cases of radiation myelopathy were seen with a median survival of 4.7 months [11]. There are a number of smaller series also published which report similar experience. The use of conventional radiotherapy techniques limits the dose that can be delivered and local control is unlikely to be durable with only 50 % of surviving patients maintaining control at 1 year. As a result, stereotactic radiotherapy techniques have been developed which enable treatment of a spinal metastases with considerable accuracy whilst avoiding spinal canal and cord. An example is show in Fig. 18.4. A recent review of selected patients comprising a total of 329 treated spinal sites reports local control rates of around 80 % approaching 1 year from treatment. One year actuarial control rates range from 66 % to 92 % [12].

Spinal cord tolerance using hypofractionated stereotactic treatment has been explored in one study of 19 patients, re-treated with stereotactic body radiotherapy of whom five developed radiation myelopathy. The preceding treatment had delivered a median equivalent dose in 2 Gy fractions (EQD2) of 40 Gy using an alpha beta ratio of 2. There was an significant difference between the dose subsequently delivered to the radiation myelopathy group (median 67.4 Gy) compared to the patients who did not experience myelopathy (median 20.0 Gy). The conclusion was that re-irradiation using SBRT was safe provided the total BED to the thecal sac did not exceed approximately 70 Gy EQD2 of which the SBRT component was no more than 50 % [13]. A number of other small series have reported successful treatment with static IMRT, VMAT and helical tomotherapy. No single technique emerges as superior, but all offer more accurate re-irradiation reducing spinal cord dose allowing the potential for dose escalation in the hope of achieving more durable local control. The question of spinal cord tolerance remains uncertain. A review

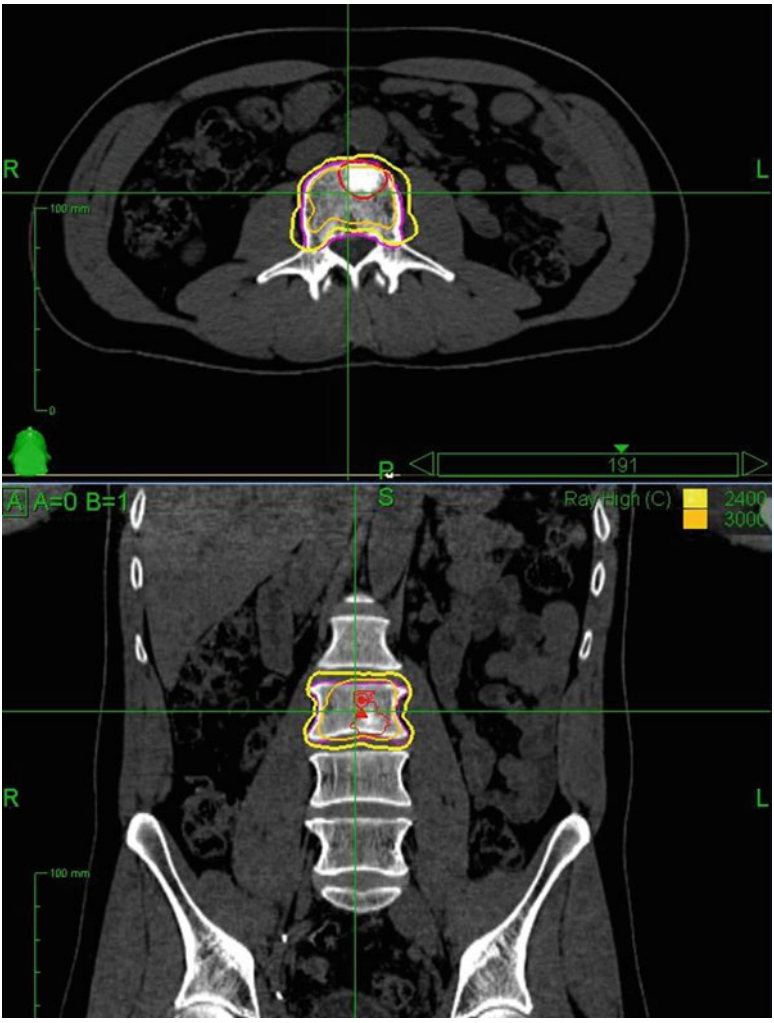

Fig. 18.4 Treatment plan for solitary spinal metastasis using stereotactic radiotherapy (Cyberknife) showing precise dose distribution within vertebral body sparing spinal cord

of 40 patients having re-treatment to the spinal cord, four on two occasions has carefully analysed the probability of myelopathy which was seen in 11 patients at 4–25 months after re-irradiation. Cumulative dose and time from original exposure to re-irradiation were important factors in predicting myelopathy. Again using the EQD2 with an alpha/beta ratio of 2, they concluded that the risk of myelopathy was small when the total EQD2 was less than 135.5 Gy and the interval was longer than 6 months [14]. A further study has suggested that provided the dose is constrained to the equivalent of 13 Gy in a single dose or 20 Gy in three fractions again the risk of clinical myelopathy is small [15].

18.5 Summary

Patients with bone metastases may survive for several years, during which time despite more effective systemic treatment, recurrent bone pain is likely to be a major cause of morbidity. Radiotherapy still has a major role in managing local bone pain. Re-irradiation with external beam treatment after initial therapy is effective with similar response rates to those seen after primary treatment. Response seen in patients who do not respond initially and second and third irradiation responses are also documented. The mechanisms of action for this remain unclear.

Radioisotope therapy is established as a safe and effective treatment for multiple bone metastases. Repeated doses can be given provided sufficient time is given for bone marrow recovery. Multiple re-treatments have been documented in the literature with response rates similar to those experienced initially and no excess toxicity.

Spinal metastases and spinal canal compression represent a bigger challenge for re-irradiation. In metastatic spinal canal compression then the relatively poor survival of patients with recurrence limits concerns with regard to myelopathy. Re-treatment with standard schedules of 8 Gy or 20 Gy in five fractions have been shown to be effective and safe in this respect. Patients with localised recurrent spinal disease may now be safely treated with modern focal techniques such as stereotactic body radiotherapy or IMRT. There remains some uncertainty with regard to spinal cord tolerances in this setting, but the ability to limit the dose to the cord means that effective high dose treatment can be delivered offering the chance of durable control in this setting.

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Chapter 19
Challenges of Bone Metastases Treatment in Elderly Patients

Gillian Bedard, Liang Zeng, Erin Wong, Natalie Pulenzas, Breanne Lechner, and Edward Chow

Abstract Cancer rates are increasing, with the majority of cancer patients being over the age of 65. As the global population ages and life expectancies increase, the number of elderly patients requiring treatment also increases, thus the added challenges of treating elderly patients need to be addressed. This chapter outlines the challenges of palliative radiotherapy for elderly patients with bone metastases. We will begin with defining the term elderly, and outline the recent demographic details of patients with cancer. An update on the current status of elderly patients in clinical trials and discussion of factors that may affect enrolment of these patients into trials will be given. With an emphasis on palliative clinical trials, we will discuss methods to promote accrual of elderly patients in this setting. A review of the safety and efficacy of treatment in the elderly is also given, and palliative radiotherapy for the treatment of elderly patients with bone metastases is determined to be an advisable treatment and should be recommended to patients regardless of age. Physical burden of treatment in elderly patients can be alleviated by hypofractionated treatments, as multiple trials and meta-analyses have demonstrated their equivalence in pain control. In elderly patients, palliative radiotherapy may be more beneficial than other treatment options, as opioid-related adverse events are greater in this population. Physicians should continue to encourage elderly participation in clinical trials as this data forms the basis of treatment guidelines. Radiation oncologists are encouraged to offer elderly patients single treatments for bone metastases to reduce the physical burden of multiple treatments.

Keywords Bone metastases • Elderly • Clinical trials • Challenges

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19.1 Introduction

According to recent statistics by the Canadian Cancer Society and Statistics Canada, the incidence rates of cancer more than double in those over the age of 60 [1]. Globally, cancer is a leading cause of death, accounting for 13 % of all deaths in 2008 [2]. Those over the age of 65 account for the majority of cancer patients with over 55 % of all new cases and over 70 % of cancer deaths in this age group [3]. The United States Census Bureau of demographics estimates that by 2030, the number of people over the age of 65 will double to be approximately 70 million [3].

Currently, there is no generally accepted definition of an elderly person. The World Health Organization (WHO) has stated that in most developed countries it has been accepted that the arbitrary cut-off for an elderly person is 65 years of age [4]. Although this value has been agreed upon by a number of developed countries, it assumes that one's chronological age is synonymous with one's biological age. Life expectancies and life spans change by location and time period, and often, it is not adequate to use the definition of over 65 years as elderly. Many countries utilize socially constructed ideals of elderly, such as role assignment or the loss of roles accompanying physical decline, as their definition [4].

Regardless of the true definition of the term "elderly", the care of these older patients differs due to a number of added challenges, such as additional co-morbidities and physical challenges. It is important for health care professionals to be aware of these added challenges, and have an understanding of how to overcome them. The purpose of this chapter is to outline elderly participation in clinical trials, determine evidence for treating elderly bone metastases patients with radiotherapy and discuss potential barriers associated with treatment and clinical trials in the elderly in hopes of finding solutions to overcome them.

19.2 Current Status of Elderly Patients in Oncology Clinical Trials

Currently in clinical trials, the elderly are an unrepresented population of cancer patients. Although the majority of cancer patients are over the age of 65, the majority of patients participating in clinical trials are under this age. Clinical trials are the basis for guidelines and treatment protocols that become the standard of practice. With relatively few elderly patients in these trials, the end result may be guidelines and treatments that may not be the most appropriate for this patient population. Analysis of data from three large oncology trial groups have confirmed the speculated low elderly patient enrolment in comparison to the expected enrolment based upon the number of elderly affected by cancer [5–8].

Yee et al. evaluated the enrolment of elderly patients in Canadian cancer clinical trials through the retrospective analysis of National Cancer Institute of Canada (NCIC)

Clinical Trials Group trials between the years of 1993 and 1996. It was determined that only 22 % of patients in these trials were over the age of 65, while 58 % of the cancer population at this time was over the age of 65. These statistics were similar regardless of cancer type, and study type. Even in supportive care trials, only 21 % of these patients were over the age of 65 [8].

Hutchins et al. analyzed cancer patient enrolment of the Southwest Oncology Group (SWOG) trials from 1993 to 1996 and compared this data to the elderly proportion of the cancer population from the 1990 United States Census and Surveillance Epidemiology and End Results from 1992 to 1994. This group determined that only 25 % of patients on clinical trials were over the age of 65 while 63 % of the general cancer population was over this age [7]. Lewis et al. confirmed this finding through analysis of enrolment in the National Cancer Institute (NCI) sponsored clinical trials, between the years of 1997 and 2000. In this study it was found that only 32 % of clinical trials patients were elderly, while 61 % of the cancer population was elderly [5]. These studies are an excellent demonstration of the underrepresentation of the elderly population in clinical trials.

19.3 Factors Influencing Elderly Accrual in Clinical Trials

It is well documented that the elderly are underrepresented in oncology clinical trials. Many groups have hypothesized reasons for this low accrual of the elderly to be due to three main factors; physician-related, patient-related and logistic [9–11].

19.3.1 Physician-Related Factors

Townsley et al. conducted a systematic review to determine barriers associated with elderly accrual to oncology clinical trials. They found that when physicians were asked what they thought potential barriers to accrual were, the majority of physicians responded with comorbid conditions and toxicity of treatment [8, 11, 12]. A fewer number of physicians also thought barriers included lack of support for elderly patients to manage side effects at home, patient preference and family influence, difficulties in understanding the trials, excessive time to enroll elderly patients and short life expectancy of these patients [11]. In this review it was found that a substantially fewer number of elderly patients were offered clinical trials by their physician than younger patients [11].

Although a number of factors were identified for the exclusion of elderly patients, the majority of these factors are due to a lack of research in tumor biology, lack of evidence of the effects of treatment on comorbid conditions and lack of research in the treatment of toxicities in the elderly [11].

Studies in breast cancer and chemotherapy have concluded that there is no difference in treatment toxicities and side effects regardless of age [13, 14]. On the contrary, hematological studies have concluded that the elderly generally experience more severe treatment toxicities [15–17]. Currently, there are relatively few studies that determine the differences between young and elderly patients in regards to treatment toxicities and side-effects. Further research is required to determine age-related changes in organ function, and the impact of comorbidities on oncology treatment. Differences in the pharmacokinetics and pharmacodynamics of drugs in the elderly should also be established, along with the impact of age on the biology of tumors. Yee et al. suggest that an increase of clinical trials that specifically target the elderly population would be useful to establishing guidelines on how to treat the elderly and to disprove many physician-related barriers to treatment [8].

19.3.2 Patient-Related Factors

Patient-related factors are important, however, it appears that physician-related factors have a more significant influence on whether or not elderly patients participate in clinical trials. Townsley et al. found that the majority of elderly patients wanted to participate in clinical trials, however they did not actively seek them and very few elderly patients were aware of their availability [18].

Elderly and young patients were interviewed to determine their reasoning for enrolling and for declining participation in clinical trials. Reasons for enrolment were slightly different between the two sets of patients, with the three main reasons for younger patients including: improvement to health, find a cure for cancer and desire for most up-to-date treatment [8, 11]. Elderly patients' main reasons for enrolment included: best treatment available, improvement to health, and find a cure for cancer [11]. Both young and elderly patients alike, expressed their reasoning for not partaking in clinical trials to be because they wanted to choose their own treatment [11, 19].

Accrual differences exist between these two age groups. Often times, elderly patients require more time and explanation of the details of clinical trials. This may be due to the fact that elderly patients, in general, have lower levels of education than younger patients [20]. These concepts of clinical trials may be more foreign to elderly patients, thus requiring a more in depth explanation of the trial and outcomes by physicians. Many physicians identified this need for greater time and effort in explanation of clinical trials to elderly patients as a barrier to accrual [11]. Kornblith et al. surveyed oncologists and found that this was a key area for improvement to increase accrual of elderly patients [12]. Other studies have determined that a larger focus on patient knowledge of clinical trials would improve enrolment [21]. Perhaps, additional support systems in the hospitals, such as social workers and research assistants would help the accrual of elderly patients onto clinical trials and would

overcome the barriers of time and knowledge. Addition of these personnel could assist in the explanation of clinical trials as well as give patients background knowledge, and answer questions that the physician may not have time to answer.

19.3.3 Logistic Factors

Logistic factors include protocol barriers, transportation barriers, and dissemination of knowledge barriers. Clinical trials are made aware to the public and physicians through dissemination of knowledge. It is crucial to the survival of a clinical trial that a large number of physicians and patients are aware of its accrual. Improving access for the elderly to clinical trials is an area that could be improved upon in order to increase accrual [22].

There are also protocol design barriers that limit elderly accrual. Primarily, the exclusion criteria of performance status often results in the exclusion of many elderly patients. Although this exclusion is the result of safety concerns, and to not cause harm to patients, the issue in this is that it is difficult to interpret performance status as it may be a limitation of mobility and not necessarily health. Alternative methods for exclusion of low performance status patients may be required in order to include those patients for whom only mobility is an issue, and they have no other contraindications for accrual onto a trial [11].

Another issue for this age group is transportation. Due to limited mobility, it may not be feasible for patients to return to the cancer centre for additional follow-ups that are only required for the clinical trial purpose. These additional follow-ups may be a burden to patients and their families. In order to improve the accrual of these patients to clinical trials, it may be better to choose alternative follow-up methods, such as over the telephone or through email. Telephone follow-ups have been proven effective in palliative cancer patients [23].

Costs associated with clinical trials may also be a deterrent to many patients. Often times, health insurance does not cover the cost of study drugs, thus patients without coverage, and those who cannot afford the costs of a trial, refuse to participate. Reducing costs associated with clinical trials may prove to increase accrual of all patients, and in particular the elderly.

19.4 Efficacy and Adverse Events of Radiation in Elderly Patients

In addition, due to the reluctance to enrol elderly patients onto clinical trials, sometimes radiation oncologists are reluctant to treat elderly patients with radiation for fear of adverse events and concerns of efficacy. The current literature on this topic only contains retrospective reviews that address these issues. Nevertheless, these

fears are misconceptions, and the majority of elderly patients treated with radiation therapy for bone metastases, or other cancers do not experience any significant adverse events [24]. A number of studies have proven the efficacy and safety of radiation therapy treatment in the elderly.

19.4.1 Efficacy and Side Effects of Radiotherapy in the Elderly

Almost 20 years ago, a study by Giovanazzi-Bannon et al. analyzed data from a number of phase II clinical trials. They determined that there were no significant differences between elderly and non-elderly patients in response to treatment, reason off study and grade 3 or greater toxicities [25].

Pignon et al. reviewed data obtained from six randomized trials on the acute and late toxicity impact of curative thoracic radiotherapy [26]. Although only 9 % of patients were over the age of 70, there was no significant difference for any side-effects including; acute nausea, dyspnea, oesophagitis, weakness and WHO performance status change. Late toxicities with a grade greater than or equal to one were also determined to not be statistically different between the different age groups. Mean time to complication, as well as survival (adjusted for primary location of the tumor) was also comparable across age groups. The authors concluded that age is not a sufficient reason to exclude patients from curative thoracic radiation therapy.

A recent study by Gomez-Millan et al. also assessed the relationship between age and radiation toxicity. Preclinical studies showed that there is little difference in the normal tissue radiation-induced toxicity with age. Clinically, they demonstrated that there is no relationship between age and incidence of toxicities; however they did mention that this may occur if radiation is combined with chemotherapy. It has been reported that concurrent chemotherapy and radiation therapy in elderly patients may result in more treatment interruptions, more functional impact and that the elderly may be more vulnerable to the secondary effects of treatment. Thus, they suggest that elderly patients undergo a specific geriatric assessment before they are offered high dose radical treatment, so as to determine the most appropriate candidates [27].

Even in patients over the age of 80 years, age was not found to be a contraindication to aggressive radiation therapy. Of the 191 patients included, 94 % completed treatment without serious complications. However, whether or not completion of treatment is an appropriate endpoint can be argued, and response rate may be a more appropriate endpoint. 77 % of patients who were treated with a curative intent showed a response (partial or complete), and 81 % of patients treated with a palliative intent, also had a response to treatment. Only 2 % of patients had a grade 3 or higher toxicity. This group also suggested that in some cases, radiotherapy may be the best treatment for those 80 years and older, due to the greater risk of other treatment complications [28].

19.4.1.1 Very Elderly (90 Years and Older)

Finally, in the very elderly (90 years and above), it has been concluded by multiple studies that radiation treatment does not pose more risk factors than in younger patients. A study by Oguchi et al. concluded that radiotherapy should be considered even in patients over 90 years, as it can be successful. The results of this study demonstrated local control rates of 62 % at 6 months, and palliation rates of 81 % [29]. Only low grade side-effects were noted. In another study of elderly patients, Mitsuhashi et al. also concluded that being 90 years or older is not a limiting factor for radiation therapy. This group treated 11 of 14 head and neck cancer patients with a curative approach, and response without severe complications was seen in 90 % of these patients. A complete response was achieved in all patients treated curatively, and palliation was achieved in all patients treated with a palliative approach [30].

19.4.2 Radiotherapy for Uncomplicated Bone Metastases in the Elderly

In palliative radiation therapy for bone metastases, multiple randomized trials have demonstrated that a single fraction of radiation treatment is sufficient and has the same efficacy as multiple fraction treatment for the palliation of painful uncomplicated bone metastases [31].

Chow et al. have conducted a recent meta-analysis that includes data from 25 randomized trials that compare single fraction (SF) to multiple fraction (MF) radiation therapy for the palliation of painful uncomplicated bone metastases [24]. In the comparison of SF to MF, it was determined that overall response rates were similar between the two, with 60 % of SF patients responding to treatment and 61 % of MF patients responding to treatment, this suggested no significant difference between the two fractionations [24]. In addition, complete and partial response rates were not significantly different between the trials. There were no differences in the number of patients developing pathological fractures (3.3 % of SF vs. 3.0 % MF), or spinal cord compression (2.8 % vs. 1.9 %) [24]. There was however, a significant difference in the number of patients requiring retreatment. Almost three times as many patients in the SF arm needed retreatment when compared to the MF arm. The authors commented that this was possibly due to the fact that physicians were more likely to retreat a patient who was initially treated with SF as opposed to MF [24].

Elderly patients can greatly benefit from these findings, as it proves that single treatment radiation therapy is as successful as multiple fraction radiation therapy. For these patients, it is possible to assess and treat the patient on the same day. Danjoux et al. demonstrate the feasibility and effectiveness of their clinic that holds consultation, treatment planning and treatment delivery on the same day [32]. This can result in the reduction of logistic and patient-related barriers to treatment of the elderly with radiation therapy.

To date, there has only been one study that has assessed age in relation to palliative radiotherapy for uncomplicated bone metastases. Campos et al. investigated the efficacy of radiation treatment in the elderly and determined that there was no significant difference in response rates in patients greater than 65, 70, and 75 years of age compared with younger patients at 1, 2 and 3 months post-treatment. Response rate was however found to be significantly related to performance status. Thus, this group concluded that age alone did not affect response rate of palliative radiotherapy for uncomplicated bone metastases, and the elderly should be referred as they will benefit equally from treatment [33].

At present, there is little data on the elderly population of oncology patients; however this population may be similar to those with a shortened life expectancy. There have been a number of studies assessing the benefits of palliative radiotherapy in those patients with life expectancies of 3 months or less. Dennis et al. found that patients who are in the last 3 months of life experience significant pain relief and improved functioning [34]. The Dutch Bone Metastases Group also obtained similar results and recommend single fraction treatments for short life expectancy patients in order to reduce their burden and allow them the same levels of pain palliation [35].

19.4.3 Radiotherapy for Complicated Bone Metastases in the Elderly

Complicated bone metastases include: metastatic epidural spinal cord compression (MESCC), neuropathic pain, pathological fracture or high fracture risk. It has previously been thought that these complicated metastases require multiple treatments and may be burdensome to elderly patients. Recent data have shown that single treatments for these complicated bone metastases may be beneficial to patients who are unable to withstand multiple treatments [36, 37].

Rades et al. analyzed data from 308 patients who were at least 75 years of age, comparing the functional outcome, local control and survival between short course and long course radiotherapy for spinal cord compression. It was found that both short and long course radiotherapy were effective in regards to functional outcome and survival. However, long course treatment provided better local control. The authors suggest that the criteria for selection of a radiation fractionation be based upon the same criteria as for younger patients [36]. In another study, it was concluded that even a single dose of 8 Gy radiation is effective in palliating spinal cord compression with minimal toxicity for patients in a phase III randomized trial [38].

For patients experiencing neuropathic pain from bone metastases, a randomized trial of 8 Gy in 1 fraction versus 20 Gy in 5 fractions concluded that a multi-fractionated treatment was more effective than a single treatment [37]. However, a single treatment was not shown to be statistically significantly worse, thus it may be recommended that patients who are elderly and unable to withstand multiple treatments, or have a short life expectancy, may be treated with a single dose of radiation to palliative neuropathic pain.

19.4.4 Side Effects of Palliative Radiotherapy for Bone Metastases in the Elderly

A physician-related barrier to the enrolment of elderly patients onto clinical trials and to radiation treatment is the concern that the elderly may experience worsened side-effects and find it difficult to manage. Although more clinical trials are needed to further investigate the side-effects after palliative radiation therapy for bone metastases, the current literature suggests that there are no significant differences between older and younger patients in this regard.

Pain flare is one of the most common side effects associated with palliative radiotherapy of bone metastases. It occurs in up to 40 % of patients who receive conventional radiation treatment and up to 70 % of patients who receive stereotactic body radiotherapy [39]. Pain flare is defined as a 2-point increase in the worst pain score (0–10) in comparison to baseline with no decrease in analgesic intake, or a 25 % analgesic intake increase with no decrease in worst pain score [39]. Typically, this pain flare occurs within the first 10 days following treatment. Hird et al. investigated this pain flare and determined that there was no age effect associated [39]. This side effect however can be reduced. In a phase II study by Hird et al., it was concluded that a single dose of dexamethasone is effective in the prophylaxis of radiation-induced pain flare [40]. The median age of participants was 67 years.

Radiation-induced nausea and vomiting (RINV) is also a common side effect in this patient population, especially in those who are radiated in the abdominal region and have a large treatment volume. This area is one of current research and current literature has not reported any differences between young and elderly patients in regard to RINV [41, 42]. Again, this side-effect can be reduced with the prophylactic prescription of Ondanestron a 5-HT3 receptor antagonist [41].

19.5 Alternatives to Radiotherapy for Elderly Patients

Very rarely will patients be ineligible for radiation; however, sometimes patients reach the upper safe limits of radiation to one anatomical area. For these patients, strategies to palliate pain often consist of increases in analgesics. However, in elderly patients, analgesics and in particular opioids can have increased side-effects than in younger patients. A study by Cepada et al. assessed the effects of gender, race and age on the side-effects of opioid treatment. They found that patients between the ages of 61 and 70 had almost three times the risk of developing respiratory depression in comparison to those between the ages of 16 and 45 years. Patients between the ages of 71 and 80 had 5.4 times the risk, and patients over the age of 80 had 8.7 times the risk [43]. Another study investigated the use of opiates in the elderly. They found that the physiological, pharmacological, and psychological changes in the elderly greatly affect the side effects experienced. The physiological changes that occur alter the pharmacokinetic profiles of opiates, and there is impaired metabolism, excretion and physiological reserve of active drug ingredients [44].

Changes in body composition that are a result of aging, such as the increase in adipose tissue and decrease in lean body mass, affect the distribution of drugs, and lipophilic drugs have been proven to take longer to be eliminated from the body [45]. A reduction in hepatic blood flow and volume can decrease the metabolism of the drug [46]. Careful titration of opioids should be employed in the elderly as they are more sensitive and more likely to be affected by opioid toxicity. The elderly often receive a greater number of medications, and have an increased number of co-morbidities that need to be taken into account when determining optimal analgesic treatment. Mercadante et al. suggest that appropriate dosage and administration may limit risk factors associated with treating the elderly with analgesics [47].

19.6 Additional Challenges of Radiotherapy in the Elderly

Not only are there challenges and concerns related to the efficacy, safety and optimal treatment of bone metastases in the elderly, there are additional psychological and family challenges to deal with. Often times, family members will request the physician to not disclose diagnoses and to keep medical information from the patient [6]. Sometimes, families also request that no tests or biopsies be conducted. The physical and psychological burden in these cases must be taken into consideration to effectively treat the patient and to satisfy the emotional needs of the family and the patient. In situations such as these, it may be beneficial to involve other health care professionals in this patient's care, such as psychologists or social workers.

Another added challenge of treating bone metastases in the elderly is the determination of whether pain is from the cancer or if it is of a degenerative or osteoporotic nature. In a study by Muijis et al. 78 biopsies were obtained of patients undergoing percutaneous vertebroplasty for vertebral compression fractures. Of the 78 patients, 3 were found to have malignant diagnoses that were not previously known [48]. The authors recommended that a routine biopsy be conducted prior to treatment. An accurate diagnosis is required before treatment; however this is made difficult in patients and families who do not want to pursue additional tests. It may be beneficial to the patient, if physicians take time to explain the need for further tests, give the patient the treatment options based upon the potential outcomes and allow the patient to decide if they want additional tests.

19.7 Next Steps and How to Increase Accrual of the Elderly in Clinical Trials

Radiation therapy has been proven to be beneficial in the elderly bone metastases population. In order to best overcome barriers associated with treatment of this patient population, treatments should be tailored specifically to elderly patients. Radiation oncologists need to be further educated in the efficacy of treating palliative patients with a single dose of radiation to palliate bone pain associated

with bone metastases. Next steps for radiation oncologists include completing consultation, planning and treatment of patients in a same day visit, as well as increasing referrals for patients with symptomatic bone metastases. In addition, other next steps include the treatment of and prophylaxis against side effects (such as pain flare and RINV) associated with radiation treatment. Establishing evidenced based guidelines for the treatment of elderly patients will be crucial in order to determine the optimal treatment of this patient population. However, this information can only be obtained through clinical trials, thus increasing elderly accrual is important.

In order to increase accrual of elderly patients, physicians need to encourage and promote the involvement of elderly patients. Health care professionals also need to work to educate each other in the benefit of the inclusion of this patient population. Misconceptions of increased burden and side effects of clinical trials in the elderly also need to be dispelled. To overcome barriers to accrual, protocol inclusion and exclusion criteria may need to be less stringent in regards to the exclusion of patients based upon age, performance status and comorbidities. In addition, health care professionals can work to make clinical trials easier for elderly patients, by allowing follow-ups to take place over the phone or less often in the centre. Lastly, the inclusion of a research assistant or social worker to the patient's health care team could greatly aid in the explanation of clinical trials and what is involved, so that elderly patients have time to process the information and ask the appropriate questions.

19.8 Closing Remarks

Palliative radiotherapy for bone metastases should be offered to all patients regardless of their age. Although there is a relatively small amount of literature on the elderly, current findings suggest that side-effects from radiation treatment are not exasperated in the elderly, thus there is no reasoning not to treat them on this basis. Radiation therapy has been found to be beneficial in palliating pain associated with symptomatic bone metastases; even just a single 8 Gy treatment is as beneficial as multiple treatments. For those patients who are very elderly, or who have poor performance status and cannot withstand multiple treatments, a single treatment can be offered for spinal cord compression as well as neuropathic pain.

Further studies are needed in order to establish evidenced-based guidelines for treatment of bone metastases in the elderly.

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Chapter 20
Management of Metastatic Bone Disease in the Elderly with Bisphosphonates and RANKL Inhibitors: Effectiveness and Safety

Vassilios Vassiliou, Panteleimon Kountourakis, and Dimitrios Kardamakis

Abstract In the last decades life expectancy of western populations has increased considerably, resulting in a steep rise in the number of elderly patients diagnosed with cancer. Metastatic bone disease (MBD) is a major concern in such patients since it may be associated with the development of skeletal related events (SREs) including fractures and cord compression. These complications may deteriorate the quality of life (Qol) of affected patients and also reduce expected survival. Due to the fact that in elderly patients there is an increased risk for the development of SREs, maintaining bone health and using effective therapies for MBD is of vital importance. Through numerous clinical trials Bisphosphonates (Bps) have proved to be effective in reducing the risk for SREs significantly in patients with MBD. Moreover, they have shown to decrease pain and improve Qol of treated patients. In elderly patients Bps should be used with caution since their use may cause serious complications such as renal function deterioration. Denosumab is a monoclonal antibody that targets and inhibits RANKL and has shown superiority over zoledronic acid in decreasing the risk of SREs. The elimination of denosumab is done through the immunoglobulin clearance pathway through the reticuloendothelial system and does not to affect renal function. It can therefore be safely used in the elderly. Osteonecrosis of the jaws (ONJ) is a serious complication that may develop after treatment with either denosumab or zoledronic acid. The incidence rates between the two were reported to be comparable. In order to

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decrease the risk of renal function deterioration or ONJ all preventive measures and treatment guidelines should be followed with caution. In this review article we comment on the effectiveness and safety of Bps and denosumab in elderly patients and discuss all indicated measures that should be implemented for minimizing the risk of potential complications. Several studies have investigated the cost effectiveness of denosumab versus zoledronic acid in terms of SRE prevention. These studies reported contradictory results mainly due to the application of different analytical perspectives and model parameters.

Keywords Bone metastases • Elderly • Bisphosphonates • RANKL inhibitors • Zometa • Renal safety • Osteonecrosis • Cost effectiveness

20.1 Search Strategy and Selection Criteria

The data for this chapter were identified and selected after a detailed search in PUBMED by using the terms 'bone metastasis', 'bisphosphonates', 'RANKL inhibitors', elderly', 'renal safety', 'SRE's', 'pain', 'osteonecrosis', 'quality of life' 'hypocalcaemia' and 'cost effectiveness'. At the time of writing this manuscript no data from phase III studies focusing on elderly patients was available. Presented data were derived from phase II or phase III studies involving subgroup analyses on elderly patients. No age 'cut off' was used and studies that defined elderly as patients aged ≥ to 65 or 70 years are included.

20.2 Introduction

In the last decades the life expectancy of the general population has increasing together with that of elderly cancer patients. It was estimated that one fifth and one quarter of the population of the western world will be ≥65 years old by the year 2020 [1]. Since most cancers and cancer related-deaths occur in elderly patients, there is an absolute need for implementing effective and safe treatments for such patients.

A major concern is that elderly patients are in most cases excluded from clinical trials due to the expected toxicity [2]. Another problem is that such patients are often undertreated and receive only supportive care. The development of bone metastases in elderly cancer patients is an important issue since it may affect both their Qol and overall survival [3, 4]. Additionally the skeletal apparatus of such patients is vulnerable and predisposes to clinical conditions and pathologies such as osteoporosis, fractures, impaired mobility and bone pain. Such conditions augment the risk of SREs which include pain, pathologic fractures, surgery or radiotherapy to bone, spinal cord or nerve root compression and hypercalcemia of malignancy (HCM) [2].

For all the above concerns maintaining an adequate bone health and implementing effective therapeutic strategies for elderly patients with MBD is of critical importance. Such treatments should target a decrease in the risk of SREs and an improvement in the level of suffering and quality of life. Additionally, bone disease free survival and probably overall survival may be increased. Both Bps and the receptor activator of NF-kB ligand (RANKL) inhibitors have shown to be effective in the management of MBD. In this review article we comment on their effectiveness and safety issues in elderly patients. The need to follow closely all indicated safety and preventive measures is very important for such patients who have a physiologic decline in their organ function.

20.3 Bisphosphonates

Bps are potent inhibitors of osteoclasts and associated bone destruction and their use in patients with MBD has increased considerably in the last decades [2]. In elderly cancer patients with MBD treatment with Bps warrants special attention due to the physiologic organ function decline and associated co-morbidities. One should always bear in mind that elderly patients may have an impaired renal function or insufficiency, with creatinine clearance not exceeding 60 ml/min. This can be related to advanced age or a consequence of underlying diseases such as multiple myeloma or treatment with nephrotoxic agents such as chemotherapy [5]. Additionally an inadequate hydration status or overuse of medications such as non-steroidal anti-inflammatory drugs, lipid-lowering agents, anti-hypertensives or anti-diabetic compounds can also impair renal function. In addition to renal function other tolerability issues that are related to Bp treatment include acute-phase reaction symptoms and ONJ.

20.3.1 SREs Prevention

Table 20.1 presents the dosing, administration duration and indications of use for Bps that are routinely used in clinical practice.

20.3.1.1 Intravenous (i.v.) Bps

Zoledronic Acid

Zoledronic acid has shown effectiveness in decreasing the rate of SREs in patients with MBD from breast or prostate cancer and other solid tumors [6–9]. In a recent meta-analysis conchrane data revealed that zoledronic acid achieves a reduction in SRE risk by 41 % (risk ratio 0.59) [7]. The effectiveness of zometa was also shown in multiple myeloma patients [6].

Table 20.1 Bps used for the management of MBD

Bisphosphonate	Clodronate	Pamidronate	Zoledronate	Ibandronate
Administration route	Oral or IV	IV	IV	Oral or IV
Indication for use	Multiple myeloma; HCM	Breast cancer MBD; multiple myeloma; HCM	MBD from any solid tumor; multiple myeloma; HCM	Breast cancer MBD; HCM
Dosing regimen	Oral: 1600 mg/day, range 800–3,200 mg/day (maximum) Intravenous: 900 mg for 2–4 h every 3–4 weeks	90 mg in >2 h repeated every 3–4 weeks	4 mg for ≥15 min in every 3–4 weeks if creatinine clearance >60 ml/min[a]	Oral: 50 mg/day IV: 6 mg in 1 h repeated every 3–4 weeks

HCM hypercalcemia of malignancy, *IV* intravenous, *MBD* metastatic bone disease
[a]If impaired renal function dose adjustments are indicated

The safety of zoledronic acid in patients with MBD from breast cancer or solid tumors was reported to be similar to that of pamidronate or placebo. In the contrary, in patients with hormone refractory prostate cancer (HRPC), renal function was shown to deteriorate in 17.4 % of patients managed with 4 mg zoledronic acid (as compared to 12.4 % of the placebo arm) [10]. A subset analysis for renal function in patients aged ≤70 and >70 years reported the percentage of patients experiencing a renal function deterioration. Interestingly, this analysis showed that the percentage differences between the two age groups were marginal for treatment with either zoledronic acid (4 mg) or pamidronate (90 mg). Within the data limits one may support that the elderly kidney may be equally sensitive as compared to a younger kidney, when administering intravenous zoledronic acid [11].

Recommendations for Use

In elderly patients renal function should be evaluated and monitored with special attention [12]. In patients with a preexisting renal function impairment or previous treatment with multiple Bp infusions, there is an increased risk for renal deterioration after treatment with zoledronic acid [13–16]. Dose adjustments are indicated in patients with mild to moderate renal function impairment based on the baseline creatinine clearance: >60 ml/min = 4 mg; 50–60 m/min = 3.5 mg; 40–49 ml/min = 3.3 mg; 30–39 ml/min = 3.0 mg [10]. In the event that creatinine clearance is below 30 ml/min the administration of zoledronic acid is not recommended.

Prior to any infusion with zoledronic acid it is recommended to measure serum creatinine and to optimize the hydration status of patients [10, 17]. Nephrotoxic compounds such as antidiabetic agents or lipid-lowering drugs or chemotherapy should not be used concurrently when possible [17]. Serum calcium levels should also be measured before treatment and patients should receive

daily adequate oral calcium (500 mg) and vitamin D (400 IU) supplementation in order to avoid hypocalcaemia.

Pamidronate

Several randomized studies have shown that pamidronate is effective in reducing the risk of SREs in patients with MBD from breast cancer or multiple myeloma [18–20]. In these studies treatment was well tolerated and only a few renal adverse events were reported. Renal function deterioration was evident in patients with multiple myeloma receiving long term treatment. However, in a study involving 22 elderly patients with a median age of 73 years, treatment was reported to be effective and safe [21].

Recommendations for Use

In patients with multiple myeloma and renal impairment (serum creatinine <30 mg/dl) ASCO guidelines do not recommend an alteration in dosage, infusion time or interval. However it may be wise to increase the treatment interval [21, 22]. Dose adjustments are not recommended in mild (creatinine clearance 61–90 ml/min) to moderate renal impairment (creatinine clearance 30–60 ml/min) [23]. However in cases with creatinine clearance <30 ml/min, treatment with pamidronate is not adviced. An exception to this recommendation may be life threatening HCM. The evaluation of renal function is recommended prior to each infusion. In the event of renal function deterioration, treatment should be stopped until it returns to within 10 % of its baseline value [23].

Intravenous Ibandronate

In a phase III placebo-controlled trial involving breast cancer patients with MBD i.v. ibandronate proved to be effective and safe. Two year evaluations showed that renal safety was comparable to that of placebo [6]. In a subset analysis of patients aged >65 years it was seen that renal function impairment was similar between the ibandronate and placebo group. In view of these data it may be suggested that i.v. ibandronate may be administered with safety in elderly patients since its tolerance is comparable to that of placebo [11].

Recommendations of Use

No dose adjustment is necessary for patients with a creatinine clearance ≥30 ml/min. In cases with even lower creatinine clearance, 2 mg infusions should be administered every 3–4 weeks with infusion times lasting for 1 h. In the European Union approved product labeling recommends monitoring of renal function only if this is advised by the physician [17]. Additionally, no dosing restrictions are required for patients receiving concurrently ibandronate and nephrotoxic antineoplastic agents.

20.3.1.2 Oral Bps

Clodronate

Oral clodronate has proved to be effective in reducing the risk of potential SREs in patients with multiple myeloma or breast cancer with MBD [24–27]. In spite of the fact that the administration of oral Bps is more practical as compared to intravenous administration, their use may be accompanied by a high rate of gastrointenstinal adverse events. This fact together with potential swallowing difficulties due to large tablet size, leads to reduced compliance.

Recommendations of Use

In clinical studies evaluating the effectiveness of clodronate patients aged >65 years were included. No adverse events were reported for these patients who received the full indicated dose. In patients with a creatinine clearance ranging between 10 and 30 ml/min the daily dose should be halved to 800 mg. In cases with a creatinine clearance not exceeding 10 ml/min the administration is contra-indicated [17, 28].

Oral Ibandronate

Oral ibandronate has shown to be both effective and safe in two randomized studies involving patients with bone metastases from breast cancer [6]. In these studies ibandronate was used in 50 mg daily tablets and an acceptable compliance was noted [6].

Recommendations for Use

No dose adjustments are required for elderly patients or patients with creatinine clearance exceeding 30 ml/min. In patients with creatinine clearance <30 ml/min the recommended dose is 50 mg/week [6].

20.3.2 Bps for Bone Pain

Metastatic bone pain is a real clinical challenge that may result in restricted mobility and decreased Qol [29]. External beam RT is the mainstay treatment for metastatic bone pain achieving considerable pain responses. Bps have also proved to be effective in pain alleviation. Interestingly, the concurrent administration of RT and Bps has shown to bring about an enhanced level of reossification in areas of bone metastases that is associated with an improved pain response [30].

20.3.2.1 Zoledronic Acid

In the comparative clinical trial both zometa (4 mg) and pamidronate (90 mg) achieved a reduction in pain scores at the evaluation time point of 12 months. Analgesic intake was reported as stable or reduced [31]. Moreover, in breast cancer patients with MBD zoledronic acid achieved a considerable reduction in bone pain as compared to baseline and placebo [32]. Additionally, in patients with HRPC and bone metastases reduced increases in pain and analgesic consumption were reported when treated with zoledronic acid versus placebo [6].

20.3.2.2 Pamidronate

Pamidronate has shown to bring about a significant reduction in pain in patients with breast cancer or multiple myeloma [18, 19, 33]. In contrary, two placebo-controlled studies involving men with prostate cancer showed that there was no significant pain response or change in analgesic consumption for patients treated with either pamidronate or placebo [34].

20.3.2.3 Ibandronate

In the three phase III trials involving patients with breast cancer and MBD ibandronate showed to achieve a significant reduction of pain scores as compared to baseline up to 2 years [6, 35, 36]. The maximal pain response was observed after about 12 weeks of treatment. In patients treated with ibandronate the reduction of pain scores was accompanied by a reduction in analgesic use ($p=0.19$ for oral group) [36].

20.3.2.4 Combined RT and Bps

The concurrent administration of RT and Bps in patients with MBD from a variety of solid tumors has shown to achieve a significant pain response and considerable improvement in the Qol and performance status of patients. These improvements were associated with an enhanced level of reossification in affected skeletal regions [37–39]. This is a result of an additive and synergistic effect of the two treatment motilities on osteoclastic activity [30, 37, 39]. It is worth to note that RT and Bps have independent limiting toxicities and can be therefore administered concurrently with safety. However, all the preventive measures and administration recommendations concerning Bp use should be followed.

Approach for Elderly Patients with Painful Bone Metastases

There are many treatment modalities that may be used either alone or in combination for the management of metastatic pain. These include analgesic drugs,

chemotherapy, hormone therapy, RT, radionuclides, Bps, and surgery. In spite of the fact that Bps have proved to be effective in reducing bone pain, they should be used as a complementary treatment and not as an alternative to analgesic medications.

20.3.3 Qol and BP Use

Ibandronate has shown to improve Qol in patients with MBD. In the study by Diel IJ et al. global functioning was reported to improve significantly ($p=0.004$) in patients receiving i.v. ibandronate [36]. Significant improvement was also noted in patients treated with oral ibandronate as compared to placebo in the two oral clinical trials ($p=0.03$) [35].

20.4 Renal Safety and Elderly Patients

As already discussed, elderly patients have a decreased renal function and treatment with Bps should be done with caution. Prior to i.v. Bp administration creatinine clearance should be calculated for all patients. Bp doses should always be adjusted according to the calculated creatinine clearance and the indicated infusion times should be used. These measures are necessary since renal function deterioration could be associated with the dose of Bps in serum and the infusion duration [6]. Additional measures that can be applied in order to further reduce the risk of nephrotoxicity are the avoidance or limitation of concurrent use of nephrotoxic medication or the use of alternative medication with a reduced renal toxicity. Moreover the hydration status of patients should be optimal before Bp infusions [17]. Last but not least oral Bps may be preferred instead of intravenous treatment in patients with poor renal function.

20.5 ONJ

Bp use may be complicated by ONJ which is a serious complication characterized by the presence of exposed necrotic bone. ONJ occurs either spontaneously, with the failure of healing for a period of 6 weeks, or after invasive dental surgery or teeth extraction [40, 41]. The development of ONJ is associated with risk factors which include traumatic dental procedures, poorly fitting dentures, female gender, poor oral hygiene, anemia, coagulopathy, advanced age, tobacco or alcohol use, chemotherapy, periodontal disease and immunosuppresed states [42]. Moreover patients treated with zoledronic acid or pamidronate have an increased risk for developing ONJ [43].

There are specific preventive measures that should to be taken both before and during treatment with Bps in order to reduce the risk of ONJ [42, 44]. Patients should be evaluated by a dental professional before the onset of Bp treatment and also during therapy every 3–6 months. Before treatment onset it is advised to extract teeth with a negative prognosis and correct any poorly fitting dentures. Since advanced age is itself a risk factor for ONJ and many elderly patients carry dentures, it is important to follow closely the aforementioned proposed measures.

20.6 RANKL Inhibitors

RANKL inhibitors disrupt the viscous cycle of bone metastases that is responsible for osteolysis and destruction. The inhibition of RANKL brings about a reduction of lytic and sclerotic changes in metastatic bone lesions and also hinders associated tumor progression. This was shown in several studies with animal cancer models and bone metastases involving both solid tumors and multiple myeloma [45–50].

Denosumab is a RANKL inhibitor that is approved in the USA and Europe for managing patients with MBD from solid tumors. It is a fully human monoclonal antibody that binds selectively to the RANKL receptor, bringing about a decrease in osteoclastic function to a similar or even greater extent as compared to intravenous Bps [51, 52]. Denosumab is administered subcutaneously every 4 weeks and the dosing is 120 mg.

20.6.1 Prevention of SRES and Denosumab

Three comparative double blind studies have assessed the effectiveness of denosumab and zoledronate in patients with breast, prostate or other solid tumors or multiple myeloma [53–55]. The primary end point of these studies was the time to the first on study SRE. In the studies involving patients with breast or HRPC denosumab achieved a delay in the time to the first SRE by 18 % as compared to zoledronic acid. The corresponding reduction in patients with solid tumors or multiple myeloma was 16 % [53–55].

20.6.2 Denosumab Safety in Elderly Patients

In the three randomized studies that evaluated the efficacy of denosumab over zoledronic acid patients with age ≥18 were enrolled and the toxicity in elderly patients was not evaluated separately. Overall denosumab showed to be well tolerated and a comparable safety profile was noted for all tumor types [53–55].

20.6.3 Renal Safety

Any patient with creatinine clearance <30 ml/min was excluded from the three pivotal studies that evaluated the effectiveness of denosumab versus zoledronic acid. This was done in order to align with the prescribing guidelines of zoledronate [50]. Moreover, in accordance with the prescription guidelines of zoledronic acid, the i.v. dose (together with blinded i.v. placebo) was adjusted based on the baseline creatinine clearance, and i.v. doses were withheld in the event that serum creatinine levels increased during the study. For denosumab and the blinded subcutaneous placebo no alterations in subcutaneous dosing was carried out in relation to renal function.

In the breast cancer trial 12.9 % of patients had an adjustment of their initial zoledronic acid dose and in 5.5 % of patients zoledronic acid infusions were withheld due to an increase in their creatinine serum levels [55]. In the study involving prostate cancer patients 22 % of cases treated with zoledronic acid had an initial dose adjustment and in 15 % treatment was withheld due to elevation in serum creatinine [53]. In the study involving patients with solid tumors/multiple myeloma there were initial zoledronic acid adjustments in 17.3 % of cases and treatment was withheld in 8.9 % of patients. In the same trial, elevation of serum creatinine to abnormal levels was evident in a fewer patients of the denosumab arm as compared to the zoledronic acid arm (16.5 % versus 23.9 %).

In spite of the fact that initial doses were reduced and subsequent treatments withheld in cases with impaired renal function, the incidence of adverse events potentially associated with renal toxicity, such as renal failure, were numerically higher (by 1.3–1.7 fold) in the zoledronic acid group as compared to denosumab. This was true for the studies involving breast cancer and solid tumor/multiple myeloma patients [54, 55]. In breast cancer patients treated with zoledronic acid serious adverse events potentially related to renal toxicity were 7.5 times higher as compared to those managed with denosumab [55]. In relation to patients with prostate cancer the incidence of adverse events potentially associated with renal impairment was similar between the two study groups [53].

20.6.4 ONJ and Denosumab

Positively adjudicated ONJ occurred infrequently in the three Denosumab SRE studies and clinical symptoms and characteristics were similar between the different treatment groups [53–55]. ONJ occurred in 1.8 % of patients treated with denosumab as compared to 1.3 % of those receiving zoledronic acid ($p = 0.13$). In the breast cancer study the reported rate for resolution of ONJ was 50 % for patients treated with denosumab and 43 % for patients on zoledronic acid. The corresponding values for patients of the prostate cancer study were 18 % and 8 %, whereas in the study involving solid tumor/multiple myeloma patients the rates were 40 % and 27 % respectively [53, 55].

20.6.5 Hypocalcaemia and Denosumab

Hypocalcaemia was evident more frequently in denosumab-treated patients as compared to those managed with zoledronic acid [53–55]. The incidence of this adverse event ranged between 5.5 % and 13 % for denosumab and between 3.4 % and 6 % for zoledronic acid [53–55]. Hypocalcemia was evident most frequently in the first 6 months of treatment and was in most cases asymptomatic. Measures that need to be taken in order to minimize the risk of hypocalcemia include monitoring and correction of calcium serum levels before and during treatment. Additionally patients under treatment with denosumab should take adequate daily oral calcium (500 mg) and vitamin D (400 IU).

20.6.6 Cost Effectiveness

Even though denosumab is a step forward as compared to zoledronic acid in terms of efficacy in SRE prevention and ease of administration, health professionals may support that its use is not justified due to its incremental cost. In the USA this is about twice than that of zoledronic acid [56–58]. Several studies have evaluated the cost effectiveness of denosumab versus zoledronic acid when used for SRE prevention. However these studies reported contradictory results mainly due to the application of different analytical perspectives and model parameters [59].

20.6.7 Approach to Elderly Patients and Recommendations for Use

The elimination of Denosumab is done through the immunoglobulin clearance pathway of the reticuloendothelial system and is therefore thought to be independent of the renal and hepatic function. The incidence of renal toxicity observed in the denosumab registration trials was lower in patients receiving denosumab as compared to those treated with zoledronic acid and similar to that reported in the observational arms of prior Bp studies [60]. It may be therefore concluded that denosumab can be safety administered in elderly patients, even in those with impaired renal function. The rate of ONJ occurrence in patients managed with zometa versus denosumab was shown to be similar. As in the case of Bps all indicated preventive measures should be followed closely both before and during treatment. Hypocalcaemia is another important potential adverse event that is more frequently observed for patients managed with denosumab as compared to zoledronic acid. Consequently close monitoring of serum calcium levels and adequate oral calcium and vitamin D intake is advised.

20.7 Conclusions

In scientific literature the data on Bp use in elderly patients with MBD is limited. Even though the administration of Bps in such patients can be beneficial, care should be taken in order to avoid treatment associated complications and toxicity. We should always take into account that elderly patients have a decline in their organ function that is related to age and the use of different nephrotoxic medications. Recommendations for Bp use and all aforementioned precautionary/preventive measures should be followed closely in order to minimize the risk of treatment related complications.

Denosumab is a monoclonal antibody that can be used in patients with MBD and has shown to be more effective than zometa in reducing the risk of SREs. Its safety profile in relation to renal function has shown to be superior to that of Bps (zoledronate) and can be used safely even in patients with impaired renal function. The occurrence rate for ONJ in the three SRE denosumab trials was shown to be comparable to that of zometa. Due to the fact that elderly patients with MBD receiving Bps or denosumab have an increased risk for developing ONJ, all recommended preventive measures should be closely implemented. A close monitoring of serum calcium and adequate oral intake of calcium and vitamin D are also recommended for patients managed with either zoledronic acid or denosumab in order to minimize the risk of hypocalcaemia. This adverse event occurs more frequently in patients managed with denosumab. Last but not least, several studies have investigated the cost effectiveness of denosumab versus zoledronic acid when used for SRE prevention. These studies report contradictory results mainly due to the application of different analytical perspectives and model parameters.

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Part IV
Assessment of Therapeutic Response

Chapter 21
Bone Metastases: Assessment of Therapeutic Response Using Radiological and Nuclear Medicine Imaging Modalities

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Abstract Radiological and nuclear medicine imaging modalities that are used for evaluating the therapeutic response of metastatic bone disease include plain or digitalized radiography (XR), skeletal scintigraphy (SS), dual energy X-ray absorptiometry (DEXA), computed tomography (CT), magnetic resonance imaging (MRI), [^{18}F] fluorodeoxyglucose positron emission tomography (FDG PET) and PET/CT. In this chapter we comment on the advantages and disadvantages of the aforementioned assessment modalities as seen through different clinical studies. Moreover, we present the well known response criteria described by the International Union Against Cancer (UICC) and World Health Organization (WHO) and the newer MDA (MD Anderson) criteria. In spite of the fact that serial XR and SS have been used for evaluating the treatment response for decades, changes are evident several months post therapy. Earlier response to treatment can be evaluated by using newer techniques such as the MRI or PET. Additionally therapeutic response may be quantified by monitoring changes in signal intensity (SI) and standard uptake value (SUV) respectively. PET/CT may be applied to follow both morphologic and

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metabolic changes in areas on skeletal metastases yielding interesting and promising results that reveal a new insight into the natural history of bone metastases. Due to the fact that only a few studies have investigated the use of these newer imaging modalities, further clinical trials are required to corroborate their promising results and establish the most appropriate imaging parameters and assessment time points. Finally, there is an absolute need to establish and adopt uniform response criteria for skeletal metastases through an international consensus in order to better evaluate therapeutic response in terms of accuracy and objectivity.

Keywords Bone metastases • Therapeutic response • Radiography • Computed tomography • Skeletal scintigraphy • Magnetic resonance imaging • Positron emission tomography • PET/CT • Radiotherapy • Chemotherapy • Bisphosphonates

21.1 Introduction

In the event of malignancy skeletal involvement is common, with bone being the third most likely site of metastatic disease after liver and lungs [1]. Tumors that show marked osteotropism are those originating from breast and prostate, with lung, kidney and thyroid carcinomas also affecting the skeleton frequently. Metastatic bone disease may bring about considerable morbidity and manifest as pain, pathologic fracture, spinal or nerve root compression, restricted mobility and hypercalcemia [2]. Such complications may deteriorate the quality of life (QOL) of affected patients, reduce their functional capabilities, and may lead to a reduced survival [3, 4].

Considering the fact that patients with metastatic disease confined only to bone may survive for years [5], there is an absolute need to use effective treatment modalities and to define accurate response criteria in order to monitor therapeutic outcome. External beam radiotherapy (EBRT) is an established treatment modality for managing metastatic bone disease since decades [6–8], with significant data proving it to achieve considerable pain response and a decrease in skeletal complication rates [7, 8]. The use of bisphosphonates (Bps) has increased considerably in the last decade becoming an integral part of the antineoplastic management of patients with skeletal disease [9–11]. Bps have shown to reduce significantly the risk of potential skeletal related events (pathologic fractures, radiation therapy, surgery to bone, spinal or nerve root compression, hypercalcemia) [12–18], and proved to be effective in reducing metastatic bone pain [12, 19, 20]. More over it was reported that Bps bring about an improvement of the QOL of affected patients [19, 21, 22]. Injectable radionuclides have also proved to be effective for the palliation of wide spread metastatic skeletal disease [22–24]. A newer trend which is promising is the combination of treatment modalities such as EBRT with Bps or radionuclides with chemotherapy or Bps [2, 3, 25–30]. Last but not least, RANKL inhibitors such as donosumab have shown to be effective in managing metastatic bone disease and reducing the risk for potential SRE's.

In spite of the fact that pain response is the most important endpoint for patients with bone metastases undergoing treatment, the use of radiologic or nuclear medicine imaging response criteria may permit an objective assessment of the therapeutic outcome which may be even quantified by following changes in associated imaging parameters. Up to date three sets of therapeutic response criteria have been proposed. The UICC [31] and WHO [32] response criteria were described three decades ago, and take into account only XR (UICC) or XR and SS (WHO) (Table 21.1). The newest response criteria are the MDA response classification criteria [33, 34] which were suggested by Hamaoka et al. and involve not only XR and SS but also CT and MRI. Even though the MDA criteria have proved to be superior as compared to the WHO classification in differentiating between those responding and those non responding to treatment (evaluated through symptom changes, tumor markers and radiologic evaluations) [34], their effectiveness and accuracy need to be established and corroborated through large prospective clinical studies. It is worthwhile to stress that the widely used response evaluation criteria used for solid tumors (RECIST) do not include skeletal metastases [35] and that the UICC criteria are valid only for lytic bone lesions.

We herein present the application of XR, SS, CT, MRI, PET and PET/CT for the evaluation of therapeutic response of metastatic bone disease in different clinical studies. The advantages, disadvantages, and limitations of these imaging modalities are discussed so that the chances that diagnostic misinterpretations lead to inappropriate clinical interventions are minimized. Moreover we point out the absolute need to establish response criteria for the treatment of patients with bone metastases though an international consensus.

21.2 Search Strategy and Selection Criteria

Data for this chapter was identified and selected after a thorough search from PubMed by using a combination of the terms “bone metastases”, “RT”, “Bps”, “response”, “radiology”, “XR”, “SS”, “DEXA”, “CT”, “MRI”, “PET” and “PET/CT”. Only articles in English language were taken into consideration. Additionally, information and data from associated published book chapters and abstracts from proceedings of major oncology conferences were used.

21.3 Plain and Digitalized Radiographs

According to the UICC criteria, osteolytic bone metastases which have been treated successfully may subsequently regain normal radiographic appearance or may even become sclerotic upon XR evaluation [31]. Reossification takes place in a centripetal fashion and an increase in bone density-calcification is evident in the affected area [2, 36, 37]. Disease progression is evident in the event of additional lysis or loss of

Table 21.1 Response criteria for skeletal metastases: UICC, WHO, MDA

Response classification	UICC: XR [30]	WHO: XR and SS [31]	MDA: XR,SS,CT, MRI [32]
Complete	Disappearance of known lesions with normal radiography. Reossification of lytic bone metastases[a]	Complete disappearance of known bone lesions on either XR or SS	Lytic bone lesions completely filled in or appear sclerotic on XR and CT. Disappearance of hot spots or tumor signal on SS, CT or MRI. Normalisation of sclerotic lesions on XR and CT
Partial	A minimum of 50 % decrease in size of measurable lesions. Absence of new disease or progression. Objective improvement of evaluable –non measurable lesions[a]	A reduction in size of osteolytic metastases or recalcification or decreased density of sclerotic lesions for at least 4 weeks	Sclerotic rim in lytic lesions or sclerosis in previously undetected lesions on XR or CT. Incomplete fill or sclerosis of lytic lesions on XR or CT. Regression of measurable lesions on XR, CT or MRI. Decreased sclerotic lesions on XR or CT. Lesion regression on SS[b]
Stable	<25 % increase or <50 % decrease in size of measurable lesions	No change. Assessment 8 weeks after the onset of treatment	No change in measurable lesions on XR or CT. Unaltered sclerotic lesions on XR, CT, MRI Absence of new lesions on XR, SS, CT or MRI
Progression	Mixed: some lesions regress whereas others progress or new ones appear Failure: some or all lesions progress and/or new ones appear. Absence of regression	Increase in size of known lesions or Appearance of new ones	Increase in size of known measurable lesions on XR, CT or MRI. Appearance of new lesions on XR, SS, CT or MRI (flare phenomena excluded). Increase in activity on SS or sclerotic or lytic lesions (flare phenomenon excluded)

[a]Assessment after two observations not less than 2 weeks apart

[b]In the case of rapid bone lysis due to disease progression, the scintigraphic appearance may show decreased osteoblastic activity. CT and XR can help in differentiating between response and progression

the initial sclerotic response [31, 36]. Disease progression is also denoted in the case of the development of new bone metastases of any type (lytic, mixed, or sclerotic) or when lesions increase in size [31, 36].

Serial radiographs are advantageous for evaluating the therapeutic outcome of metastatic bone disease both because of convenience and limited expense. Drawbacks of XR use are the fact that up to 3–6 months and more than 30–60 % mineral bone loss are needed before any changes are evident [38, 39] and that XR can only depict structural skeletal alterations, providing no information on any associated soft tissue mass. Furthermore, it is not easy to differentiate between new osteoblastic bone lesions resulting from disease progression versus lesions which are a result of healing and reossification [36]. Moreover, the measurement of bone density from plain radiography is limited by the fact that it can be used only for bones that are not located between complicated layers of moving organs, as in the cases of the thorax and abdomen [40].

Plain and digitalized XR have been employed in several studies for assessing therapeutic outcome of patients with metastatic bone disease. In a study by Harada H et al., 72 patients with femoral metastases treated with RT were evaluated by plain radiographs at a median time point of 3 months after completion of treatment. For lytic, mixed and undetectable bone lesions prior to RT, the criteria for response were normalization of bone, sclerosis and regression in size. For sclerotic lesions response to treatment was indicated in the event of bone normalization and regression in size. In cases where no change was detected response was classified as 'no change' whereas in cases with an increase in size of bone lesions or appearance of new lesions, progressive disease was indicated. The authors reported that 42 % of patients achieved a radiological response, whereas disease progression was noted in 23 % of patients [41].

A different study involved 274 breast cancer patients with skeletal disease who were managed with local RT and/or systemic treatments. Signs of response were considered to be the presence of recalcification of lytic lesions (11.6 %), appearance of marginal sclerosis in areas of bone defects (13.6 %) and the absence of progression for a period of 1 year (10.5 %). In patients with osteoblastic lesions response to treatment was indicated by a decrease in sclerosis or structural loosening (2.5 %). The appearance of new bone lesions or an increase in their size, or depiction of bone destruction in initially sclerotic or mixed metastases, was classified as disease progression (recorded in 56.9 % and 2.5 % of patients respectively) [42]. The duration of response in lytic bone lesions was less favorable and the combination of systemic treatments with RT achieved a favorable objective response [42].

Digitalized XR has been used to monitor the therapeutic response in patients with skeletal metastases from a variety of solid tumors treated with concurrent RT and pamidronate [43–46]. Images analysis was carried out by measuring first order statistics of the mean value and energy gray-level histograms (MVGLH and EGLH respectively). In these studies the radiologic response (increased bone density) was associated with a statistically significant decrease in pain scores [43–45]. The authors concluded that the application of digitalized radiographs to asses bone density changes in regions of bone metastases was feasible and cost effective.

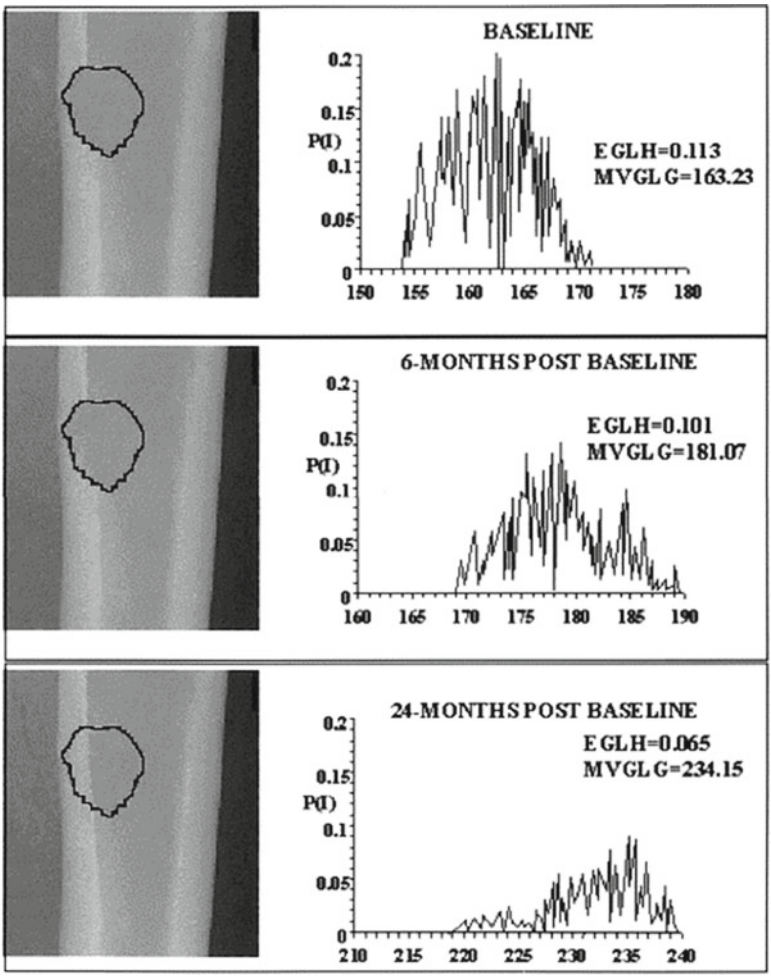

Fig. 21.1 Plain radiographs depicting a lytic lesion in the femur at baseline and at 6 and 24 months thereafter. On the *right of each image* the corresponding grey level histograms in terms of MVGLH and EGLH are shown. A complete response is seen by using the UICC criteria (This figure is reprinted from the International Journal of Radiation Oncology Biology Physics 2003;57:143–157, figure 2, copyright 2003, after a kind permission of Elsevier Inc)

Moreover digitalized XR detected bone loss at an earlier stage as compared to of conventional XR [46]. Figure 21.1 shows the recalcification achieved after combined therapy [45].

XR has been used as an assessment imaging modality in all of the set criteria that have been described up to date (WHO, UICC, MDA). The advantages of XR are that it is convenient and inexpensive. A disadvantage of XR is that up to 3–6 months and more than 30–60 % of mineral bone loss is required before any bone changes are evident. Moreover XR can only reveal structural bone changes without

providing information of any associated tumor. Additionally, XR can only be used for bones that are not found between complicated layers of moving organs such as the thorax and abdomen.

21.4 Skeletal Scintigraphy

SS has shown to be more sensitive than XR. However due to the fact that it depicts radioactivity that concentrates in areas of hyperemia or reossification and not the tumor itself, it lacks in specificity and anatomical detail [39]. Response to therapy is evident through a decreased avidity for the bone-seeking radiopharmaceutical for any type of skeletal metastasis [47]. It should be though noted that any detectable response may be evident 6–8 months post treatment and more than 2 years may be required for a complete resolution to be achieved [48]. A therapeutic response may bring about an increased activity on SS (flare phenomenon) that is depicted within 4–12 weeks after treatment [36, 49–51]. This phenomenon results from the healing process and it may be misinterpreted as failure of treatment since it has the same characteristics as disease progression [52]. As a result, the assessment of SS should be done with care for the first 6 months after the onset of treatment and tentative response criteria including additional clinical and radiological evaluations should be used to avoid false diagnoses [51, 53]. Progressive disease is indicated when new foci are formed on SS or an increased activity and enlargement of known lesions is evident. It should be however stressed that in patients with a rapidly progressing disease, bone formation is limited and a reduced uptake may be seen instead [36]. Figure 21.2 depicts the therapeutic outcome of a patient with metastatic bone disease from breast cancer managed with systemic treatment.

Three phases of scintigraphic appearance have been described after RT. The first phase lasts for a few days and is evident just after RT. It's main characteristic is hyperemia that is associated with an increase of radionuclide uptake. The second phase lasts for several months and involves an increased uptake that is a result of reossification. This phase depends on the RT fractionation scheme. In the last phase a decrease in the radionuclide uptake is depicted, resulting from a prolonged

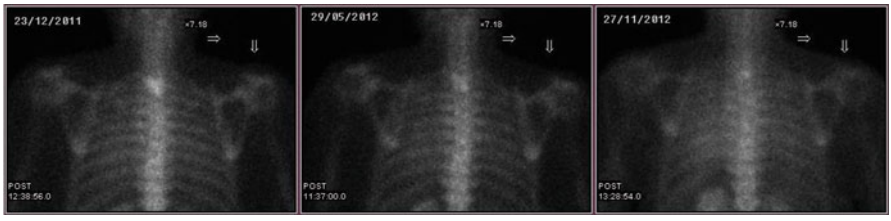

Fig. 21.2 Consecutive skeletal scintigraphy images of a patient with thoracic bone metastasis from breast cancer receiving systemic treatment. After treatment the radionuclide uptake in the affected vertebra shows a marked and gradual decrease

decrease in reossification and vascularity. This phase may last for years and the uptake ultimately returns to normal [47].

Serial SS was used in several clinical studies in order to evaluate the therapeutic outcome of patients with metastatic skeletal disease [54–58]. In a study by Citrin DL et al. serial SS and XR were applied to assess the therapeutic response of 34 women with breast cancer and skeletal metastases managed with systemic treatment [54]. The authors concluded that SS was more accurate and sensitive than XR for assessing the status of skeletal lesions and that SS correlated well with the response of soft tissue and visceral disease [54]. In a different trail, 51 breast cancer patients with bone metastases managed with zoledronic acid were assessed by SS prior and at least 6 months after the onset of treatment to avoid the flare effect. After treatment 4 (8 %) patients had a complete response (no bone lesions were imaged), 21 (41 %) a partial response (reduction in the number and intensity of known lesions), 16 (31 %) patients were classified as having a stable disease (no changes in scintigraphic appearance) and 10 (20 %) fulfilled the criteria for disease progression [55].

SS was also used together with clinical, biochemical and radiographic evaluations to assess the therapeutic response of 50 breast cancer patients with metastatic skeletal disease treated with combination chemotherapy. Treatment response in metastatic lesions other than bone correlated well with radiographic findings (91 %), but less well with changes on SS (57 %). Interestingly, a concordance between clinical and XR findings was shown suggesting disease progression in 81 % of patients. A concordance between the results of SS and clinical evaluations was reported for 72 % of patients. The changes in the carcinoembryonic antigen (CEA) serum levels closely reflected the changes in clinical and XR assessments. The authors reported that the use of SS and XR together with clinical and tumor marker assessments results in a highly selective and accurate method for the evaluation of therapeutic response [56].

SS was also successfully used to evaluate the extent of metastatic bone disease, that was shown to correlate with prognosis [57, 58] and therapeutic response [54, 58]. The extent of skeletal involvement was evaluated in a trial involving 191 patients with hormone resistant prostate cancer by using the bone scan index (BSI). In this evaluation system each bone is evaluated separately and assigned a score number. The overall score is the result of the product of the percentage of a specific bone affected by tumor, times the weight of that bone derived from the reference man. Through this study it was shown that the extent of skeletal disease correlated well with prognosis. More specifically, patients with BSI values <1.4 %, 1.4–5.1 % and >5.1 % had a median survival of 18.3, 15.5 and 8.1 months respectively [54]. In a different study patients with skeletal metastases from prostate cancer receiving hormonal treatment were enrolled. Skeletal metastases were quantitatively evaluated by serial SS involving computer-assisted image analysis. In the study the extent of disease (EOD) and the percentage of positive areas on SS (%PABS) were quantified for 33 months of follow up. Serial values of EOD and %PABS were reported to reduce during treatment in 11 patients (partial response) and in 12 with progressive disease for whom there was no progression of skeletal metastases. In 19 patients, progression EOD grades and %PABS were reported to increase (disease progression). Interestingly survival curves

showed that the %PABS was a useful prognostic indicator, with patients having a >25 % decline after treatment surviving longer than the ones with a smaller percentage decrease in %PABS [58].

Serial SS has been used in many clinical studies for assessing the therapeutic response of patients with bone metastases and is an imaging modality employed in the response criteria described by UICC and MDA. An advantage of SS is that the whole skeleton can be assessed. However, it lacks in specificity and anatomical detail, depicting only the uptake of the injected radiopharmaceutical in areas of hyperemia or reossification. An additional disadvantage is that any detectable response may be delayed for up to 6–8 months and take more than 2 years for complete resolution to be depicted. Moreover, the flare phenomenon that is observed within 4–12 weeks from the onset of treatment may lead to a false diagnosis. Consequently, the evaluation of SS should be done with caution in the first 6 months after the onset of treatment.

21.5 Dual-Energy X-ray Absorptiometry

DEXA is a widely used method for the assessment of bone mineral density (BMD) in patients with osteopenia or osteoporosis [38]. It has also been used in several clinical studies for evaluating the therapeutic response of patients with skeletal metastases undergoing systemic treatments. In a study by Berruti A et al., 14 patients with bone metastases from various primary tumors were evaluated with serial DEXA scans prior and post systemic treatment. From patients with lytic bone lesions one patient had stable BMD, in four there was an increase and in the rest a decrease. BMD changes in these patients were reported to parallel the variations of biochemical markers and symptomatology. In patients with sclerotic lesions, BMD remained stable in one patient and increased in four. Increased BMD was associated with pain relief and decreased PSA levels or with pain progression and increased PSA [59].

BMD alterations were also assessed with DEXA in 6 prostate cancer patients with lumbar bone metastases receiving systemic treatment. As compared to the initial evaluation at baseline, BMD was reported to increase over 12 months in three patients with biochemical progression, and decreased in patients responding to therapy [60]. In the last study that will be commented upon, nine breast cancer patients with osteolytic metastases receiving treatment were evaluated with DEXA, XR, CT, and SS at baseline and at 2 and 6 months post treatment. In responders the median percentage change in BMD was 10.7 %, 5.0 % and 16.7 % at 0–2, 2–6 and 0–6 months respectively. The changes in BMD were statistically significant at 0–2 and 0–6 months and were shown to correlate well with the alterations on XR (Spearman rank order correlation coefficient [Rs] $=0.51$, $p=0.011$) and CT ($Rs=0.41$, $p=0.05$), and to a lesser degree with SS ($Rs=0.293$, $p=0.19$) [61].

DEXA has been successfully used for monitoring the therapeutic response of patients with bone metastases under treatment by evaluating changes in BMD.

A major advantage of this method is that it entails minimal radiation exposure. However larger studies should be carried out in order to corroborate the aforementioned results and establish the value and effectiveness of DEXA.

21.6 Computed Tomography

CT provides skeletal images of high spatial resolution and the anatomical and structural bone alterations in relation to the tumor. Moreover, it depicts cortical and trabecular bone with accuracy and can readily reveal reossification that is evident after a successful treatment [2, 3]. CT is reported to be sensitive and specific for detecting bone metastases [47] and has proved to be especially useful for the evaluation and confirmation of equivocal metastatic skeletal lesions. Such examples are patients with increased uptake on SS and normal XR, or cases with a solitary hot spot on SS [36, 62, 63].

The first study that will be discussed is by Reinbold WD et al., involving 19 patients with osteolytic vertebral metastases undergoing fractionated RT. Quantitative CT was carried out for all patients at the onset and completion of RT and 3 months thereafter. Interestingly, it was shown that just after completion of RT a reduction of bone density by 24.7 % was noted, followed by a 60.6 % increase at the evaluation time point of 3 months. Reossification was followed by a considerable pain response, with 13 out of 19 patients having a complete pain relief [64]. In a feasibility study by Chow E et al., CT was used to monitor the bone density changes in 25 patients treated with either single (8 Gy) or multifraction (total dose of 20 Gy in five fractions or 30 Gy in ten fractions) RT. CT scans of irradiated skeletal lesions were performed prior to treatment and 3 months after the completion of RT. At the time point of 3 months the median percentage change of bone density after single fraction RT was 128 %. The corresponding values after 20 Gy and 30 Gy were 141 and 145 respectively [65]. Reossification accomplished in the region of skeletal metastases after RT was evaluated by quantitative CT in other studies as well [66, 67].

In a recent trial CT, MRI and functional scintigraphy were used to assess the therapeutic response in patients with bone metastases from neuroendocrine tumors managed with the peptide receptor radionuclide. Response to treatment was assessed by using the MDA response criteria which were modified for this study. After a median follow up of 32 months 4.8 % of patients achieved a complete, 33.3 % a partial and 11.9 % a minor response. Stable disease was reported in 38.1 % of patients. Interestingly responders exhibited a trend towards a better overall survival [68].

In several studies by Vassiliou V et al. the radiologic response of patients with bone metastases from different solid tumors managed with concurrent RT and Bps was successfully evaluated by the application of CT [2, 3, 69, 70]. In these studies patients were treated with external beam RT administered concurrently with

monthly Bp infusions. Patients underwent both clinical and radiologic evaluations prior treatment and at 3, 6 and 10 months thereafter. Two radiologists delineated metastatic bone lesions (irradiated sites) in representative CT images and bone density was measured in Hounsfield Units (HU). The considerable clinical response observed in the studies was accompanied by a significant increase of bone density. In one of these studies bone density increased by 20 % at 3 months and by 46 % and 73 % at 6 and 10 months respectively. Moreover at 10 months 80.8 % of patients had a complete pain response (pain score of zero). Last but not least in the study it was reported that bone pain was the main factor affecting negatively the patient's functioning and performance status and that it's correlation with bone density was strong negative and statistically significant (Rs = −0.43) [2].

In a different study by the same author CT was used to both monitor reossification and group patients according to the type of their bone metastasis: lytic, mixed or sclerotic [3]. Through this study it was shown that the level of reossification and clinical response differed between the three groups, with patients with lytic bone metastases having the highest radiological and clinical response as compared to the baseline evaluation. More specifically, at 10 months post treatment onset, bone density was found to almost triple for patients with lytic metastases and almost double for those with mixed bone lesions. For the sclerotic group bone density was found to increase by 138 HU (mean value). In respect to clinical response, statistically significant improvements were reported at all time points of evaluation for all groups of patients for parameters such as pain (0–10), QOL (EORTC QLQ-C30, physical functioning scale) and performance status (Karnofsky performance status). The mean pain score of patients with lytic bone metastases was reported to decrease from 8.1 to 0.5 points at 10 months, with the corresponding decrease for the patients with mixed and sclerotic metastases being from 6.2 to 0.3 and from 4.4 to 0.7 points respectively. Additionally, the percentage of patients having a complete pain response was >76.4 % was at all time points and for all groups. The authors reported that CT showed to be a practical and effective radiologic method for classifying bone metastases and evaluating the therapeutic response [3]. Sample CT images are presented in Fig. 21.3 [2].

CT provides skeletal images with a high spatial resolution and anatomical detail in relation to the tumor. Additionally, it depicts accurately both cortical and trabecular bone. Through many clinical trials CT showed to be effective for assessing and monitoring reossification that is evident upon therapeutic response. Reossification can be quantified by measuring the alterations in bone density in HU within regions of interest. Even though one may suggest that that CT can not be routinely applied to evaluate and monitor the therapeutic outcome of patients with metastatic bone disease due to the high accumulated radiation dose, this is partly correct if we consider that currently the majority of cancer patients undergo routine CT scans (thorax, pelvis, abdomen) for staging and follow up [71–73]. It should also be stressed that a CT scan of thorax, abdomen and pelvis depicts most metastatic bone lesions, since the most commonly affected skeletal regions are the thoraco-lumbar spine, pelvis and proximal femora and humeri [69, 70].

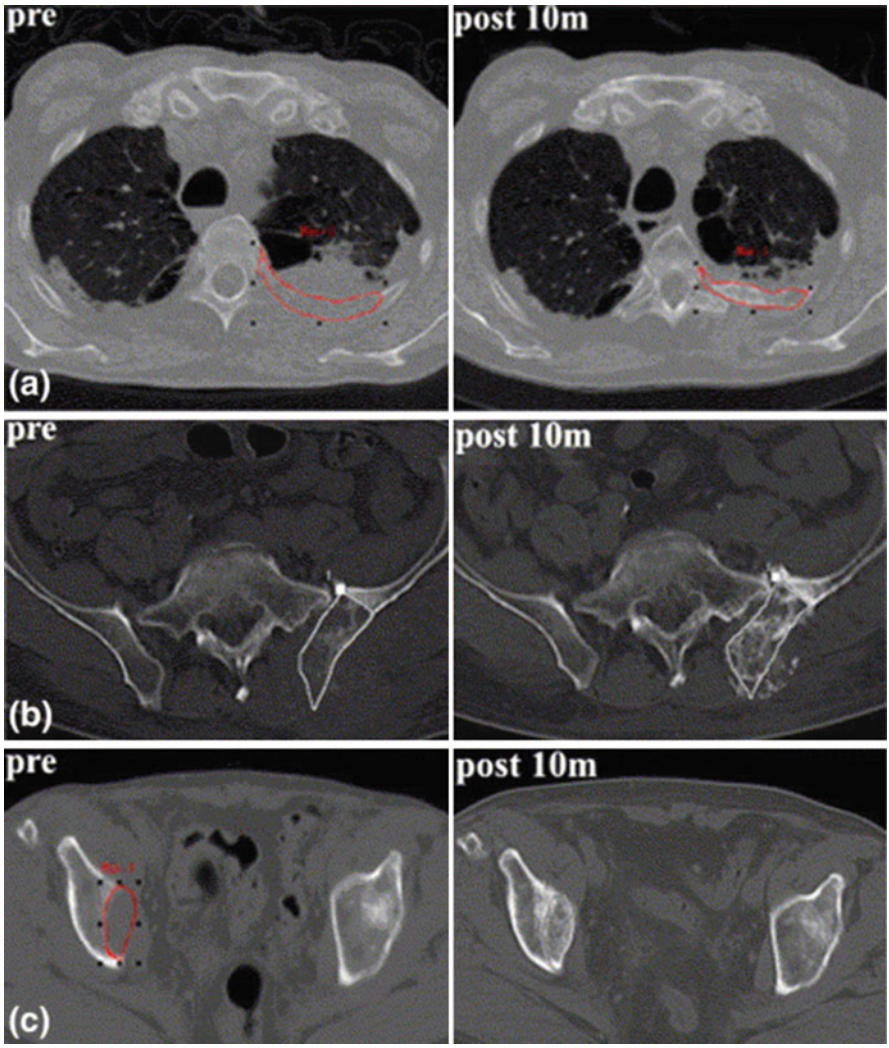

Fig. 21.3 CT images of patients with lytic bone metastases before and 10 months after the onset of concurrent application of RT and Bps in a patient with (**a**) lung carcinoma and two different patients with renal carcinoma (**b**, **c**) showing significant reossification in an upper left rib, left iliac bone and right iliac bone respectively (This figure is reprinted from the International Journal of Radiation Oncology Biology Physics 2007;67:264–272, figure 6, copyright 2007, after a kind permission of Elsevier Inc)

21.7 Magnetic Resonance Imaging

MRI has proved to be the imaging modality of choice for revealing bone marrow and early cancellous tumor involvement [74]. Apart from detecting early bone involvement, MRI and CT are more sensitive than XR for depicting minor alterations of bone

density [62]. However, it is not suited for evaluating blastic or lytic bone changes [34]. Only a few trials have applied MRI for evaluating the therapeutic outcome of patients with metastatic bone disease and a number of them are presented below. Notably MRI is one of the imaging modalities employed in the MDA assessment criteria.

Ciray I and co-workers used MRI for evaluating the early response of 18 breast cancer patients with bone metastases receiving systemic chemotherapy. MRI scans were carried out prior to treatment and after a median of six chemotherapy cycles. The therapeutic outcome was assessed by following changes in tumor size and by monitoring alterations in the pattern and SI of bone metastases by applying T1-weighted and long echo-time inversion-recovery turbo-spin-echo (long TE IR-TSE) sequences. The aforementioned MRI sequences were found to be equally effective in evaluating patients with progressive (n=2) or stable disease (n=4), with long TE IR-TSE showing to be more accurate in demonstrating partial response [75]. In a different study T1-weighted MRI was employed for evaluating the therapeutic response of 41 breast cancer patients diagnosed with vertebral metastases [76]. MRI scanning before and after treatment was carried out in order to investigate changes in number, size and SI of bone metastases during 68 intervals (mean length 6.9 months). For each interval between MRI scanning, an objective assessment of overall therapeutic response (regression, no change, progression) was carried out by using standard assessment criteria. After treatment the number of bone metastases was reported to be stable in 53 % of patients and increased in the rest. Moreover, the size of bone metastases increased in 43 %, was unaltered in 54 % and decreased in 3 % of cases. Changes in SI were revealed in about one-third of patients. The change which was most commonly observed was the one from a low homogenous SI to a low heterogeneous SI. The authors concluded that T1-weighted MRI responses based on size and number of metastatic bone lesions predicted disease progression (79 % of cases) and stable disease (75 % of cases) with accuracy, but could not predict cases with disease regression. No correlation between SI changes and treatment response was evident [76].

MRI and other conventional methods such as XR, SS, pain and analgesic scale and serum CA 15-3 were employed to evaluate the therapeutic outcome of 18 breast cancer patients with metastatic bone disease [77]. The MRI evaluation was done by using T1-weighted sequences to measure the volume of bone lesions as well as tissue component. A patient was considered to have a complete or partial therapeutic response in the event that a complete or partial response was observed in any of the conventional methods used in the study. The authors concluded that treatment response was more concordant between XR and MRI findings (91 %), with the concordance rate between conventional methods and MRI being 61 %. MRI enabled an accurate evaluation and follow up of bone metastases as in the case of secondary soft tissue lesions [77].

Axial-skeleton MRI (AS-MRI) was used to evaluate the therapeutic response of 20 prostate cancer patients with skeletal metastases undergoing chemotherapy. Both T1 and T2-weighted sequences were used and AS-MRI was performed before treatment and 6 months after treatment completion [78]. Response to therapy was evaluated by using the RECIST criteria [35]. AS-MRI was reported to enable a precise measurement and monitoring of bone metastases as in the case of soft tissue metastases. Overall a complete response was observed in two patients, partial response in two, stable disease in five and disease progression in eleven [78].

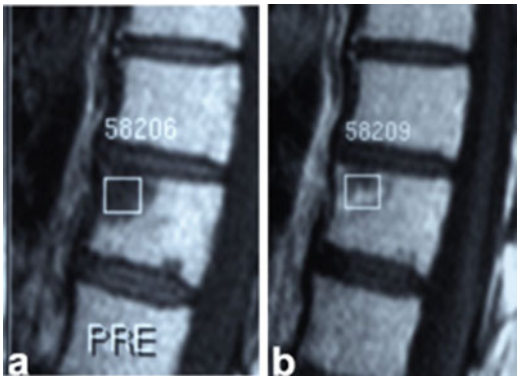

Fig. 21.4 Sagittal MRI images (T1TSE sequence) showing bone metastasis in the eighth thoracic vertebra in a patient with lung carcinoma. Before treatment (**a**) a low signal intensity was evident (**b**) that was significantly enhanced after Gd administration (This figure is reprinted from the book Bone Metastases: A translational and clinical approach, chapter 17: Assessment of therapeutic response pages 344–370, figure 17.3, copyright 2009, after a kind permission of Springer Science and Business Media B.V.)

In a more recent trial Dynamic Contrast Enhanced MRI (DCE-MRI) was used to evaluate the treatment response of 10 breast cancer patients with metastatic bone lesions managed with Bps and endocrine treatment. DCE-MRI was performed at baseline, within a period of 3 weeks from the second Bp infusion and after 4 and 8 months from the onset of treatment. Specific alterations in the shape of time-signal intensity curves in ROI denoting disease regression were observed in treatment responders [79]. In a different study DCE-MRI was also applied to assess the therapeutic response of patients with skeletal disease from a variety of solid tumors [2]. Seven patients receiving combined RT and Bps were evaluated with MRI prior to treatment and 3 months post therapy by using the T1TSE sequence with and without gadolinium (Gd) enhancement. Three months after the onset of treatment the signal intensities in bone lesions with and without Gd enhancement were found to be significantly lower than those at baseline ($p < 0.001$). More specifically, at baseline Gd enhancement brought about a 57 % increase of signal intensity, whereas at the evaluation time point of 3 months the observed enhancement was to only by 15 %. Figures 21.4 and 21.5 depict the signal intensity alterations after Gd enhancement prior to treatment and at 3 months post the onset of therapy [80].

Diffusion-weighted MRI is a different technique that was used to evaluate the therapeutic response in 24 patients with vertebral metastases from a variety of solid tumors. These patients received external beam RT and MRI was performed at different time points after treatment completion [81]. Before RT the signal intensity of metastatic bone lesions was reported to be hyper-intense as compared to normal vertebral bodies. In 23 patients with clinical response (pain relief and decreased radionuclide uptake depicted in follow up bone scans) after therapy, bone metastases were found to be hypo-intense as compared to normal vertebral bodies. In non responders the bone marrow was hyper-intense and on SS an increased uptake was depicted.

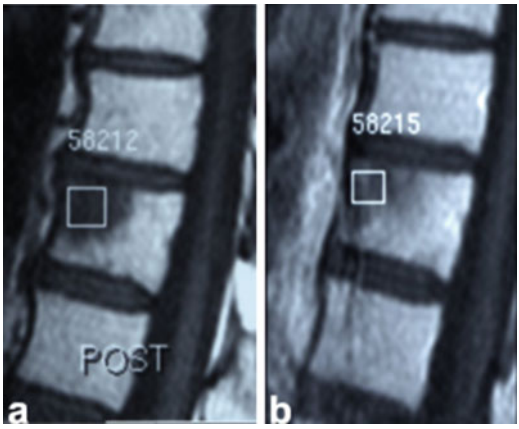

Fig. 21.5 Sagittal T1TSE MRI images of the same patient 3 months post the onset of treatment. The signal intensity before Gd enhancement (Fig. 21.4a) was lower than that the corresponding value before treatment (Fig. 21.3a). After Gd administration the difference in enhancement between the images before (Fig. 21.3b) and after treatment (Fig. 21.4b) was not as high as in the case before treatment (Fig. 21.3a vs b) (This figure is reprinted from the book Bone Metastases: A translational and clinical approach, chapter 17: Assessment of therapeutic response pages 344–370, figure 17.4, copyright 2009, after a kind permission of Springer Science and Business Media B.V.)

The authors reported that diffusion weighted MRI was successful in assessing the therapeutic outcome of patients with bone metastases and that therapeutic response was evident in the case of a decreased signal intensity at the follow up evaluations [81]. Even though the results of other studies employing diffusion-weighted MRI were reported to be promising, the response to treatment that was evident by monitoring the changes in the apparent diffusion coefficient was heterogeneous. Moreover, other studies showed that this method is inappropriate for monitoring the therapeutic response of bone metastases [82, 83].

MRI has proved to be an effective, reliable and safe (in terms of radioprotection) imaging modality for assessing the therapeutic response of patients with metastatic bone lesions. However further studies need to be performed in order to establish response criteria with the most appropriate imaging parameters. It should be stressed that MRI may reveal early bone involvement and in contrary to XR or CT it can not reveal lytic or sclerotic bone changes. Drawbacks for the routine MRI use are the high cost, limited availability and the examination duration.

21.8 PET and PET/CT

FDG PET has an important role for staging of cancer patients at diagnosis [39] and monitoring treatment response. Recently the Position Tomography response Criteria in solid Tumors have been described, allowing the evaluation of response through

Table 21.2 Response criteria according to PERSIST

Response category	Response criteria
Complete response	Normal metabolic activity of all lesions (target and non target) to SUL less that the mean liver SUL and equal to normal SUL of surrounding tissue
	Verification with a follow up study in 1 month if anatomic criteria suggest progressive disease
Partial response	>30 % decrease in SUL peak; minimum decrease in SUL peak by 0.8 units[a]
	Verification with a follow up study if anatomic criteria suggest progressive disease
Progressive disease	>30 % increase in SUL peak; minimum increase in SUL peak by 0.8 units
	>75 %increase in TLG of the five most active lesions
	Visible increase in extent of FDG uptake
	New lesions
	Verification with a follow up study if anatomic criteria suggest complete or partial response
Stable disease	No other criteria met

SUL standard uptake value using lean body mass, *TLG* total lesion glycolysis

[a]The outcome of the primary outcome is determined based on the measurement of the single most active lesion on each scan. The secondary outcome determination is the summed activity of up to five most intense lesions (maximum two lesions per organ)

functional imaging (Table 21.2) [84]. Interestingly, several studies have reported that FDG PET is more specific and sensitive than SS for detecting metastatic bone lesions from different primary tumor types such as breast, lung and renal-cell carcinoma [85–87]. It should however be pointed out that FDG PET has a lower sensitivity for detecting osteosclerotic than osteolytic lesions due to their reduced metabolic activity [88]. This limits the use of PET for the assessment of osteosclerotic metastases from prostate [89] or other primary tumors giving rise to osteosclerotic lesions. Another drawback of PET is that it does not depict anatomic changes in relation to treatment [34]. This problem is solved by the combination of PET with CT (PET/CT) that provides both anatomic and metabolic information [34].

In a retrospective study by Stafford SE et al., FDG PET was used to evaluate the therapeutic outcome of breast cancer patients with disease mainly confined to bone. A total of 24 women managed with antineoplastic treatment were assessed with FDG PET at several time points after the onset of therapy. The evaluation of response to therapy involved the measurement of the alterations in the standard uptake value (SUV) of the most active metastatic lesions during a follow up period of 4.9 months. The SUV alterations after treatment correlated strongly with the clinical response and the changes in the levels of the tumor marker CA 27. The authors concluded that serial whole-body FDG-PET can be very useful for evaluating the therapeutic outcome of breast cancer patients with metastatic bone disease quantitatively [90].

In a more recent study involving 13 breast cancer patients with metastatic disease (including bone) treated with antineoplastic treatment, carbon-11 methionine (11-C-MET) PET was applied for monitoring early response to treatment. MET accumulation in areas of metastatic lesions was measured as SUV and pretreatment values were compared to the ones post treatment. SUV values were

reported to decrease significantly (30–54 %) in responding metastatic lesions ($p<0.05$). In non responding lesions SUV values were found to alter marginally or remained stable [91].

In the next section we will present three studies in which PET/CT was employed to assess the response of breast cancer patients with bone metastases. In an innovating study by Georgi U et al. patients with breast cancer and bone metastases receiving systemic treatment, the therapeutic response was monitored by using FDG-PET and by measuring the circulating tumor cell (CTC) count [92]. PET/CT and CTC counts were carried out before the onset of treatment and 2–4 months thereafter. CTC counts at follow up were in agreement with the findings of PET/CT in 43 (78 %) of 55 evaluable patients. FDG PET/CT and CTC findings were found to correlate significantly with both progression free survival ($P=0.02$ and $P<0.0001$, respectively) and overall survival ($P=0.02$ and $P<0.01$, respectively). The authors reported that FDG PET/CT was a useful tool for assessing the therapeutic outcome of patients with bone metastases receiving systemic treatment [91].

In a different study 102 women with metastatic bone disease underwent PET/CT prior and post treatment. Both morphologic patterns and lesion attenuation were evaluated and the SUV and total lesion glycolysis (TLG) were analyzed in order to assess metabolic changes. At baseline 33 bone metastases were classified as lytic, 22 sclerotic, 42 mixed and 5 could not be classified. After therapy a progression of sclerosis was seen in 49 patients (48 %). It also reported that post treatment the mean attenuation of skeletal lesions was increased and the SUV and TLG values decreased. Interestingly the increases in attenuation were found to correlate significantly with decreases of SUV ($p<0.001$) and TLG ($p<0.001$). Through univariate analysis it was seen that the attenuation increase and the SUV reduction were potential predictors of the response duration. Moreover, multivariate analysis revealed that increases in SUV were significant predictors of response duration ($p=0.003$) [93].

In the last study that will be presented PET/CT was used to investigate the clinical relevance of FDG uptake characteristics of skeletal metastases with different radiographic appearances. Twenty-five women with breast cancer and metastases to bone underwent sequential PET/CT during an average follow up period of 23 months. A total of 146 lesions were evaluated for the FDG uptake and radiologic morphology and were correlated with treatment response retrospectively. The radiologic evaluation showed that 77 lesions were osteolytic in type, 41 sclerotic and 11 mixed. Seventeen lesions were negative on CT. Most lytic (93.5 %) and mixed (81.8 %) lesions but fewer sclerotic (25.6 %) had an increased FDG uptake. After treatment 58 lytic lesions (80.5 %) became FDG negative and sclerotic on CT and only 14 large lesions remained FDG avid. From the 25 FDG avid sclerotic lesions, 13 were shown to be FDG negative and the remaining continued to have a high FDG uptake related with an increased CT size. Five mixed lesions continued to have an increased FDG uptake post therapy. All of the 17 CT negative metastases became FDG negative, with nine becoming osteosclerotic on CT. Finally one of the lesions which was initially FDG negative showed avidity during follow up. The authors reported that the FDG uptake reflects the tumor activity in skeletal lesions and that the changes in radiological morphology vary greatly with time and among patients [94].

A common potential drawback of FDG PET and SS for assessing the therapeutic outcome of metastatic skeletal disease is the early flare in tracer uptake that is evident following systemic antineoplastic therapy [95]. Moreover, PET and PET/CT are currently expensive imaging modalities with a limited availability [39]. However the combination of both metabolic and anatomic information through PET/CT is promising and has yielded interesting results. Last but not least, through PET/CT treatment response may be quantified by measuring the changes in bone density and SUV.

21.9 Conclusion

Even though pain response is the main endpoint for the management of patients with skeletal metastases, the use of radiologic and nuclear medicine imaging modalities for the evaluation of therapeutic response allows an objective assessment of the therapeutic outcome. In this chapter we present the old (UICC and WHO) and newer (MDA and PERCIST) criteria for evaluating the treatment response of patients with skeletal metastases, stressing the need to establish a set of validated response criteria by carrying out large scale clinical trials and an international consensus. This will allow an accurate and objective evaluation of the therapeutic response of patients with skeletal metastases. Moreover a correlation of quantitative imaging parameters with clinical and survival end points will be enabled. Furthermore possible misinterpretations that may lead to false treatment management can be avoided, and end point comparisons between various clinical studies involving patients with metastatic bone disease will be possible.

Both the advantages and disadvantages of radiological and nuclear medicine imaging modalities for evaluating the treatment outcome of patients with bone metastases are also discussed, emphasizing their application in clinical studies. Even though serial XR and SS have been employed for evaluating the therapeutic response of patients with skeletal metastases for decades, several months are required before any alterations are depicted. Newer techniques such as the MRI and PET may allow an earlier response assessment that may be quantified by following changes in SI and SUV respectively. Moreover, the employment of PET/CT that can monitor both morphologic and metabolic changes has yielded interesting and promising results that provide a new insight into the natural history of metastatic skeletal disease.

Finally, as in the case of MRI and PET, CT may be quantitatively used to evaluate bone density changes in regions of metastatic bone lesions. A possible incorporation of quantitative measurements of bone density (HU units) and SI (MRI) changes in the MDA response criteria may improve their accuracy and objectivity [96]. Only a few studies have investigated the use of newer techniques such as CT, MRI and PET or PET/CT for the evaluation of the therapeutic response of patients with bone metastases and further clinical studies are required in order to corroborate their promising results and establish the most suitable imaging parameters and assessment time points.

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Chapter 22
Assessment of Therapeutic Response Through Clinical Assessment Measures

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Abstract Bone metastases from advanced stage cancers are common. They pose a significant added burden on both the patient and the health care system as a whole. There has been extensive interest in developing new strategies to improve patient care in this area. Traditionally, trials have focused on the incidence and timing of skeletal-related events (SREs) to compare the efficacy of bone–targeted agents against placebo and against each other. However, there are fundamental issues with translating clinical trial data into widespread clinical care. As seen in clinical trials that tend to include patients with better performance status, enroll fewer patients with bone only disease, and use more bone imaging than is used in the real world setting. Therefore, we need more practical tools that will allow us to assess therapeutic response in the clinical setting. In reality, this will prove challenging, as so far we have been unable to combine commonly used clinical trial endpoints with endpoints that are pertinent to an individual patient in a pragmatic and validated manner. This chapter will review the common clinical outcome measures used to assess response and progression in patients with bone metastases.

Keywords Bone metastases • Bisphosphonates • Denosumab • Morbidity • Pain

22.1 Introduction

Bone metastases are particularly common in patients with breast, prostate, thyroid, lung and renal cell carcinomas [1, 2]. Metastatic bone disease results in worsening patient morbidity and mortality, and has significant associated costs to both the patient and the health care system as a whole. There is extensive interest in developing

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new strategies to improve patient care. Advances in the understanding of the biology of bone metastasis behaviour have enabled the development of new therapeutic options for patients. While the management of these patients is truly multidisciplinary with surgery and radiotherapy being essential components of care, the majority of the literature around bone metastatic-patient care is focused on the use of bone-targeted agents such as bisphosphonates and more recently the RANK ligand antibody, denosumab. Traditionally, trials assessing the benefits of bone-targeted therapies have focused on a composite endpoint known as skeletal related events (SREs) to compare the efficacy of bone-targeted agents against placebo and against each other. However, it is important to note that, in the clinical trial setting, many of the documented patient SREs are asymptomatic, and are not associated with adverse patient events. As SREs are also used for health care funding decisions around the use of these agents, the measurement of SREs has taken on a position of importance possibly to the detriment of other measures of patient care such as pain and quality of life.

There are fundamental issues with translating the findings of clinical trials into widespread clinical care. Clinical trials tend to include patients with better performance status, include less patients with bone only disease, include patients with fewer co-morbidities, and use more bone imaging than would be used in the non-trial setting. In particular, trials comparing two active bone-targeted agents may show statistically significant results in reducing SREs, but how meaningful these results are to individual patients in the real world setting remains unanswered. This is particularly important given that, at present, use of bone-targeting agents has not been associated with differences in patient overall survival. In an era of personalised medicine where "one size fits all" approaches (i.e. giving 3–4 weekly bone-targeted therapies to all patients irrespective of their individual SRE risk) are no longer acceptable. We therefore need improved tools to translate the findings from clinical trials into everyday practice to monitor patient progress and allow more tailored treatment regimens. In this chapter, we will discuss each measure used in clinical trials of bone-targeted agents and their application to the non-trial, "real world" setting.

22.2 Response Rate, Overall Survival, and Progression Free Survival Measures

Benefit from new therapies in oncology has been traditionally assessed by using measures such as radiological response rate, progression free survival (PFS) and overall survival (OS).

22.2.1 Objective Response Rate and Diagnostic Imaging

Response rate is commonly used in clinical trials and can evaluate change in tumour size by measuring anatomy on imaging or through metabolic activity with positron

emission tomography imaging [3]. Within a clinical trial RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) [4] guidelines suggest that a maximum of five target lesions representing all affected organ systems be monitored for tumour reduction. RECIST 1.1 considers a target lesion to be measurable if a soft tissue mass greater than 10 mm is present. Drug efficacy is calculated by the sum of the greatest longitudinal dimension of each target lesion. Response rate to therapeutic agents are divided into four categories according to RECIST 1.1, complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD) (Table 22.1) [4].

The types of diagnostic imaging used to assess response in metastatic bone disease include standard radiographs, technetium-99 methyl diphosphonate bone scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), and positron-emission tomography with fluoride-18 and furodeoxy glucose [6]. The more commonly used methods include standard radiographs, scintigraphy, CT and MRI. Although, these imaging techniques have contributed to the development of the WHO criteria and more recently the RECIST criteria for anatomical tumour response, they do have some draw backs in assessing the effects of therapeutic agents. For instance, a phenomenon known as 'false-flare' can occur with bone scans using technetium-99 scintigraphy, which ultimately leads to high false positive readings due to difficulty in differentiating bone healing from new metastases or progressive disease [7, 8]. This may arise for a few reasons, including scintigraphy's lack of anatomical detail and specificity compared to conventional radiography [8]. In addition, the uptake of the radioactive dye, technetium-99, by bone surfaces requires blood flow and osteoblastic activity, which can be high in both the healing process and progressive disease. Time delay is another drawback. It may take several months to detect a therapeutic response on imaging because by definition of the Union Internationale Contre le Cancer, a positive response must show signs of healing and recalcification present on imaging. In addition, attributing changes seen on imaging to only therapeutic response can be very difficult since the appearance of bone metastases can continuously change independently and not necessarily due to therapy [6]. Finally, the reproducibility of diagnostic imaging can be questionable. Variability and lack of reproducibility are often observed when using diagnostic imaging to assess tumour size, hence lesion changes observed between intervals in studies may be due to either true tumor changes or associated measurement errors. Measurement error can be caused by scan-rescan variability and errors in test reproducibility due to the observer (s) [7].

These are all challenges faced in radiological imaging that contribute to the complexity in assessing therapeutic response of metastatic bone disease. One solution to such a problem is to implement multiple imaging techniques to compare and correlate parametric maps [7]. The assumption is that multiple tests will limit the effect of the inherent drawbacks of a single type of test. Of course the same principle is already implemented when treating any patient with metastatic bone disease, as biochemical tools (tumour markers, bone resorption markers, bone formation markers) are usually assessed in conjunction with radiological tests [6, 7].

Table 22.1 Response rate to therapeutic agents divided into four categories according to RECIST 1.1

Complete response (CR)	Complete Response is defined as the disappearance of all target lesions. It can be validated on CT and further by biopsy. Fludeoxyglucose (FDG) position emission tomography can be used as an alternative to biopsy when a residual mass is present that may be indicative of fibrosis and scarring
	Complete sclerotic fill-in of lytic lesions on XR or CT
	Normalization of bone density on XR or CT
	Normalization of signal intensity on MRI
	Normalization of tracer uptake on SS
Partial response (PR)	Defined by a decrease in the sum of diameters of all target lesions by at least 30 % compared to the patient's baseline sum of target lesions via CT
	Development of a sclerotic rim or partial sclerotic fill-in of lytic lesions on XR or CT
	Osteoblastic flare- Interval visualization of lesions with sclerotic rims or new sclerotic lesions in the setting of other signs of PR and absence of progressive bony disease
	≥50 % decrease in measurable lesions on XR, CT or MRI
	≥50 % subjective decrease in the size of ill-defined lesions on XR, CT or MRI
	≥50 % subjective decrease in tracer up take on SS
Progressive disease (PD)	Progressive disease is categorized as an increase of the sum of target lesion diameters by at least 20 % and an absolute increase of at least 5 mm compared to the patients smallest baseline sum of target lesions
	≥25 % increase in size of measurable lesions on XR, CT, or MRI
	≥25 % increase in the size of ill-defined lesions on XR, CT or MRI
	≥25 % subjective increase in tracer uptake on SS
	New bone metastases
Standard disease (SD)	Standard disease includes all patients who do not meet the criteria of the three other categories. These lesions have not shrunk enough to contribute to a partial response or have increased to contribute to progressive disease
	No change
	<25 % increase or < 50 % decrease in size of measurable lesions
	<25 % subjective increase or <50 % subjective decrease in size of ill-defined lesions
	No new metastases
Objective response rate	Can be calculated by the sum of the complete response and the partial response

Measurements are based on the sum of a perpendicular, bidimensional measurement of the greatest diameters of each individual lesion

XR radiography, *CT* computed tomography, *SS* skeletal scintigraphy, *MRI* magnetic resonance imaging

Table is modified from Costelloe et al. [4] and Hamaoka et al. [5]

22.2.2 Overall Survival

An inherent limitation of response rate measurement is that it does not always correlate with patient survival. In clinical trials, overall survival (OS) can be defined as the proportion of people alive after the onset of treatment at a given time point. During trials of many agents OS is considered the gold standard measure of therapeutic benefit, bone-targeted agents are usually viewed as supportive care agents, and therefore OS is rarely used as a primary end point [9, 10]. The use of OS has benefits and shortcomings. The benefit of OS as an endpoint in the clinical setting is that it is easy to measure and record. In terms of the patient, OS is ultimately the measure of the end goal for all therapeutic management. The downside of using OS as a primary endpoint in a clinical setting is the prolonged time it takes to get a result. In addition, OS results will not just reflect the effects of the agent under study, but also the effects of all subsequent therapies too. This effect would cloud any survival benefit in subgroups of patients [10, 11].

22.2.3 Progression Free Survival

Progression free survival is typically defined as a time-to-event endpoint. It encompasses the time from the registration of a patient in a clinical trial to death or objective tumour progression, whichever occurs first [10]. Tumour progression can also be termed as time to progression (TTP) instead of PFS. PFS is frequently used in Phase II and III trials of new agents [12–14]. Initially PFS was felt to be a useful surrogate for survival [15]. While this has been shown to be the case in advanced colorectal cancer and ovarian trials, it has not been so in advanced breast, prostate and small cell lung cancer trials [14]. The main advantage is that PFS more directly measures the efficacy of the therapeutic agent. PFS is also less affected by subsequent therapy. Further benefits with the use of PFS in clinical studies include the ability to generate meaningful data from fewer enrolled patients, have trials of shorter duration, and generate results more rapidly as compared to using OS as the primary endpoint [14]. However, possibly the greatest limitation of PFS in studies of bone disease is that, by definition, PFS requires a radiological response, [4] and as noted in the response section above, assessment of radiological response is very difficult with bone metastatic disease [16–20].

22.3 Skeletal Related Events (SREs)

Patient morbidity in clinical trials of bone-targeted agents is traditionally assessed with a composite clinical end point known as skeletal related events (SREs) [21]. SREs are defined as pathological fractures, radiotherapy or surgery to the bone,

spinal cord compression and hypercalcaemia [22]. Most large trials investigating the efficacy of bone-targeted agents in metastatic bone disease use SREs as the gold standard clinical endpoint [23]. In the absence of use of a bone-targeted therapy, the incidence of SREs varies depending on the type of cancer; breast cancer patients experienced on average 3.7 SREs per year while prostate cancer patients experience 1.5 SREs per year [24–28]. Measuring an SRE can capture data on multiple clinically relevant events. This is beneficial when treatment effects and disease morbidity are multifaceted, as occurs with bone targeted agents, and thus SRE measurement will ultimately be more likely to detect therapeutic benefits [21].

A composite definition of skeletal events provides the flexibility to assess the effect of treatments using a variety of outcome analyses. These outcome analyses include first-event analysis, skeletal morbidity period rates (SMPR), and multiple event analyses [29].

First Event Analysis- First event analysis is a measure of the proportion of patients with ≥1 SRE or the time to first on-study SRE [21]. These are objective endpoints which are preferred by the FDA to measure the effect of treatment [21]. However, the consequence of measuring the time to the first skeletal event or patients with one or more SREs is that subsequent events that can occur in a patient are often disregarded.

Skeletal Morbidity Period Rates- SMPR, expressed as events per year, is another SRE outcome analysis. It is a measure of the total number of events that occur during a designated time period. The SMPR is useful for detecting multiple skeletal events, but with the assumption that the events occurred at a constant rate. This has its own challenges. Studies have shown that cancer patients with bone metastases experience variable numbers and rates of SREs [30, 31]. As well, there can be overestimation of treatment effects if events are assumed to occur at a constant rate (i.e. a linear rate), because skeletal events do not demonstrate random distribution but rather tend to occur in clusters [32].

Multiple Event Analyses- Multiple event analyses measure all events and the time between skeletal related events during the course of a patient's follow-up. It takes into account the variability in SRE events that SMPR fails to consider. Additionally, it measures non-constant event rates. Ultimately, it is better able to account for variation in event rates within a patient as well as between patients. It is generally believed that the use of multiple event analyses in combination with first event analysis provides a statistically sound and a thorough assessment of skeletal morbidity [29].

Although SREs are commonly used as a primary endpoint in clinical trials, they may not be entirely accurate in assessing the effects of therapeutic agents on morbidity. First, the impact of different types of SREs is not equivalent for an individual; however it is documented as such. For example, a single asymptomatic bone fracture is arguably less debilitating than a multi-level symptomatic spinal cord compression; however both are considered an equivalent SRE numerically [23]. Another limitation in using SREs as a clinical endpoint is the

risk of underestimating the true value of bone-targeted agents. Depending on the method of analysis, a patient who has a pathological fracture in the morning, radiotherapy to that area in the afternoon and surgery to the same area in the evening may be documented as having a single SRE. However, in the perspective of the health care provider and patient, there were three separate events experienced, not just one. Hence, the effect of a therapeutic agent in preventing these events is undermined when viewed as a single SRE [23]. Finally, it is often discussed that the use of SRE occurrence as a main outcome in clinical trials ignores the impact that metastatic bone disease has on quality of life, pain and survival. However, it is debatable that in a palliative setting the main outcomes are well represented by measuring SREs.

In order to better use SREs as a primary clinical endpoint, trials should be obligated to report exactly the types of SREs occurring, and whether or not they were symptomatic versus or asymptomatic. This would potentially show that the differences between bone-targeted agents in the real world are considerably less than that described in the trial setting. Furthermore, SREs are associated with decreased quality of life and patient survival [33–36]. Therefore, incorporating these clinical endpoints (Quality of life, pain, and survival) along with SRE analysis may allow us to generate an enhanced assessment of patient benefit.

22.4 Pain Scores

Skeletal pain is the most common complication of metastatic bone disease [37] and it can be both severe and debilitating [38]. Multiple treatment modalities are available for the management of pain in these patients, such as radiotherapy, analgesics, surgery and use of bone-targeted agents [39]. Due to their effectiveness in clinical trials, bone-targeted agents have emerged as the primary treatment option to reduce the incidence of SREs, as well as to provide pain relief resulting in improved quality of life [39]. Here we will discuss some of the various instruments presently used to measure bone pain and quality of life.

In clinical trials, pain, a subjective measure of the patients' present experience of their psychosocial and physical well-being, must be evaluated objectively. This is done through the use of patient reported outcomes (PRO). The FDA Guidance on Patient Reported Outcomes defines PRO as any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else [40]. A recent review which investigated possible PRO measures in clinical research identified 12 categories of pain measures in their investigation of 49 studies involving bisphosphonate therapy for bone metastasises. They were grouped as multi-item scales, single item scales, and additional groups of measure. The more commonly used multi-item and single-item scales are shown in Table 22.2 [39].

Table 22.2 Multi-item and single item pain scales [40]

Multi-item scale	Brief pain inventory (BPI)	There are two versions of the BPI, short and long, and both include questions regarding demographic data, use of medication, as well as sensory and reactive components of pain
		The sensory components of pain include pain location, severity, relief, chronicity and interference. Furthermore, pain severity and interference of function is rated using a 0–10 NRS
		The reactive components of pain include depression, suffering and perceived availability of relief
	Wisconsin brief pain questionnaire (BPQ)	Assesses history of pain, intensity, quality, interference with activities and cause. The location of the pain is illustrated by shading a human figure drawing
		Intensity of pain is assessed using a NRS 0–10, at its worst, usual and worst manageable
		Patients are asked to input their list of medication or treatment for pain relief. Interference is measured using a 0–4 scale to evaluate how the pain affects their mood, relations with other people, walking ability, sleep, normal work and enjoyment of life
	McGill-Melzack pain questionnaire	Consists of three major measures of pain. The first includes the pain rating index, the second is the number of words chosen and last measure is the present pain intensity measure based on 1–5 scale
		The pain index is a calculated value based on the mean scale values of words chosen and rank values of those words
		The word list is separated into three categories. The first category describes sensory qualities such as temporal, spatial, pressure, thermal and other properties of pain. The second category describes affective qualities of pain which include tension, fear, and autonomic properties of pain. The final category, describes evaluative words that evaluate the subjective overall intensity of pain
		The PPI describes the intensity of pain, where 1 is mild and 5 is excruciating
Single item scales	Visual analogue scale (VAS)	VAS is a 100 mm horizontal line, with one end representing minimum pain intensity and the other end maximum pain intensity as defined by categorical descriptors
	Verbal analogue scale (VRS)	VRS consists of list of descriptors or phrases that represent varying degrees of pain intensity. These words are chosen commonly from their association with pain in the literature. Patients are asked to associate and assigned a number from 0 to 4 to each word. These numbers represent the following: 0 = none, 1 = mild pain, 2 = moderate pain, 3 = severe pain, 4 = intolerable pain
	Numerical rating scale (NRS)	Patients are asked to evaluate the level of pain intensity from 0 (no pain) to 10 (extreme pain)

22.5 Conclusion

Bone metastases are common. However, there have been significant advances in therapy, in part due to well defined clinical measures implemented in clinical trials to assess the effects of interventional agents. These clinical measures include response rates, overall survival and progression free survival. Also, we must not neglect the importance of pain scores and quality of life scores as they assess the impact therapeutic agents have on the patient's overall well-being. Often these measures are used as secondary clinical outcomes of bone metastasis, while the common primary clinical end point has been the measurement of SREs in the bone metastatic setting.

However, we are now faced with the challenge of translating clinical trial findings into the real word setting to optimize therapy. This will likely require a composite tool rather than a single tool to comprehensibly assess therapeutic agents. The availability of a large volume of clinical measures signifies that in reality, progress will be slow. Therefore, trials will need to integrate multiple endpoints so that we can ascertain which are the most important. Such integrated clinical trials are already underway.

One of the major current research directions in bone metastasis therapy is optimizing scheduling of bisphosphonate treatment to reduce the burden on the patient. Dose de-escalating trials with bone-targeted agents are integrating these clinical measures as either primary or secondary outcomes to optimise scheduling of treatment. These studies are excellent examples of attempting to assess efficacy of therapeutic agents from a multidimensional perspective in a single clinical trial in order to improve the likelihood that clinical findings will translate to benefits for the non-trial patient.

It is clearly evident that it will be difficult to directly translate clinical study findings to individual patient assessment of response outside of a trial. Combining the clinical endpoints to generate a composite assessment of therapeutic agents should direct us towards providing better patient care for patients suffering from metastatic bone disease. We will also require more trials exploring the benefits of radiotherapy and surgery as these are other treatment options that contribute to the overall management of the patient. Eventually, we may develop a series of tools that will allow us to practically combine commonly used clinical trial endpoints with endpoints that are pertinent to an individual patient in a pragmatic and validated manner. Only through this will we ultimately enhance the care we are offering to larger number of patients.

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Chapter 23
Outcome Measures in Bone Metastases Clinical Trials

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Abstract The most common site of metastatic disease in advanced cancer is bone. Management of bone metastases is becoming increasingly multi-disciplinary in nature and many advances have been made to both localized and systemic therapies. With the expanding body of literature, it is important to recognize that there is still extensive variation in response or outcome definitions, and that standardization and consensus of how to analyze clinical data is needed. This will ensure that therapy options can be accurately monitored for both their benefits and adverse effects and allow for better cross-study comparisons. This chapter will outline the outcomes of interest in radiation and bone-modifying agent clinical trials, as well as introduce outcomes used in pain flare and radiation induced nausea and vomiting assessment. The evaluation of pain response in previous trials and the establishment of the International Bone Metastases Consensus Working Party endpoints will also be presented.

Keywords Bone metastases • Clinical endpoints • Outcome measures • Side effects • Clinical trials

23.1 Introduction

Metastatic disease in advanced cancer most commonly manifests itself in bone. Between 65 % and 75 % of patients with advanced breast cancer or prostate cancer and 30–40 % of patients with advanced lung cancer develop bone metastases [1, 2].

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The management of these bone metastases is becoming increasingly multidisciplinary in nature. In many cases, treatment of these bone metastases entails the individual use or combination of localized therapy (such as external beam radiotherapy), surgery, and systemic interventions, including chemotherapy, hormonal therapy, and bisphosphonates among others.

Clinical trials are conducted in the hopes of gaining insight into safety and efficacy data for changes in treatment of bone metastases. Numerous randomized trials have evaluated the potential benefits to changes in practices of radiation, bisphosphonates, palliative, and surgery. However, due to varying endpoint definitions, different conclusions can be drawn from the same body of data. This makes comparisons between trials extremely difficult. These differences also make proper evaluation of standard healthcare practices intenable.

Substantial improvements in survival of patients with bone metastases have been seen. In certain subsets of bone metastases patients, such as breast and prostate cancer patients, life expectancies now range from 2 to 5 years, with advances in treatment and supportive care [3]. As survival increases, there is an increasing need to accurately monitor the benefits and side effects of patients' treatment over a longer period of time. By doing so, the risk of skeletal complications can be minimized and patients' functional status optimized.

As treatment intent for patients with advanced cancers shifts from survival to the preservation of quality of life (QOL), the principal goal of therapy becomes symptom relief. In many cases, management and prevention of complications secondary to bone metastases is the target of treatment. Common clinical endpoints have included survival and tumour control as primary endpoints. However, due to the goals of treatment, palliative endpoints such as pain scores, analgesic consumption, skeletal related events (SREs) and QOL warrant inclusion as routine trial endpoints.

This chapter will discuss traditional bone metastases radiation clinical trial endpoints, as well as present common endpoints seeking to facilitate the comparison of patient responses in bisphosphonate clinical trials. Endpoints in pain flare and radiation induced nausea and vomiting will also be presented.

23.2 Evaluation of Radiotherapy Clinical Trial Endpoints

23.2.1 Results of Previous Studies

In the past two decades, there has been much debate on the effectiveness of single versus multiple fraction radiotherapy (RT) to alleviate metastatic bone pain [4]. Three well-conducted meta-analyses have been performed to elucidate the compared effectiveness of these treatment courses with the conclusion that for the purpose of pain relief, there is no significant difference between the fractionation schedules [4–6]. However, the rate of re-treatment is significantly greater in both intention-to-treat and evaluable patients treated with single fraction [4].

Despite this evidence, there is no consensus on optimal fractionation regimens and healthcare professionals practicing in countries still debate the proper treatment course. For this reason, much variation exists worldwide. This discord stems from trial conclusion differences that arise depending on the endpoints evaluated. In surveys of patterns of practice among radiation oncologists, it has been found that healthcare professionals are reluctant to adopt single fractionation as standard practice [7–19]. Therefore, it is important to recognize that the use of inconsistent endpoint definitions can be reflected in different trial conclusions, limiting our ability to advance standard practices [20].

In a randomized trial comparing the efficacy of a single 8 Gy treatment course to a 20 Gy treatment delivered in five daily fractions in the treatment of bone metastases, pain relief was found to be significantly higher for patients treated with multiple fractions. In this study, pain relief was defined as a reduction in the pain score at the treated site with reduced analgesics or with a pain score of zero at the treated site without an increase in analgesics [21]. However when the endpoint definition was altered and response was defined as solely pain relief regardless of analgesic consumption, the same response rates were incurred by the two regimens [21].

In a randomized dose fractionation trial performed by the Radiation Therapy Oncology Group study (RTOG 7402), it was initially concluded that low-dose short course schedules were as effective as high dose protracted programs [22]. However, with or without re-treatment combined pain and analgesic scores suggested improved complete response with protracted schedules [23].

In a Danish bone pain trial, where pain relief was defined by a categorical scale requiring improvement of at least one category on the 5-point categorical scale, pain relief was found in 62 % of patients at 4 weeks, in the single fraction arm. However, the response dropped to 49 % when pain relief definitions were defined as 50 % reduction in pain on the visual analogue scale [24]. If the criteria included no use of morphine this percentage would be 12 % and this number decreased further to 4 % if a global QOL score that recorded complete well-being was required [24]. This shows that the type of pain scale selected, inclusion of QOL as an endpoint, and the duration of study follow up also influenced the observed treatment response. It is exactly this diversity in endpoint definitions that hinders direct comparison of one study with another.

In addition to clinical trial endpoint definitions, there is an inherent difficulty in measuring patient response when radiotherapy is given as a local treatment as pain is often palliated by other systemic agents. This includes the use of a variety of analgesics, chemotherapy, hormonal therapies, and bisphosphonates. Other ever-present confounding issues include the role of analgesic consumption in assessing treatment response, the definition of partial response and the interpretation of re-treatment. In future trials in radiotherapy for bone metastases, the evaluation of clinical outcomes must not only account for eligibility criteria, radiotherapy technique s and assessment tools, but possible treatment effects from an increasingly complex multidisciplinary management of this patient population.

23.2.2 International Consensus on Palliative Radiotherapy Endpoints

In an effort to promote consistency in future clinical trial design for palliating bone metastases, an International Bone Metastases Consensus Working Party on endpoint measurements was established in April 2000. This initiative involved an international faculty representing the American Society for Radiation Oncology (ASTRO), the European Society for Therapeutic Radiology and Oncology (ESTRO), the Faculty of Radiation Oncology of the Royal Australian and New Zealand College of Radiologists (RANZCR), and the Canadian Association of Radiation Oncology (CARO) [25]. The working party aimed to encourage investigators to adopt a common set of bare-minimum endpoints for future clinical trials in bone metastases. In 2002, the International Bone Metastases Consensus Working Party reached its' first consensus on future radiotherapy trials involving external beam radiotherapy [26]. This collaboration formulated a framework for palliative RT trials in patients with bone metastases.

This international consensus was updated and refined in 2012 to identify both new areas requiring consensus and aspects of the previous consensus in need of update in a two-phase survey of healthcare professionals. Representation from the four major membership/credentialing radiotherapy organizations previously mentioned were included in this update (ASTRO, ESTRO, RANZCR, and CARO).

23.2.2.1 Eligibility Criteria for Future Trials

It is recommended that for studies involving more than one tumour site, stratification should be made by the tumour type involved. An inclusion criterion that patients should have measurable pain, defined as requiring patients to report a worst pain score of at least 5 on a scale from 0 to 10, with 10 being the worst possible pain, may be recommended. Also since performance status has been shown to correlate with the duration of survival [27, 28], performance status should be an eligibility criterion for studies designed to assess pain relief for a duration of more than 3 months. Because healthcare professional prediction of life expectancy is often inaccurate [29, 30] minimum life expectancy has limited reliability as an entry criterion [26]. A "run-in" period, otherwise known as an interval between analgesic dosing adjustment and initiation of irradiation, of 1 week is recommended. Changes in systemic chemotherapy, hormonal therapy or the use of bisphosphonates for 4 weeks before and after the delivery of radiotherapy are allowed, but recording and accounting for this in the statistical analysis is required [25].

23.2.2.2 Pain and Analgesic Assessment

A patient-assessed assessment with an ordinal pain scale of 0–10 was recommended, with the boundaries of 0 representing no pain and a score of 10 representing maximal pain [25]. The measured pain should relate to only the worst for the previous 3 days at

the treated site(s), not the average pain. Net pain relief can be considered concurrently to evaluate absolute decreases in pain scores and changes in medication dosing. The use of a body diagram to define the painful site(s) is encouraged at clinic visits and in mailed questionnaires [26]. If necessary, assistance in pain scoring from caregivers, family members or healthcare providers should be allowed.

All narcotic analgesics, including regular and breakthrough doses, should be converted into a daily oral morphine equivalent for analgesic scoring [31]. Adjuvant analgesics should also be recorded [26]. The incorporation of validated QOL instruments specific to bone metastases, is recommended for all clinical trials. This includes the EORTC QLQ-BM22 or EORTC QLQ-C15-PAL [25].

23.2.2.3 Follow-up and Timing of Assessments

The baseline pre-treatment assessment is essential and should be undertaken as close to the time of treatment delivery as possible. Follow-up can be performed any combination of the following options: clinic visits, mailed questionnaires, telephone interviews, and/or electronic tallying. The minimum follow-up agreed upon was at 2-weeks, 1-month, and then monthly until 6 months after delivery of radiation treatment. Longer follow-up are encouraged for patients with prolonged survival [26].

23.2.2.4 Endpoints

Prior to 2002, heterogeneous response definitions made cross-study comparisons difficult and could result in different conclusions being drawn from the same sets of data within individual trials. With the consensus, response definitions were created with regard to both pain and analgesic scores.

Response rates should be determined at 1-, 2-, and 3-months following radiotherapy [26]. Assessment of pain should be on a scale of 0–10, with boundaries of 0 representing no pain and 10 representing maximal pain. The following definitions were agreed upon [25]:

Complete response: a pain score of 0 at treated site with no concomitant increase in analgesic intake (stable or reducing analgesics in daily oral morphine equivalent (OMED)).

Partial response: either (1) a pain reduction of 2 or more at the treated site on a scale of 0–10 without analgesic increase or (2) analgesic reduction of 25 % or more from baseline without an increase in pain.

Pain progression: either (1) an increase in the pain score of two or more points above baseline at the treated site with stable analgesic use or (2) an increase of 25 % or more in daily oral morphine equivalent compared with baseline with the pain score stable or one point above baseline.

Indeterminate response: any response that is not captured by the complete response, partial response, or pain progression definitions.

Reporting response rates at fixed time-points (aforementioned 1-, 2-, 3-months) may result in lower observed rates compared to reporting response occurring at any time during follow-up, as illustrated in the Danish study [24]. However, responses occurring outside this 3-month time frame may reflect secondary interventions. These would include re-irradiation, new systemic therapy, or more aggressive pain management. The timing and clinical indications for re-irradiation need to be clearly defined in future clinical trials. Re-irradiation should be recorded but the response to re-irradiation should not be included in the primary outcome of the first radiation. If re-irradiation is given, the response to re-irradiation should also be analyzed independently.

It has been pointed out that the actuarial rate of response assumes that non-evaluable patients that are lost due to death or illness will have the same probability of demonstrating the desired response. This assumption may overestimate the true patient response rate' as such it should be reported as well. A measure of "sustained response" would be dependent on the survival duration of study patients and the frequency of the follow-up assessments.

As was discussed, the response rate to radiotherapy is a function of endpoint [26]. In a study comparing response rates employing the International Bone Metastases Consensus endpoints versus the traditional response endpoints, the former takes in to account both pain scores and analgesia. The result of this is reduced complete and partial response when compared to the traditional pain only endpoints. Nevertheless, these consensus endpoints more accurately reflect the efficacy of palliative radiotherapy as significant increases in pain medication are not misconstrued and attributed as radiotherapy response.

23.2.3 Patient Assessment Tools

Valid pain assessment tools are required to adequately evaluate pain intensity and the effectiveness of the pain management plan [32]. Common scales used to assess this construct include visual analogue scales (VAS), verbal descriptor scales (VDS), or numeric rating scales (NRS). The VAS is a 10 cm line where patients can mark their pain intensity with ends of "no pain" and "pain as bad as it could be"; the VDS contains a list of adjectives that describe levels of pain (i.e. no pain, mild, moderate, or severe pain); and the NRS allows patients to describe the intensity of pain in numbers. For example, NRS may use an 11-point scale where zero indicates no pain and 10 represents worst possible pain. Numerical scales are also frequently used for measuring changes in pain over time and correlating pain intensity with other important outcomes, such as quality of life or functional interference. NRS are utilized in the International Bone Metastases Consensus Working Party endpoints for evaluation of pain response following radiotherapy for bone metastases [26].

The Brief Pain Inventory (BPI) is one of the most commonly employed NRS used to measure pain intensity and functional interference in cancer-related research [33]. Developed by Cleeland and Ryan [34], this validated patient-based assessment tool

evaluates pain on three dimensions: worst pain, average pain, and current pain. In addition, seven indicators of function interference are explored: general activity, normal work, walking ability, mood, sleep, relationships with others, and enjoyment of life [34]. Analgesic consumption over the preceding 24-h period is also recorded. Multiple studies have shown the intensity of the worst pain rating correlates most substantially to functional interference [33–38]. As such, it has been recommended that a patient's worst pain score should be used in the assessment of overall radiotherapy response [33].

Utilizing the BPI in the palliative cancer population has also revealed varying levels of correspondence of the three dimensions of pain (mild, moderate, or severe) with functional interference [33]. To date, a number of studies have attempted to establish cut-off points for mild, moderate and severe pain on a numeric scale. Such investigations are important for several reasons, as outlined by Anderson [39]. Most patients prefer to describe their pain severity using verbal rating scales such as mild, moderate or severe when communicating with healthcare providers [40]. However, some current clinical practice guidelines for cancer pain, such as the World Health Organization analgesic ladder, are based on the assessment of pain using categorical scales (i.e. mild, moderate or severe), while others, such as the American Pain Society Cancer Pain Guidelines [41] and the National Comprehensive Cancer Centre Network guidelines [42], are based on both categorical and numerical pain scales. A lack of consensus as to what these pain categories mean numerically may result in difficulty for clinicians to interpret and follow treatment guidelines. The categorization of pain into three grades help clinical research studies to summarize the prevalence of different levels of pain intensity within a population (for example, the number of patients experiencing an increase of pain from mild to moderate). To compare results across studies, consistent definitions of mild, moderate and severe pain are required [43].

In 1995, Serlin et al. [38] began an investigation of grading mild, moderate and severe pain on a numeric scale using a novel multivariate statistical approach. Using the BPI responses of over 1,800 patients with cancer-related pain from four countries, it was found that the optimal upper cut-off points for mild and moderate pain was four and six, respectively. A non-linear relation between pain severity and functional interference was also observed. Subsequent studies with other populations and origin of pain using the same method were conducted. However, pain severity cut-off points were inconsistent across studies, where the upper boundary for mild and moderate pain varied between three to five and six to eight, respectively [43].

A similar study replicated the methodology employed by Serlin et al. [38]. Results confirmed a non-linear relationship between cancer pain severity and functional interference in 199 bone metastases patients treated with palliative radiotherapy [43]. The optimal cut points for mild and moderate pain were four and six (mild = 1–4, moderate = 5–6, and severe = 7–10) [43], verifying Serlin et al.'s findings.

The classification of discrete pain categories is valuable for clinical evaluation, research and public policy. More research, however, is needed to determine if the

three categories of pain are adequate; to determine the minimal clinically meaningful reduction in pain measured categorically; and lastly, if this reduction is the same as that for pain measured numerically [43].

23.2.4 When Should We Define Response?

Although it was recommended by the International Bone Consensus Working Party to assess pain response at 1-, 2-, and 3-months following radiotherapy [26], validation of this recommendation was required. A study by Li et al. concluded that 2-months after radiotherapy is the most appropriate time point to measure response rates for the following reasons: (i) the maximum pain relief for some patients may take more than 4 weeks to achieve; and (ii) attrition poses a major problem when response rates are measured at a later date [44]. In addition, response occurring beyond 3-months may reflect secondary interventions, such as re-irradiation, new systemic therapy, or more aggressive pain management [25]. Therefore, a 2-month interval from treatment to evaluation of response may be ideal.

23.2.5 What Constitutes a Meaningful Change in Pain Score?

Benefits of palliative radiotherapy for bone metastases are assessed by the change in pain intensity as measured by pain scores. Previous studies have shown that health-care providers and family members tend to overestimate the benefits of treatment interventions [45–52]. Patient self-assessment should therefore be the preferred measure of benefit or success of the treatment.

Patients are often not informed of what pain score they provided at baseline when they are asked to score their current pain during a follow-up assessment. Some patients inform their pain is better when compared with the baseline pain but the current pain score is increasing when compared with that at the baseline. The reverse also happens. It is therefore important to determine a meaningful improvement or decline in scores to assess the benefits of the treatment such as palliative radiotherapy.

In a 2005 study, patients were asked their pain score and pain perception over a period of 11 days (for patients who received a single treatment) to 22–24 days (for patients who received ten daily treatments) [53]. Seven hundred and ninety seven pain scorings from 88 patients were collected. Patients perceived an improvement in their pain status when their self-reported pain score decreased by at least two points on a scale of 0–10 [53].

A subsequent study was launched to validate the 2005 finding [54]. A total of 1,431 pain scorings were obtained. A pain score decrease of two to ten points at follow-up was consistently reported by patients as an improvement when compared

to the baseline pain. However, when the change in pain score decreased by only one point, only 39 % of patients reported the pain as the same and 41 % of patients reported the pain as better when compared with baseline [54]. Through the results of these two studies, it appears that patients perceived the current pain to be less than the baseline pain when they reported a decline of their pain score of two or more. Recent bone metastases randomized trials [55, 56] and the International Bone Metastases Consensus endpoints [26] defined partial response as a reduction of pain score by two or more points on a pain scale of 0–10. This definition appears to be supported.

23.2.6 Patient Perspective of Minimal Meaningful Pain Relief

Traditional clinical trial endpoints have been solely defined by investigators with no contribution from patients as to what constitutes a meaningful partial response to treatment. This coincides with the endpoint definitions suggested by the International Bone Metastases Consensus Working Party [25]. Partial responses have been arbitrarily defined independently of the severity of the bone pain before radiotherapy. The perception of the treatment benefit varies among individuals. It also depends on the health status of the individual and is subject to change with time and experience [57].

Studies are required to investigate the magnitude of the minimal significant pain reduction from the patient perspective. Investigators would then be able to incorporate patient derived definition of partial response in future trials. This is important as many patients receiving palliative radiotherapy will not achieve a complete response [58].

Our group explored the minimum reduction in pain level with no change in analgesic consumption that an individual patient would expect by 2 months in order to justify the proposed course of palliative radiotherapy—a patient derived definition of partial response. Study patients were asked to rate their current level of pain at the time of interview (on a scale of 0–10, 0 = no pain, 10 = worst pain ever). Subsequently, patients were asked to quantify the minimum level of pain reduction (by 2 months) that they think would justify their palliative radiotherapy [58].

Patients with higher pain score required a greater magnitude of minimum pain reduction. A reduction of six and seven were expected in patients with pain scores of nine and ten respectively, whereas a reduction of one and two were expected in patients with pain scores of three and four, respectively. When expressed as a ratio for this magnitude compared with the baseline pain score, it appeared that patients expected a reduction of 50–70 % in their baseline pain following radiation treatment [58]. From these results, it would be reasonable to consider a pain score reduction of two thirds from the baseline as the partial response. Farrar et al. recommended using a benchmark of 33 % total pain relief as a clinically meaningful response [59].

We have come far along in employing patient based assessment of pain-related symptoms. Nevertheless, it is high time to incorporate patient expectation in our future definition of a treatment response [58]. Moreover, patients' subjective evaluation of quality of life requires further exploration.

23.3 Evaluation of Bone-Modifying Agent Clinical Trial Endpoints

23.3.1 Use of Endpoints in Literature

In phase III, randomized clinical trials of bone-modifying agents, there is heterogeneity in the reporting of SRE outcomes. This variation in endpoint definitions in the literature prevents accurate cross-study comparisons of bone-modifying agents and could result in ambiguity in the conclusions being drawn from the same set of data.

Early bisphosphonate trial endpoints were based on subjective parameters, such as pain assessment and analgesic use, or on objective measures, such as serum calcium levels or rate of pathologic bone fractures [60]. However, over time, composite endpoints based on skeletal related events (SREs) have been increasingly adopted to properly evaluate prevention and treatment of skeletal complications [60].

Patients with bone metastases possess a high risk of developing SREs, such as: bone pain requiring analgesics or palliative radiotherapy, spinal cord compressions (SCC), pathological fractures, hypercalcemia of malignancy (HCM), or a need for surgery which can greatly reduce QOL [61]. In retrospective analyses of several tumour types, patients with bone metastases who experience an SRE have been shown to be more likely to experience subsequent SREs [62]. SREs undermine patients' functional wellbeing, lead to significant morbidity, and may reduce patients' survival. As the intent of treatment for patients with advanced cancers shifts from survival to the preservation of QOL, the management and prevention of SREs secondary to bone metastases becomes a principal concern.

Composite endpoints based on SREs have been found to be valid in the evaluation of skeletal morbidity [60, 63–66]. Their use was supported by regulatory authorities for phase III clinical trials comparing pamidronate to zoledronic acid and was reinforced in a publication from the US Food and Drug Administration [66]. However, an optimal method of statistical analysis of SREs remains to be agreed upon. SREs as a quantifiable clinical end-point were initially defined as pathologic fractures, irradiation or surgery of bone, SCC, or HCM. This definition was first applied to studies assessing pamidronate use in breast cancer patients with bone metastases [67]. While in the past, HCM was highly prevalent in breast cancer patients with bone metastases, today it is a rarely seen condition due to a better understanding of bone disease and the frequent use of anti-resorptive therapies. In fact, in comparisons of HCM

rates reported in studies performed in the 1990s, significantly lower rates of HCM are seen in comparison to those conducted in the 1970s and 1980s [1].

Therefore, in more recent studies, HCM has been excluded from the standard definition of SREs.

23.3.2 Common Bone-Modifying Agent Clinical Trial Endpoints

23.3.2.1 Skeletal Morbidity Rate

The skeletal morbidity rate (SMR) is defined as the ratio of the number of SREs for each subject divided by the subject's time at risk in years [1, 67, 68]. For example, if a study follows 1,000 patients for 1 year and among those 1,000 patients 300 SREs occur, then the SMR value would be 0.30 SREs/year.

In phase III, randomized bisphosphonate and other bone-targeted therapy trials acquiring SRE data, SMR has only been used as a primary endpoint in a limited number of studies including pamidronate and zoledronic acid comparison studies against placebo [1, 69, 70]. While in many studies it is not the primary outcome of interest, SMR is a commonly presented endpoint [1, 64, 67–69, 71–78]. The advantage to using SMR as an endpoint is that it standardizes the rate of SREs over a time period, typically 1 year, whereas pure numerical events would unequally weigh trials to those with the longest follow-up or largest cohort.

23.3.2.2 Skeletal Morbidity Period Rate

Skeletal morbidity period rate (SMPR) is defined as the number of periods with at least one morbidity event over the time in study per patient [79, 80]. In a study performed by Tripathy et al., SMPR was defined as the number of 12-week periods with at least one new skeletal complication (vertebral and non-vertebral fractures, bone radiotherapy or bone surgery), divided by the number of periods on the study [68]:

$$\begin{aligned}\text{SMPR} = {} & \text{number of periods with new skeletal events} \\ & + 1 \,/\, \text{number of } 12-\text{week periods on study} + 0.5\end{aligned}$$

An assumption was made that with an arbitrary constant added to the numerator and denominator, the effect would be marginal, especially considering the process of ranking of morbidity scores for treatment comparisons [79]. The rank correlation between measures using this arbitrary constant and alternative definitions was found to be greater than 0.97 [79].

23.3.2.3 Proportion of Patients with SRE

The proportion of patients experiencing at least one on-trial SRE, which is prospectively defined as a pathologic fracture, spinal cord compression, radiation therapy or surgery to bone, or change in the antineoplastic therapy to treat bone pain [60, 70].

23.3.2.4 Time to First On-Study Skeletal-Related Event

Time from baseline to first SRE experienced [70, 79]. This endpoint has been frequently used in phase III randomized trials of bone-modifying agents and was prospectively defined as a pathological fracture, radiation therapy, surgery to bone, or spinal cord compression in a comparative study of denosumab, a human monoclonal antibody RANKL inhibitor, and zoledronic acid [81].

23.3.2.5 Bone Pain Measures

In several randomized, placebo-controlled studies of pamidronate severity and frequency of pain were individually graded on a 4-point Likert scale scoring system from 0 to 3 [67]. The final bone pain score was equal to the product of the two individual scores with a score of 0 indicating no pain, while a score of 9 indicated severe and constant pain. The score for the medication type was then multiplied with a score for the frequency of its administration to give a final score.

In phase III, randomized trials comparing intravenous to oral ibandronate, a 5-point Likert scale ranging from 0 (no pain) to 4 (intolerable pain) was used for pain assessment [68, 72, 82, 83]. Analgesic usage was then measured on a 7-point scale, spanning 0 (none) to 6 (greater or equal to 100 mg daily morphine equivalent).

In the placebo-controlled trial of zoledronic acid performed by Kohno et al., the Brief Pain Inventory (BPI) was used in combination with a 5-point analgesic use scale ranging from 0 to 4 (no analgesic use- strong narcotics) [73].

A host of other assessment scales for analgesic use and pain assessment have been employed. This includes the visual analogue scale, variants of pain-point scales, and analgesic use on a 4-point scale. An example of the considerable endpoint variation can be seen with the instrument used by Groff et al. In this case, a Likert verbal scale was used to measure pain intensity (no pain = 0; a little = 33.3; much = 66.6; very much = 100) [84].

In a literature review performed by Mazta et al. on instruments to assess pain in studies of bisphosphonate treatment in metastases, it was found that the BPI was the most commonly used multi-item instrument in the assessment of pain-related outcomes [85]. However, the most common approach used in data analysis were single item scales like the visual analogue scale [85]. Currently, use of pain-related outcome measurements remains too varied; future studies should seek to valid instruments used, standardize measurements, and clearly define pain relief endpoints.

23.3.2.6 QOL Measures

QOL measurements are typically subjective, seeking to assess patients in several domains simultaneously. QOL has been poorly assessed in bone-modifying agent trials [70]. In the past, pamidronate studies have used the Spitzer QOL instrument which focuses on five core items: activity, daily living, health, support, and outlook [86]. In contrast, studies of clodronate and ibandronate have used the 30 item European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30) which includes five scales assessing physical function, role function, cognitive function, emotional function, and social function [72, 82, 87, 88]. Neither of these instruments however directly addresses the QOL issues specifically pertaining to complications experienced by bone metastases patients. A more comprehensive assessment of QOL may be found using a bone metastases specific module, such as the EORTC QLQ-BM22 [25].

23.3.3 Analysis of Endpoints Used in Bisphosphonate Trials

In the past, a number of endpoints and statistical methods have been applied in clinical trials studying bisphosphonates, such as: the proportion of patients experiencing at least one on-trial SRE, the median time to first SRE, the SMPR and the SMR. However, each of these methods is limited by inherent assumptions that underlie the statistical models from which they are based on.

Analyses of data collected to the first on-trial SRE have been used as the primary endpoint in various zoledronic acid and pamidronate studies [71, 89]. These endpoints focus exclusively upon the first-event experienced by patients and fail to assess the effects of treatment through the progression of disease [70]. Since bisphosphonates reduce the occurrence of subsequent SREs, in many cases, use of these endpoints may oversimplify the entirety of the treatment effects and may mask the true benefit(s) of the agent [60]. SRE analyses also often ignore adverse events or SREs experienced subsequent to the first.

The impact of treatment on skeletal morbidity is best assessed by endpoints that account for multiple events that occur over the course of treatment and in its aftermath [70]. As previously stated, all endpoints based on SREs are limited by their inherent assumptions. Skeletal morbidity rate collapses all SRE incidence data into a linear measurement, regardless of SRE onset timing. This results in oversimplification of the disease trajectory and how bone-modifying agents affect their course because SREs do not necessarily occur at a constant rate. Typically, a patient's risk of experiencing an SRE increases with time as metastatic disease progresses. Variation also exists in both the frequency of SREs and the timing in which they present between patients [70, 79]. Some patients experience SREs as isolated events, whereas other may experience these complications as clusters of symptoms. This clustering is unaccounted for in SMR analysis, as SMR assumes that all events are expressed independently of one another [70, 79]. Alternatively, the definition of

SMPR can account for the interdependence of SREs. This method also incorporates how patient experiences are varied and allows for simple adjustment to analyze by observation time in study [79]. SMPR is however limited in other ways by the assumptions inherent to its definition. SMPR analyses assume that all events are causally linked within a certain time period. Therefore, as that time period increases this assertion becomes less valid. Criticisms have also been made that both the scoring of SMPR and the time period used are not based on medical judgement but are rather arbitrary [90].

Symptom relief (pain relief and analgesic use) and preservation of QOL have also been commonly used as clinical trial endpoints for bone-modifying agents. Many patients with bone metastases experience severe bone pain, which can lead to deleterious effects upon QOL as well as can cause morbidity [91, 92]. While insights can be gained from these endpoints, conclusions on bisphosphonates and other bone-modifying agents drawn from these endpoints are limited by the necessity to quantify subjective data [65]. How patients interpret their condition and the question within the assessment tool also vary from patient to patient. Quantifiable endpoints for analgesic score can also be confounded by numerous variables, including patients' assessment of pain and the caregivers' assessment [93]. Also, while functionally a decrease in analgesic use or pain assessment scores represent improved pain relief, the heterogeneity of reporting and lack of consensus in assessment complicate comparison between bone-modifying agents.

23.4 Pain Flare

23.4.1 Definition of Pain Flare Endpoints

Pain flares are a temporary worsening of bone pain experienced at a metastatic site following RT. It is a common side effect following radiopharmaceutical therapy [94–97]. To be considered an incidence of pain flare, both criterion (a) and (b) listed below at a particular treated site must be experienced [98]:

(a) Changes in Pain Score and/or Analgesic Intake
Pain flare is defined as a minimum of a 2-point increase in worst pain score on a scale of 0–10 when compared to the baseline worst pain with no decrease in analgesic use, or a 25 % or more increase in analgesic intake (employing daily oral morphine equivalence) compared to the analgesic intake at baseline with no decrease in worst pain score. In cases where the worst pain score recorded is already 9 or 10, the criteria for pain flare are met if the follow-up worst pain score is a value of 10 with no decrease in analgesic intake [98].

(b) Return to Baseline
In order to distinguish pain flares from progression of pain the worst pain score and analgesic intake must return to levels that are the same or less than those recorded prior to treatment. This must occur within the 11-day on-study period (within a 10 day follow-up period) [98].

Pain response to RT is another commonly used endpoint in the analysis of pain flares and is defined in the same manner as previously mentioned for RT clinical outcomes.

23.5 Radiation Induced Nausea and Vomiting

How radiation-induced nausea and vomiting (RINV) is experienced by patients is variable. However, typically, a latent asymptomatic period 1–2 h following treatment with sudden onset of vomiting and nausea that can last for 6–8 h is experienced [99]. In recent years, the incidence of RINV has decreased as large-field treatments such as total body, total nodal, half body and whole abdominal irradiation are no longer common practice and have been replaced by novel radiation techniques [100]. However, large observational studies suggest that the overall rate of occurrence of some degree of RINV among patients undergoing radiotherapy remains at 50–80 % [101, 102].

Nausea and vomiting are symptoms that can induce a broad range of physical, psychological and emotional factors. However, as nausea and vomiting is thought to be less prevalent and less severe than for chemotherapy, in many cases it is a symptom that is undervalued and disregarded by healthcare professionals [103]. Primary and secondary endpoints, in studies on RINV, differ considerably. These subtle differences in endpoints can insensibly prevent inter-study comparisons [100].

Vomiting is relatively easy to identify and record for patients and investigators in comparison to nausea. However, difficulties can be incurred when trying to distinguish vomiting episodes from retching episodes [100]. In some studies, retching is coded as an equivalent event as patients may not be able to distinguish it from vomiting [102]. Future studies should seek to illuminate whether these two events evoke a similar symptomatic impact in patients, but until this relationship has been determined, these should be treated as independent events and be recorded separately.

Far more difficulties are experienced when trying to define and investigate nausea as there is heterogeneity in patients' understanding of the event [104]. Patients can refer to nausea as a brief episode lasting mere seconds or a prolonged period of symptoms that can last hours or days [100]. In many cases, nausea episodes are ambiguous and symptoms can be mistaken or confused by patients. Modern assessment for nausea episodes is also binary, i.e., nausea is encompassed for as a single symptom experienced by patients. However, in reality the manifestations of these symptoms and their effect on QOL vary. Problematically, until qualitative studies define nausea more accurately and tools are constructed to distinguish the nuances of this symptom, nausea will continue to be viewed as all-or-nothing events in the same way as vomiting.

The time of initiation of nausea and vomiting events as well as the length should be carefully documented in diaries during future studies. In many studies, patients are only followed for a short period of time: 24–48 h following single-fraction radiotherapy or just the early stages of a course of more protracted therapy [102]. Some studies also only ask patients to complete diaries until the onset of nausea or vomiting.

In these cases, no further data collection is pursued beyond the first symptom. This is problematic as delayed nausea and vomiting after initial period following RT has been identified in the RINV literature.

Ultimately, the goal would be for practitioners to use study data to educate and prepare their patients regarding the risks of nausea and vomiting for an entire course of radiotherapy, i.e., cumulative incidence rates of both nausea and vomiting, as opposed to only daily incidence rates for these events should also be tabulated [100]. Consensus among leaders in the RINV field is required so that guidelines for reporting endpoints in future trials in RINV can be created.

23.6 Closing Remarks

This chapter has outlined the outcomes of interest in radiation and bone-modifying agent clinical trials, as well as introduced outcomes used in pain flare and radiation induced nausea and vomiting assessment.

With the expanding body of literature, it is important to recognize that there is still extensive variation in response or outcome definitions, and that standardization and consensus of how to analyze clinical data is needed. This will ensure that therapy options can be accurately monitored for both their benefits and adverse effects and allow for better cross-study comparisons. We especially encourage investigators to develop and validate bisphosphonate and RINV assessment tools for clinical trials to aid in this process.

Widespread use of the updated International Bone Metastases Consensus endpoints for assessment of pain response will continue to facilitate inter-study comparisons and reveal optimal systemic and localized bone metastases specific treatments. However, it is suggested that the consensus be re-evaluated regularly in order to tailor assessments to clinically relevant issues.

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Chapter 24
Quality of Life in Patients Suffering from Metastatic Skeletal Disease

Marko Popovic, Liang Zeng, and Edward Chow

Abstract Bone metastases are the most common manifestation of metastatic disease in advanced cancer patients. Health care professionals (HCPs) agree that maintenance or improvement in quality of life (QOL) is the main goal of palliative treatments for bone metastases. Historically, QOL was measured by generalized assessment tools. With advancement in treatments for bone metastases patients, there has been a need for the development of a bone metastases-specific QOL module. Recognizing this need, the European Organization for Research and Treatment of Cancer (EORTC) QOL Group developed the EORTC QLQ-BM22 (BM22). The BM22 is used to assess QOL in bone metastases patients in four domains: painful sites, pain characteristics, functional interference and psychosocial aspects. Input for the module came from both patients and HCPs from several countries with different cultures; the BM22 was subsequently subject to reliability and validity testing and the minimal clinically important differences of the module were explored. The Bone Metastases Quality of Life Questionnaire (BOMET-QOL) was also developed using input from HCPs and patients; however, unlike the BM22, the module has not been significantly validated cross-culturally. Notably, the module is shorter than the BM22 (10 vs. 22 items, respectively) and does not contain any specific QOL subscales that it assesses. Development of a third assessment module, the Functional Assessment of Cancer Therapy-Bone Pain (FACT-BP), involved solely input from patients. The 16 item FACT-BP is made up of three distinct subscales: general functioning, physical and bone pain and is shorter than the BM22. Investigators are encouraged to facilitate direct comparison between the three QOL assessment tools available for bone metastases patients which will allow HCPs to establish a globally standardized QOL module in this patient population.

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Keywords Bone metastases • Quality of life • Advanced cancer • Palliative treatment

24.1 Introduction

Bone metastases are the most common manifestation of metastatic disease in advanced cancers, particularly in breast, prostate, and lung carcinomas [1]. Treatment of bone metastases involves localized therapies, such as external beam radiotherapy, as well as systemic interventions, including chemotherapy, hormonal therapy, and bisphosphonates. Management of bone metastases has become increasingly multidisciplinary in nature.

With advances in effective systemic treatment and supportive care, survival of patients with bone metastases has improved substantially. Certain subsets of patients with bone metastases (e.g. breast and prostate cancer with predominately bone or bone-only metastases) have life expectancies that range from 2 to 5 years [2]. Successful management of bone metastases during these years is essential for reducing skeletal complications and for maximizing patient quality of life (QOL). There have been clinical trials in various disciplines addressing the optimal management of bone metastases. As the survival of bone metastases patients increases, there is an greater need to accurately monitor the benefits and side effects of their treatment. Clinical trials have routinely included survival and tumour control as primary endpoints. As most treatments aim at relieving symptoms, palliative endpoints such as pain score, analgesic consumption, skeletal related events, and quality of life warrant inclusion as routine trial endpoints [3].

Over the last few years, QOL has seen a growing focus among professionals caring for this patient population. Presently, health care professionals (HCPs) agree that maintenance or improvement in QOL is the main goal of palliative treatments for bone metastases [4]. Thus, there exists a need for physicians, therapists, nurses, and others to stay updated on the evolving body of QOL-centred literature which remains a crucial consideration in deciding between various treatment regimens.

This chapter will discuss relevant quality of life issues in patients with bone metastases. Quality of life assessment will be thoroughly explored, with a particular emphasis on historical techniques as well as recent clinical trials outlining the development and validation of quality of life assessment modules in present use.

24.2 Overview of Historical Issues Concerning the Assessment of Quality of Life in Patients with Bone Metastases

The World Health Organization describes health as ‘not merely the absence of disease or infirmity, but a state of physical, mental and social well-being’ [5]. QOL is a subjective, multidimensional construct reflecting functional status, psychosocial

well-being, health perceptions and disease- and treatment- related symptoms from the patient's perspective. It incorporates expectation, satisfaction, a value system among other aspects of a patient's life [6]. In palliative trials, as well as symptom control, QOL is a major endpoint. Since palliative interventions are unlikely to lead to survival prolongation and significant tumor regression, QOL is a more meaningful endpoint when compared with traditional endpoints such as survival times and local control. Quality of life issues are an important consideration for patients when making decisions for the treatment of bone metastases. More interventional studies now aim towards enhancing patients' QOL, often by reducing toxicity. In addition, regulatory bodies are giving increasing importance to QOL studies as an independent endpoint in determining the cost-effectiveness of competing therapies.

With advancement in systemic treatment of advanced cancer with osseous metastases (e.g. radiopharmaceuticals, bisphosphonates, chemotherapies, orthopedic interventions, and additional systemic treatments), there was, historically, more need than ever for the development of a QOL assessment tool specific to bone metastases patients in order for a comprehensive assessment of the benefits and side effects of these specific interventions [3].

Traditionally, patients with bone metastases in clinical trials have completed general QOL assessment tools. These instruments are generic for malignancy and not designed with the intent to cover key QOL issues relevant for cancer patients with bone metastases. Patients uniformly expressed that these instruments were not relevant for their situations as they did not thoroughly address the QOL issues related to the disease and the complications of bone metastases such as hypercalcaemia, pathological fractures, spinal cord compression, mobility and functional impairment of the diseased bone, nor the side effects of specific treatments.

There is general agreement that the patient is the most appropriate source of information regarding his/her QOL [7]. Only the patient can report their subjective experiences and priorities. Unfortunately, at the end of the twentieth century, there was a gap between theory and practice of QOL assessment in the clinical setting. It was been reported that 85 % of physicians felt patients are the best judge of their own QOL [8], yet definitions and measures of QOL were usually based, to a great extent, on the researchers' and clinicians' perception of what QOL issues are most relevant to their patients [9]. Many studies have shown that the agreement between patient and physician responses is poor and physician assessments are not appropriate as substitutes for self-assessment in palliative care. Furthermore, in a survey by Bezjak et al., 78 % of responding physicians acknowledged that when physicians and patients discuss QOL issues they may not be talking about the same thing [6].

Patients with bone metastases experience their own distinct symptoms and emotional issues when facing advanced cancer and its treatment. While pain is the most common symptom, it is not clear exactly which pain characteristics and patient characteristics influence the QOL of these patients [10]. Understanding the patient's perspective and how it compares to that of HCPs assists in recognizing the differences and develops management strategies better addressed to individual patient needs.

In a study by Detmar et al., almost all patients expressed a willingness to initiate and discuss the physical aspects of his or her disease [11]. On the other hand, 25 % of patients felt it was only appropriate to discuss emotional functioning at the initiative of their physician. An even greater reluctance was observed concerning the issues of social functioning and family life, with 28–36 % of patients waiting for the doctor to first raise the topic and another 20 % preferring not to hold a discussion on these issues at all. This suggests that patients may be uncertain about which issues are appropriate to discuss with their physician [11]. Physical issues such as symptoms from the disease or treatment may be thought of as the primary responsibility of the physician, while psychosocial problems, including 'worry' issues, seem to fall into a more private domain and patients may be uncomfortable bringing them up with HCPs.

Several physicians echo this position on the discussion of psychological issues. It was reported that physicians felt that discussion of the physical aspects of their patient's health was primarily their responsibility, while a number indicated that the discussion of psychosocial health problems should be shared with other HCPs [11]. In the case of emotional and social functioning, all physicians indicated that they generally defer the initiation of the topics to their patients [11]. Consequently, this miscommunication may hinder the discussion of psychosocial issues, which can lead to inaccurate diagnoses and inadequate treatment [12] as physicians tend to overlook problems or symptoms that are not obvious or mentioned explicitly by the patient [13].

24.2.1 Early Quality of Life Assessment in Bone Metastases Clinical Trials (1990–2005)

Before the introduction of bone metastases-specific QOL questionnaires, QOL as an outcome measure was increasingly being incorporated into trials that utilized general QOL assessment tools in the palliative care setting [14]. Five localized palliative radiotherapy trials for bony metastases were cited as of particular importance for examining QOL as an endpoint before QOL was widely explored in this patient population [14–18].

In a randomized trial comparing two fractionation schedules (10 Gy in a single fraction versus 22.5 Gy in five fractions) in 280 patients, Gaze et al. [17] assessed QOL and emotional status, and found no differences in these measures when comparing single to extended fractionation. The physicians in the study completed the Spitzer QOL index [19] according to the verbal description most closely reflecting the patient's status. The Spitzer index contains five items relating to activity, daily living, health, support and outlook, each rated from zero to two. The patients completed a Hospital Anxiety and Depression (HAD) questionnaire to assess clinically significant levels of anxiety and depression. Assessment occurred at baseline, at 1-week, and anywhere between 3 and 4 weeks after completion of radiotherapy and then at two monthly intervals. Of 216 patients assessed post treatment, the QOL and

HAD scores were available for 209 and 200, respectively. The study found no association between initial QOL parameters and the likelihood of achieving pain control. The prevalence of both anxiety and depression, as per the HAD scale, was reduced following treatment. The median HAD score was reduced from six pre-treatment to five after irradiation. The prevalence of definite (HAD score ≥ 11) and borderline (HAD score 7–10) anxiety and depression at baseline were 49 % and 39 %, respectively. After treatment, these levels had been reduced to 35 % and 32 %, respectively. The QOL as assessed by the Spitzer Index improved from a median pre-treatment score of six (range 0–10) to a median of seven (range 1–10) post radiotherapy. There was no difference in changes in HAD or QOL according to fractionation schedule. It must be noted that the physicians assessed QOL in this study; therefore, the possibility of over-estimation of post-treatment Spitzer scores existed. Nevertheless, there was a trend of improvement of patient self-rated anxiety and depression [17].

Nielsen et al. examined global QOL using the VAS (visual analogue scale) in a trial of a single 8 Gy versus 20 Gy in four fractions [15]. Two hundred and forty-one patients were enrolled in this trial. The patients completed the pain and global QOL evaluation forms on the first day of radiation treatment and then at clinic visits 4-, 8-, 12- and 20-weeks after treatment. The authors reported that there was no difference in the relative change in QOL at any stage between the two treatment arms. At 4-weeks, approximately 34 %, 20 %, and 11 % of patients in each arm achieved increases of greater than or equal to 25 %, 50 %, and 75 % respectively in their VAS QOL when compared to their pre-treatment status. However, the proportion of patients achieving complete well-being was only 7 % in each arm [15].

In the largest reported randomized prospective trial for the palliation of bone metastases comparing two fractionation schemes (1,157 patients evaluated), QOL assessment was one of several endpoints [16]. Steenland and colleagues used an extensive questionnaire comprising the Rotterdam Symptom Checklist [20] and the EORTC QLQ-C30 [21]. In addition, overall QOL was also measured using five EuroQOL questions on mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The questionnaire (containing almost 60 questions) was filled out by the patients at baseline, then weekly for 3 months, and monthly for up to 2 years. The analysis of repeated measures showed that no statistically significant differences in overall QOL were observed between the two fractionation schedules ($p = 0.22$) [16].

A single arm trial by Fossa et al. [18, 22] specifically examined the endpoint of QOL after palliative radiotherapy for men with hormone refractory prostate cancer. In this trial, 31 patients were treated with the radioisotope ^{89}Sr (strontium-89) and 106 received external beam radiotherapy. Of the latter group, 24 patients with poor performance status were treated with single fraction hemi-body irradiation (HBI) and the remainder with fractionated treatments to localized fields. Only 19 of 31 men treated with strontium-89 and 54 of the 106 men receiving external beam radiotherapy completed the 3-month questionnaire. The 73 patients who completed the questionnaire reported slight pain relief, with their mean scores decreasing from 51 to 44.

This is not surprising given that only one patient in the strontium-89 arm and eight patients in the external beam radiotherapy arm had less than six hot spots on bone scan. In fact, two thirds of the study population had 20 or more hot spots. Three-months after radiotherapy, 20 of 57 evaluable patients had reduced their analgesic intake, 17 reported no change in dose and 20 had increased their analgesic requirement. Their global QOL was virtually unchanged, with a mean of 54 pre-treatment and of 52 at 3 months. Given the advanced disease in this study population, there were likely other sites of pain outside the irradiated fields. This may explain the lack of impact on QOL in this study.

A study by Chow et al. [14] was in keeping with the findings by Gaze et al. and Nielsen et al. [15, 17]. Chow et al. utilized the Edmonton Symptom Assessment System (ESAS) to evaluate QOL in their cohort. Other than global and index pain, there was statistically significant improvement in patient anxiety and sense of well-being with palliative radiotherapy. They found that there was a slight worsening of fatigue scores immediately after the delivery of radiotherapy in the entire cohort. Chow et al. noted that measures may be employed to overcome this transient period of worsening fatigue. However, further studies are required to correlate clinical significance with the statistical significance of the ESAS symptoms [14].

Most treatment interventions have associated side effects. It is vitally important to document if these interventions have an impact on QOL while attempting to palliate specific symptoms. Though external beam radiotherapy is a local treatment, studies have shown it can improve patient QOL as well [14].

24.2.2 QOL Issues in Patients and HCPs

It is generally accepted that the patient's perspective is the gold standard for the measurement of QOL and, as a result, they should be the primary source regarding what issues are included in a QOL assessment tool [9]. What one patient regards as a severe problem may be considered only minimal to another patient [13]. The relevance of each domain may vary according to the stage of illness, treatment, age and cultural background [9], which makes it important that a wide range of patients are interviewed in the development of any QOL instrument. If we are able to understand the patient's perspective of their illness, we can develop management strategies appropriate to their individual needs [23].

Health care professionals provide a more objective evaluation of the patients' problems and symptoms [13]. They tend to outline what is typical in any given situation [24]. Some feel that HCP assessments are more meaningful for determining clinical significance because patient improvements are evaluated on clinical parameters [25]. The HCPs' perspective is also important in the development of QOL instruments as they are responsible for the administration and incorporation of the tools into their everyday practice. Therefore, it is important that HCPs contribute to questionnaire development in terms of content and structure.

Quality of life research has proven that it is necessary and can be applied to the clinical setting. Results of QOL assessments have provided significant contributions to the approval of new chemotherapeutic agents and supportive care measures [26, 27]. The next step is moving it into the "patient's realm" [24] so that they can use this information to lead a healthier and more meaningful life. One suggestion is to have physicians sit down with patients and go through their QOL scores to identify potential changes since their last visit. Although this may be time-consuming, it would facilitate discussion [28] and would help physicians understand the patient's total environment so that they could better manage their treatment. In a study by Detmar et al., physicians who had access to patient QOL scores identified a greater percentage of patients with moderate-to-severe health problems than those that did not [28]. It is important to help the patient interpret the data and suggest how they can employ this information into their daily life, just as HCPs do with their disease and treatment information [23].

It is clear that patients and HCPs have different opinions on what the most important issues in QOL are for patients with bone metastases. It is important that HCPs recognize these differences in their clinical practice to better improve their understanding of the patient's situation and diagnostic capabilities. Although it may not be possible to alleviate patient worries and concerns in a population where the disease is essentially incurable, a simple discussion of these issues is very important to patients. It was suggested that ongoing developments of QOL instruments should aim at identifying issues that most affect patients' QOL experience and providing an objective assessment tool for HCPs to adopt into their everyday practice. Only through this, they say, can we hope to improve the chances that physicians and patients will use the generated QOL information effectively [23].

24.3 The Development of the Bone Metastases-Specific Quality of Life Module: The EORTC QLQ-BM22

For more than two decades, the European Organization for Research and Treatment of Cancer (EORTC) has cultivated a modular approach to the evaluation of QOL in cancer patients in clinical trials. This advancement in QOL assessment began with the development of the EORTC QLQ-C30 general questionnaire [21] and has since led to the development of several validated modules for specific cancer diagnoses. More recently, the EORTC QLQ-C15-PAL was developed from the C30 to accommodate palliative cancer patients—those with a low performance status and for whom a 30-item questionnaire would prove quite tiresome and challenging [29]. The module development process is highly specific and regulated by the EORTC Quality of Life Group. This process consists of four phases: Phase I: Generation of relevant QOL issues; Phase II: Operationalization; Phase III: Pretesting of the provisional module; and Phase IV: Large scale international field testing of the module [29].

The use of diverse QOL questionnaires in trials in the late 1990s and early 2000s indicated that there was a strong need for a comprehensive QOL assessment tool

developed directly with bone metastases patients and their treating HCPs. Previous generalized questionnaires may not have properly addressed the specific conditions of the bone metastases population; in addition, these general questionnaires were often lengthy and therefore potentially burdensome for patients. These reasons were compelling to patients and HCPs who both wanted Phase I testing to commence on a bony metastases-specific quality of life questionnaire. In conjunction with the EORTC Quality of Life Group, a bone metastases-specific module, the EORTC QLQ-BM22 (BM22), was developed to supplement the generalized EORTC cancer module, the EORTC QLQ-C30 [21]. The BM22 was developed to address the prevalent, immediate need for a comprehensive QOL assessment tool for use in clinical trials and routine clinical assessment of bone metastases patients. In the initial phase of its development, it was noteworthy and evident that patients and HCPs presented a difference in perspective with respect to the most important issues for cancer patients with bone metastases [30].

Preliminary open-ended interviews with HCPs and bone metastases patients constituted the first step in the development of the BM22. Any issues relating to QOL of patients with any stage of bone metastases were recorded. HCPs from a variety of disciplines (i.e. radiation oncology, medical oncology, palliative care services, orthopaedic surgery, nursing, radiation therapy, pharmacy, and psychosocial-spiritual care) were consulted for the initial list of items. Likewise, patients with bone metastases from a wide spectrum of disease states and treatment clinics (i.e. receiving chemotherapy, radiation, orthopaedic services, pain management, and supportive care) were interviewed. Both populations were heterogeneous in nature in order to accurately assess which issues were most relevant across a variety of bone metastases treatments and prognoses.

Preliminary interviews with patients and HCPs generated a list of 61 items relevant to patients with bone metastases (Table 24.1). This list was formatted into a questionnaire and distributed to a new cohort of bone metastases patients and HCPs. A total of 413 patients (174 male and 239 female) and 152 HCPs were interviewed. The interviews took place at five cancer centres: Odette Cancer Centre (OCC), Toronto, Ontario, Canada; Princess Margaret Hospital (PMH), Toronto, Ontario, Canada; Tom Baker Cancer Centre (TBCC), Calgary, Alberta, Canada; Liverpool Hospital, Liverpool, New South Wales, Australia; and Charité Hospital (Universitätsmedizin Berlin), Berlin, Germany.

The extent to which patients experienced each of the 61 issues during the course of his or her illness was compared to how relevant HCPs felt each item was to bone metastases patients in terms of quality of life scores [(1) “not at all” to (4) “very much”]. Patients and HCPs had significantly different mean scores for all of the 61 items ($p < 0.0055$) except for the item “feel in control, positive and confident”, for which the mean scores were 3.07 and 3.10 respectively ($p = 0.2215$). In addition, the mean scores reported by HCPs were almost always higher than that of patients [30].

Both patients and HCPs were asked to list five to ten issues that affected bone metastases patients most profoundly (Table 24.2), Patients and HCPs agreed that four items affected bone metastases patients profoundly: “long-term (chronic) pain”, “difficulty carrying out usual daily tasks”, “able to perform self-care” and “able to perform role functioning”. However, the difference in ranking between the

Table 24.1 List of 61 quality of life issues rated for relevancy by bone metastases patients and health care professionals

Symptom	
1	Long-term (or chronic) pain
2	Short-term (or acute), severe pain
3	Pain at rest (i.e. when sitting)
4	Pain with activity (i.e. when walking)
5	Pain aggravation with movement or weight-bearing
6	Uncontrolled, unmanageable pain
7	Pain at night preventing sleep
8	Aches and stiffness
9	*Lack of energy*
10	Numbness
11	Tingling
12	Burning sensation
13	Postural problems
Function	
14	Limited movement due to pain
15	Difficulty planning activities outside the home
16	Difficulty travelling outside the home (i.e. using public transportation, driving, sitting in a car)
17	Difficulty in carrying out meaningful activity (including employment)
18	*Able to perform self-care*
19	Able to return to work promptly
20	*Difficulty carrying out usual daily tasks* (i.e. *grocery shopping*, *work outside the home*, *housework*)
21	Difficulty bending
22	Difficulty lifting
23	Difficulty standing up
24	Difficulty climbing stairs
25	Difficulty sitting
26	Difficulty lying in bed
27	Difficulty lying flat
28	Ability to have sex
Side effect from treatment of bone metastases	
29	Drowsiness
30	Confusion
31	Dizziness
Psychosocial	
32	*Able to perform role functioning* (*including domestic and family roles*)
33	*Feeling socially isolated*
34	Strengthened relationships with family/friends
35	*Have a clear*, *alert mind*
36	Feel in control, positive, and confident
37	Hope to live as long as possible
38	Reluctance to pain medication
39	Fear of addiction to pain medication
40	*Anxiety*

(continued)

Table 24.1 (continued)

41	Frustration
42	*Mood changes*
43	Emotional stress of diagnosis of advanced, incurable cancer
44	Increased focus on spiritual issues
45	Loss of interest in activities you normally enjoy
46	Loess of interest in sex
47	Worry about pain
48	Worry about suffering
49	Worry about loss of mobility compromising independence
50	Worry about becoming dependent on others
51	Worry about current health status
52	Worry about the future
53	Worry about becoming bed-bound
54	Worry about disease progression, deterioration in condition, and future complications
55	Worry about running out of medical treatments
56	Worry about hospitalization
57	Worry about ending days in a hospital or nursing home
58	Worry about death
Treatment expectation	
59	Hope for sustained pain relief (reduce pain for as long as possible)
60	Hope treatment will reduce pain as much as possible
Other issue	
61	*Financial burden due to the illness*

Issues in *italics* are in the EORTC QLQ-C30

two groups was substantial with respect to the somatic and psychosocial issues. Patients focused more on psychosocial items (four of ten items) and included three 'worry' issues within their top ten ("worry about becoming dependent on others", "worry about loss of mobility compromising independence" and "worry about disease progression, deterioration in condition and future complications"). These issues ranked 20th, 22nd, and 16th respectively by HCPs. Instead, HCPs focused more on items respective to symptoms (seven of ten items) with an emphasis on issues relating to pain (seven of ten items). Overall, somatic issues received much lower rankings from patients than from HCPs [30].

In this study, HCPs tended to focus on issues relating to cancer pain when rating items for the module [30]. Cancer pain is a significant problem in the bone metastases population [1] and many of the HCPs interviewed are involved in its treatment. Unrelieved cancer pain can have a negative impact on patient QOL [31–37], but it is not necessarily the sole or the most significant influencer. Rustøen et al. found that pain characteristics only had a small impact on QOL, explaining just 8.6 % of the variance of QOL scores [10]. When physical and social functioning were added to the analysis, the explained variance increased to 28.4 %; depression seemed to have the most significant impact with an increase of 14–42.4 % explained variance [10]. Therefore, pain is a problem for patients with bone metastases but there are additional and more important issues to patients in terms of influencing QOL.

Table 24.2 Patient and health care professional top ten relevant quality of life issues in bone metastases patients

Rank	Issue	% Patients	Issue	% HCP
1	**Long-term (or chronic) *pain***	41.4	**Able to perform self-care**	62.1
2	**Difficulty carrying out usual daily tasks (grocery shopping work outside the home housework)**	39.7	Uncontrolled unmanageable *pain* not relieved by pain killers	61.0
3	*Worry* about becoming dependent on others	38.7	**Long-term (or chronic) *pain***	54.2
7	*Worry* about loss of mobility compromising independence	37.3	Short-term (or acute) severe *pain*	52.4
5	*Worry* about disease progression deterioration in condition and future complications	32.9	*Pain* at night preventing sleep	50.0
6	**Able to perform self-care**	32.6	Limited movement due to *pain*	46.9
7	Difficulty in carrying out meaningful activity (including employment)	32.1	*Pain* at rest (when sitting)	45.1
8	**Able to perform role functioning (including domestic and family roles)**	32.0	*Pain* with activity (when walking)	41.0
9	Financial burden due to the illness	24.3	**Able to perform role functioning (including domestic and family roles)**	39.3
10	Hope treatment will reduce *pain* as much as possible	23.6	**Difficulty carrying out usual daily tasks (grocery shopping work outside the home housework)**	35.9

Boldface represents items that patients and HCPs agree should be included in the top ten

In the care of bone metastases patients, HCPs are frequently involved in the management of cancer pain, which could explain why they felt it was such a significant problem. However, in terms of QOL, HCPs need to realize that psychosocial issues tend to have a larger impact [30].

After the data from the 61 items was gathered and the most relevant aspects of QOL were found, the 61 item list was truncated into a 22 question list and was subsequently operationalized and formatted in accordance with EORTC templates: questions were arranged for a week-long recall time; phrased in the "have you had" question format and measured on a 4-point Likert-like scale from (1) "not at all" to (4) "very much".

24.3.1 Phase III: Pretesting the BM22

The original English version of the BM22 was translated, using a rigorous translation process based on iterative forward-backward procedures into a multitude of languages, including Chinese, Danish, Dutch, French, German, Greek, Italian, Japanese, Norwegian, Spanish (European and South American), Swedish and Turkish.

Table 24.3 Issues included in the bone metastases quality of life questionnaire (EORTC QLQ-BM22)

Location of pain
1. Back
2. Leg(s) or hip(s)
3. Arm(s) or shoulder(s)
4. Chest or ribs
5. Buttocks
Pain characteristics
6. Constant pain
7. Intermittent pain
8. Pain not relieved by medications
Functional interference
9. Pain while lying down
10. Pain while sitting
11. Pain when trying to stand up
12. Pain while walking
13. Pain with activities such as bending or climbing stairs
14. Pain with strenuous activity
15. Pain interfered with your sleeping
16. Modify your daily activities
Psychosocial aspects
17. Felt isolated from those close to you
18. Worried about loss of mobility
19. Worried about becoming dependent on others
20. Worried about your health in the future
21. Felt hopeful your pain will get better
22. Felt positive about your health

Phase III tested the acceptability and relevance of the BM22 on 170 patients from nine countries [4]. Participating countries included Argentina, Australia, China (Hong Kong), Canada, Germany, Greece, the Netherlands, Spain and the United Kingdom. The majority of patients (68 %) were non-English speaking. Overall, there were 83 men (49 %) and 87 women (51 %). The median age was 60 years (range: 29–92). Median time from primary cancer diagnosis to diagnosis of bone metastases was 1 year (range: 0–21). Patients interviewed were from a variety of ages and primary cancer sites that were undergoing various therapies. Problems identified relating to the clarity and wording of certain items were considered when determining whether items needed to be added or deleted. This phase was especially important as it assessed whether the module items were comparable cross-culturally, mainly among non-English-speaking nations [4].

The BM22 (Table 24.3) was well received in all nine countries. Patients found the questionnaire easy to complete and relevant to their condition.

Following completion of Phase III, two changes were made to the questionnaire based on multiple patient concerns, resulting in the deletion of one psychosocial item and the division of one functional interference item into two [4]. The development

process as well as the final questionnaire subsequently underwent review by the executive members of the EORTC QOL Module Development Committee and both were approved [4].

24.3.2 Phase IV: Large Scale International Field Testing of the Module

The final phase of development of the EORTC QLQ-BM22 was international field testing of the module [38]. Specifically, psychometric testing in terms of reliability, validity and sensitivity to change was conducted for the instrument. A total of 400 patients from seven different countries were accrued during this phase to examine the module's reliability and validity. The majority of the patients (72 %) completed both the core module and the BM22 in less than 15 min. Many of them (93 %) did not have a problem with the wording or phrasing of items, and did not find them difficult (89 %), confusing (91 %) or upsetting (94 %). Only 21 % of patients required help completing the questionnaires.

24.3.2.1 Reliability and Validity of the BM22

Factor analysis of the QLQ-BM22 confirmed the presence of four distinct scales (painful sites, painful characteristics, functional interference and psychosocial aspects) [38]. In internal consistency testing, Cronbach's alpha ranged from 0.67 to 0.94 at baseline, and from 0.70 to 0.93 at follow-up for the four scales [4]. Therefore, items within each scale highly correlated with one another compared with items of another scale. Test–retest analysis of the QLQ-BM22 in patients with stable bone metastases revealed that all four scales showed 'good' reliability (all intraclass correlations exceeded 0.80) [38]. Correlations between the scales on the QLQ-C30 and the QLQ-BM22 verified that those scales assessing similar aspects were correlated, and conversely those scales assessing distinct areas of QOL were not. The QLQ-BM22 therefore covers relevant QOL aspects in bone metastases patients that are not evaluated by the QLQ-C30. Validity of the QLQ-BM22 was further supported through the known group comparisons, where all four scales are able to discriminate between patients of a better performance status and those of a poorer performance status [4].

In a later study, Zeng et al. compared bone metastasis-specific QOL scores among patients who responded differently to radiotherapy by using the BM22 in conjunction with the C30 [39]. A total of 79 patients from the original 400 patient group who received palliative radiotherapy from six countries (Canada, Cyprus, Egypt, Brazil, India and France) were included. At baseline, patients who had a partial response, pain progression and an indeterminate response had comparable QOL scores [39]. However, when QOL scores for the same sample were taken at 1-month follow-up, patients who did not respond to radiotherapy reported significantly different scores than those that responded [39]. Three of four BM22 scales were significantly different among groups. Responders had lower scores for painful

sites ($p<0.0001$), painful characteristics ($p<0.0001$) and functional interference ($p<0.0001$). The psychosocial scale did not reach statistical significance and it was hypothesized that additional issues, not addressed by radiotherapy, may play a larger role in this scale. Overall, Zeng et al. were able to show that the BM22 was able to differentiate between patients who respond to treatment and patients who do not [39].

24.3.3 Minimal Clinically Important Differences of the BM22

An important consideration for QOL instruments is the minimal clinically important differences (MCID) of the tool. Traditionally, analysis of QOL differences between arms in clinical trials was conducted purely via statistical methods. Given large enough sample sizes, even minor differences may be statistically significant, but whether this is of clinical relevance is unknown. Therefore, early establishment of MCID is important to assist clinicians in adopting QOL instruments in their trials. Using two commonly applied methods (anchor and distribution based analyses) and data from the Phase IV BM22 validation study, Zeng et al. established the MCID of the BM22 [40]. It was found that three of four scales of the QLQ-BM22 (painful sites, painful characteristics and functional interferences) demonstrated statistically significant MCID for improvement; no BM22 subscales had statistically significant MCID for deterioration. Changes of at least 20.1 (95 % CI: 7.1–33.2), 30.5 (13.8–47.3), 19.6 (5.0–34.3) and 30.5 (9.0–52.0) in the painful sites, painful characteristics, functional interferences and pain scales, respectively, constituted clinical significance for improvement. In addition, it was noted that a clinically meaningful improvement requires a greater change in QOL than a meaningful deterioration for the QLQ-BM22. It should be noted that due to the relatively low sample size for patients that improved or deteriorated, these data should be interpreted with caution, as evidenced by the wide confidence intervals.

Generally, the authors noted that patients that improved, deteriorated or were stable reported QOL scores appropriate to such change [40]. On average, a mean decrease in symptom severity and improvement in functional scales was recorded in patients that improved while those that deteriorated reported the opposite [40]. The validity of the QLQ-BM22 alongside the C30 was therefore strengthened as the BM22 was able to discriminate between these two different groups.

24.3.4 Features of the BM22

The BM22 is used to assess QOL in advanced cancer patients suffering from bone metastases. It encompasses four general areas of well-being: painful sites, pain characteristics, functional interference and psychosocial aspects. Items on the BM22

are grouped according to the subscale assessed; however, they appear as 22 unrelated questions on the module. Items are all formatted as questions in which response options utilize a Likert scale (1–4 inclusive). Along with the core QLQ-C30 questionnaire, administration of the BM22 is 52 questions long (30 questions of the C30 in addition to the 22 questions of the BM22). Recall period of the BM22 is 7 days. 1–4 numerical scores are converted to a 0–100 scale; higher scores on the QLQ-BM22 represent worse QOL for the subscales of painful sites, painful characteristics and psychosocial aspects, whereas higher scores on the functional interference subscale equate to better functioning.

24.4 Other Instruments for Assessment of QOL in Patients with Bone Metastases

Although the BM22 is most rigorously validated and most commonly used assessment tool for the evaluation of QOL in patients with bone metastases, previous investigators have developed other instruments aimed at this patient population.

24.4.1 The BOMET-QOL: Development and Validation

The Bone Metastases Quality of Life Questionnaire (BOMET-QOL) was developed in three phases [41, 42]. The first phase was concerned with item generation. Similar to the development of the QLQ-BM22, this first phase included an extensive literature search to determine the main issues of the bone metastases population [42]. Fifteen health care professionals (ten oncologists, one haematologist and four urologists) and 15 patients also identified main issues they felt were associated with QOL for this population [42]. Phase two was the item selection phase and required health care professionals to score items according to their frequency, importance and clarity. A preliminary questionnaire consisting of 25 items was then devised and delivered to 92 patients. Patients who were diagnosed with primary lung, breast, prostate cancer or myeloma, who were over the age of 18 and who had an expected survival of at least 6 months were included in this part of development. Factorial analysis and Rasch modeling were conducted on these completed questionnaires and this resulted in 25 items that were identified as most relevant for patients with bone metastases. Eight dimensions were recognized, accounting for 73.2 % of total variability [41, 42]. In addition, the questionnaire showed internal consistency [42]. The final development phase of the BOMET-QOL was conducted as an observational study with 263 patients with bone metastases who had primary breast, prostate, lung cancer or myeloma [41]. About one third of these patients had undergone chemotherapy and approximately three quarters had received zoledronic acid in the months before they completed the questionnaire. 6.1 % of patients who completed the

questionnaire were receiving chemotherapy at the time. This final development stage reduced the 25 items of the BOMET-QOL to 10 [41]. Reduction of the questionnaire occurred in two distinct parts. Part one consisted of factor analysis with varimax rotation of primary BOMET-QOL items [41]. Part two consisted of the resulting factors computed by the Rasch rating scale models [41]. Determination of the contribution of each item to the global health measure was determined by the infit and outfit statistics of the Rasch analysis. Those items whose infit or outfit value was greater than 1.3 were excluded from the questionnaire. Rasch analysis was continued until the questionnaire was reduced to 10 items [41].

24.4.1.1 Features of the BOMET-QOL

The BOMET-QOL module was developed with the goal of evaluating QOL in patients with bone metastases [41]. The module has not been developed with the intention of being coupled with a general cancer questionnaire; rather, developers of the module recommend that the assessment tool be combined with cancer-specific tools. The BOMET-QOL consists of only ten items and is therefore by itself much shorter than the BM22 (22 items). The BOMET-QOL uses a 0–4 Likert scale as response options. Recall period for the questionnaire is the past 7 days. All of the questions on the BOMET-QOL are unrelated and all items appear as statements. In addition, items within the BOMET-QOL are not grouped into subscales. Simple summation of the 0–4 scores is used to score the BOMET-QOL; these raw scores are then standardized on a scale from 0 to 100. Higher scores on the BOMET-QOL represent better QOL in bone metastases patients.

24.4.2 The FACT-BP: Development and Validation

In contrast to the BM22, the development process of the FACT-BP did not involve four distinct phases of development, such as that required by the EORTC [43]. Instead, the first part of development was the item-content validation of the FACT-BP which involved ten patients. Important feedback provided by these patients was used to determine if the bone pain questions were relevant and comprehensible [43]. The scale was then adjusted accordingly based on all input collected.

The second part of development of the FACT-BP was undertaken with the help of patient samples from two separate clinical trials [44, 45]. The two studies examined the efficacy of either zoledronic acid or ibandronate in patients with metastatic breast cancer and either progressive bone metastases or skeletal-related events. The first trial involved 31 patients who received intravenous zoledronic acid (4 mg every 4 weeks) for 12 weeks [44], while the second trial followed 30 patients who received oral ibandronate (50 mg daily) for 12 weeks [45]. Data collected from these 61 patients were used to evaluate the validity of the FACT-BP module.

24.4.2.1 Features of the FACT-BP

Like the QLQ-BM22 and the BOMET-QOL, the FACT-BP was developed with the purpose of measuring QOL in cancer patients with bone metastases. The FACT-BP is comprised of three distinct subscales: general functioning, physical and bone pain [4]. When coupled with the FACT-G, the FACT-BP is 43 items long (27 FACT-G items in addition to 16 FACT-BP items). The FACT-BP uses a 0–4 inclusive Likert scale; recall period of the questionnaire is 7 days [4]. Fifteen items are formatted as questions while one item is a statement on the questionnaire [4]. All items on the module are organized based on the subscale assessed. Simple summation of raw FACT-BP scores is used to score the FACT-BP, albeit with some items reversed. Higher scores on the FACT-BP indicate better QOL and less bone pain.

24.5 Closing Remarks

This chapter has outlined the trials and tribulations that have been encountered leading to the development of standardized outcome assessment tools for use in bone metastases clinical trials—from establishing meaningful pain response endpoints to balancing what patients and HCPs believed were the most relevant QOL issues to bone metastases patients and harmonization of these items into the three comprehensive bone metastases-specific QOL questionnaires that we have today: the EORTC QLQ-BM22, the FACT-BP and the BOMET-QOL.

Widespread use of the International Bone Metastases Consensus Endpoints and the EORTC QLQ-BM22, the FACT-BP and the BOMET-QOL for assessment of pain response and QOL will facilitate inter-study comparisons and reveal optimal systemic and localized bone metastases-specific treatments, tailored to the needs of the patient. We encourage investigators to use patient-based assessment of pain scores, analgesic consumption, health related QOL, as well as any other study-specific endpoint evaluation tools in future bone metastases clinical trials. Furthermore, direct comparison between the three QOL assessment tools available for bone metastases patients will allow HCPs to establish a globally standardized QOL module in this patient population.

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Part V
Cost of Managing Metastatic Bone Disease

Chapter 25
Cost Effectiveness of Treatment Modalities for Bone Metastases

Yvette M. van der Linden and Andre A. Konski

Abstract Analysis on cost effectiveness in medicine is a type of economic analysis that compares the relative costs and outcomes of two or more different medical treatments in order to choose the most optimal treatment modality in terms of costs versus outcome. In bone metastases research, several studies on costs and effectiveness have been published. In this chapter, the different types of cost analyses, their relative usefulness and impact on daily clinical practice will be discussed.

Keywords Bone metastases • Costs • Effectiveness • Quality of life

25.1 Overall Introduction

In an era where ageing of the total population, subsequent scarce health care resources, budgetary restraints, and rising costs of medical care are increasingly and inevitably becoming important topics, the objective averaging of costs versus gain seems a sensible step. When deciding which treatment gives better value for money, economic evaluations may help to identify, measure, order, and compare costs and benefits of alternative treatments. It helps clinicians, other health care workers, insurers, and politicians in making rational choices in selecting the most appropriate treatments. Furthermore, cost effectiveness outcomes also steer the focus on areas for further research.

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Table 25.1 Types of economic evaluations analyses

	Type of analysis	Type of outcome	Question analysed
1	Cost-minimization	Effects are equivalent	What is the least costly treatment?
2	Cost-effectiveness	Clinical effects	What is the most efficient treatment alternative in terms of the defined outcome?
3	Cost-utility	Quality of life effects	
4	Cost-benefit	Financial effects	Which treatment is most efficient if both costs and outcomes are evaluated in monetary terms?

(Reproduced from Ref. [4], with permission)

In the literature, a number of studies have been published concerning the subject of costs versus outcome of different palliative treatments for painful bone metastases. In order to value such studies accurately, the reader first has to have a quantity of background information on economic assessments which is provided below [1–4].

25.1.1 Introduction in Economic Evaluation in Health Care

Based on the distinction between the types of outcome, different types of economic evaluations can be defined (Table 25.1). In cost-minimization analyses (CMA) the effectiveness of the treatments under investigation is considered equal, therefore, the focus lies on the costs. The preferred choice, from an economic point of view, is the treatment with the lowest costs.

In cost-effectiveness analyses (CEA) the health effect between different treatments is considered. Only one clinical outcome at the time can be addressed, such as life years gained, or local relapse averted, in order to make easy comparison possible. If more outcomes, such as toxicity or quality of life also are important to study, then, these multiple effects can be combined into one common denominator, such as the quality adjusted life expectancy (QALE), expressed in the amount of quality-adjusted life years (QALYs) gained. This type of analysis is called the cost utility analysis (CUA). It compares the incremental, or rising, costs of a treatment to its global health improvement. Utilities are defined as the preferences of patients for health states and range between 0 (=death) and 1(= perfect health). Lastly, in cost-benefit analyses (CBA) the clinical effects of treatments are converted into a monetary value. These types of economic analyses are hardly performed in studies on cancer treatments, because it is regarded as difficult to translate clinical effects into money.

To interpret the results of economic analyses, one has to agree on a threshold level above which the intervention is thought to be cost effective: the willingness-to-pay threshold. In the literature, levels of 50,000 USD per life-year saved have been suggested as being acceptable, whereas 100,000 USD might not be acceptable [5]. Such outcome can be plotted in a cost-effectiveness plane, showing the ceiling ratio for decision making, and making the results more transparent (Fig. 25.1) [1]. If, for example, the majority of points lie below the willingness-to-pay line in quadrants 1 and 7, then the experimental treatment is more effective and less costly.

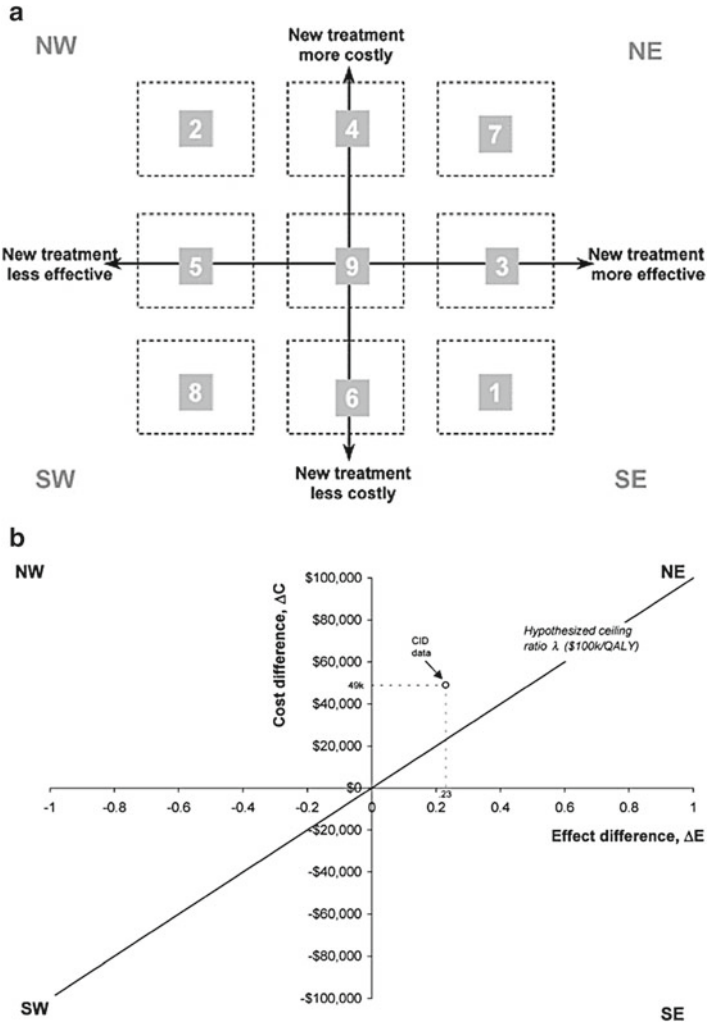


Fig. 25.1 Cost-effectiveness planes (**a**) schematic example of nine possible situations that can arise (1 = new treatment better and less costly, 2 = old treatment better and less costly, 7 = new treatment better and more costly, 8 = old treatment better and more costly). (**b**) For situations 7 and 8, ceiling ratio's are plotted on a line to distinguish which treatment is considered to give more value for money. The outcome of the Canadian Implantable Defibrillator (CID) study showed that the new treatment was more effective, but also more costly, above the defined ceiling ratio (Reproduced from Ref. [1], with permission)

Statistical significance of cost-effectiveness depends on how much one is willing to pay per QALY. Cost-effectiveness can be tested by comparing the net benefit, which is by testing whether the difference in costs is equal to the willingness-to-pay for the difference in QALYs. This outcome can be plotted in acceptability curves (Fig. 25.2) [6].

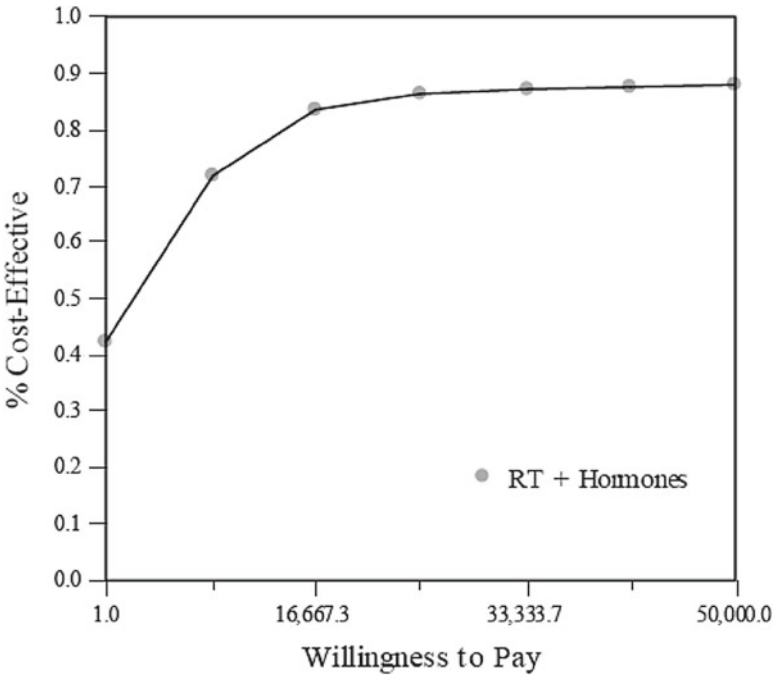


Fig. 25.2 Acceptability curve. Cost-effectiveness acceptability curve with a >80 % probability of RT hormones being cost-effective compared with radiation therapy alone at a willingness-to-pay of US$ 50,000/ QALY (Reproduced from Ref. [6], with permission)

Costs that can be included in economic analyses are

- Direct medical costs: costs of health care resources consumed in the care for patients, e.g. hospitalization, drug use
- Direct non-medical costs: costs consumed by the patients and their relatives, e.g. travel costs, housekeeping
- Indirect costs: costs related to lost productivity and lost leisure time, e.g. time spent caring for the patient

Sensitivity analyses should be performed to test the robustness of the results of economic evaluations: it evaluates how the final results are affected by varying the values of costs, effects, utilities etc.

Ideally, an economic analysis should be performed using cost and outcome data from prospective randomized trials. If not all the information is available to perform a thorough analysis, then a model can be constructed to try to answer clinical questions and perform cost-effectiveness and cost-utility analyses, such as a Markov model (Fig. 25.3) [7]. In such a model, each health state is assigned certain costs and utilities. Definitions are made on how patients transition between these states and

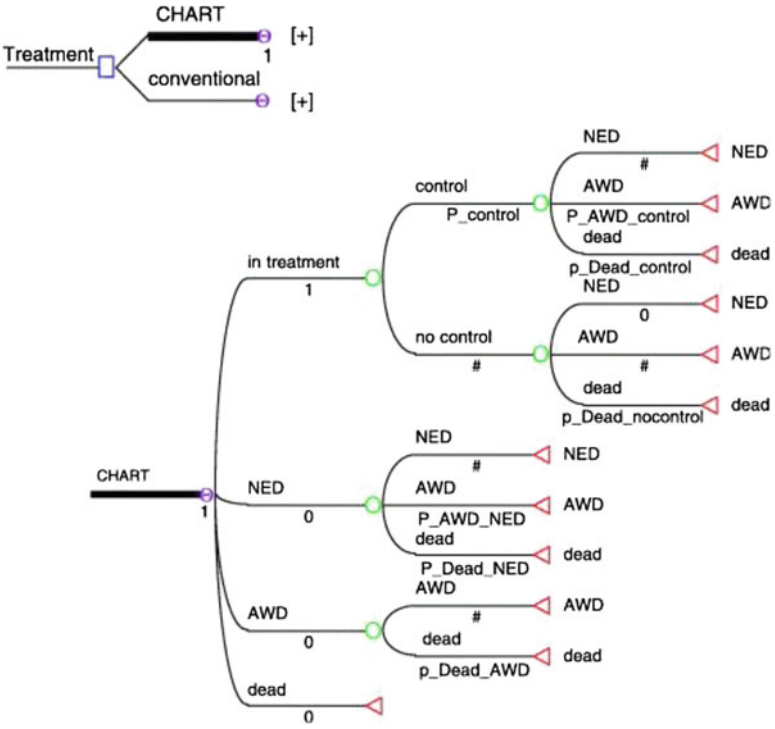


Fig. 25.3 Markov model for patients with non-small cell lung cancer treated with conventional or hyperfractionated accelerated (CHART) radiotherapy (Reproduced from Ref. [7], with permission)

with what probability. Then, a cohort of patients is run through the model using Monte Carlo simulation, and at the end all utilities and costs are summed up to reach a conclusion.

In short, important items to be conscious of when interpreting reports on economic analyses are:

- Which type of economic analysis is performed,
- Is the study on a prospective or retrospective database,
- Does it concern true costs and, clinically relevant, utilities,
- Which modeling assumptions have been made,
- Are sensitivity analyses and cost effectiveness planes provided,
- Which time frame is considered.

In the literature, most analyses that have been performed on the costs and effects of various treatments for bone metastases are cost-minimization or cost-effectiveness analyses, and, most of these focus only on the direct medical costs. In the next section an overview of current literature on costing in patients with painful bone metastases will be given.

25.2 Literature Overview on Economic Evaluations of Treatments for Bone Metastases

A few studies calculated costs only, for different palliative treatments.

Hillner et al. performed a study on the costs of the oral bisphosphonate pamidronate in the prevention of bone complications in metastatic breast cancer. They calculated costs to be US$ 775 per month [8].

Ferrel et al. estimated that the costs for oral analgesics taken for cancer bone pain were US$ 1,000 per patient/month, whereas parenteral use of analgesics mounted to US$ 4,000 per patient/month [9].

In 1996, a study from the Swedish Council estimated the costs of palliative radiotherapy as approximately US$ 2,000 per patient [10].

Glazebrook calculated the costs for radiotherapy in Canada to be C$ 661 per person per year [11] .

Macklis et al. performed a cost minimization study on analgesics and radiotherapy [12]. They estimated that the fully allocated costs (direct and indirect) of a course of palliative radiotherapy ranged from US$ 1,200–2,500, depending on the number of fractions and the technical complexity of the treatment. Narcotics intake for a 6 month period, i.e. the time frame in which the radiotherapy treatment was considered successful, varied from US$ 9,000–36,000.

A few small studies were performed on costs, response and survival.

Stevens et al. found that the costs per month of survival for patients treated with palliative radiotherapy in 1988 was AUS$ 105 [13].

Rees et al. performed an analysis in which costs, response rate and duration of survival were used as parameters [14]. For palliative radiotherapy, i.e. ten fractions, response rate 75 %, mean response duration 4 months; they calculated the cost per year to be 1,200 lb.

In the literature, five recent larger studies have been published in which costs and effects were evaluated.

In 2003, Barton et al. performed a minor cost utility analysis on mostly retrospective data [15]. For the calculation of the utility, duration of survival was used, adjusted for degree of response to pain treatment. For that reason, survival was calculated in a group of 903 patients treated from 1991 to 1996 at the Westmead Hospital in New South Wales, and degree of response was distilled from a literature review of published trials on bone metastases. Average survival was 14.6 months, and adjusted average response was 59 %, therefore, the average utility was $14.6 \times 0.59 = 8.5$ months. Note that this somewhat utility is not according to the classic definition. For costs, they took the 1,991 costs of delivering a radiotherapy treatment which was calculated by Smith et al. [16]. Average costs per patient were AUS$ 855 (i.e. 10.9 treatment fields × cost per field AUS$ 78). Utility-adjusted costs were AUS$ 100/month (i.e. total costs AUS$ 855/total number of utility-adjusted months of response 8.5). In addition, a sensitivity analysis in which the response rates from the literature were varied and hence the costs showed a range of costs from AUS$ 80 to 139.

Table 25.2 Markov model on costs of different treatment modalities for painful bone metastases

Treatment	Cost	Incremental cost	Effectiveness (QALM)	Incremental effectiveness (QALM)	Incremental cost effectiveness $/QALY
Pain medication	$11.700		5.75		
SF radiotherapy	$11.900	$200	6.1	0.35	$6.857
MF radiotherapy	$13.200	$1.500	6.25	0.5	$36.000
Chemotherapy	$15.300	$3.600	4.93	–0.82	–

(Reproduced from Ref. [17], with permission)
QALM quality adjusted life per month

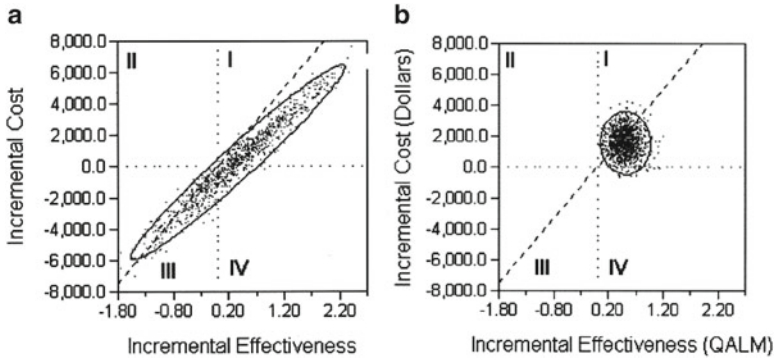


Fig. 25.4 Cost effectiveness planes for pain medication versus SF radiotherapy (**a**) and versus MF radiotherapy (**b**) in the Markov model (Reproduced from Ref. [17], with permission)

In 2004, Konski developed a Markov model to evaluate the effectiveness of different palliative treatments for painful bone metastases [17]. Therefore, he constructed a patient case: a man with hormone refractory prostate cancer. In the model, patients spent 1 month in each transition state, which differed per each treatment. The end of the model was reached at 24 months. Three treatments were analyzed: pain medication, chemotherapy, and radiotherapy (single and multiple fractions). For each of the three models, costs and utilities were calculated separately. For pain medication, costs were calculated on morphine medication combined with a laxative. Higher doses were used along the model. Utilities were set at 0.4 for the first 3 months and decreased by 0.05 every 2 months afterwards. For chemotherapy, for the calculation of costs and utility the outcome of a Canadian trial on mitoxantrone + prednisone was used [18]. The radiotherapy regimens were chosen from the recent RTOG 9,714 trial which studied the palliative effect of a single fraction of 8 Gy vs. 10 fractions of 3 Gy [19]. Costs were based upon true Medicare reimbursement, and utility was obtained from the study by van den Hout et al. [3]. Table 25.2 shows the outcome of the three models: single fraction radiotherapy was the most cost-effective treatment with a cost-effective ratio of US$ 6.857 per QALY. Figure 25.4 shows

Table 25.3 Primary analyses of total costs

Cost component	8 Gy/1 fr.	20 Gy/5 fr.	Average difference between 20 Gy/5 fr. and 8 Gy/1 fr.
Initial RT (protocol)	138 AUS$	669 AUS$	531 AUS$
Retreatment	84 AUS$	55 AUS$	−20 AUS$
Medication	192 AUS$	229 AUS$	37 AUS$
Admissions related to RT or pain	1,411 AUS$	1,893 AUS$	482 AUS$
Total average costs per patient	1,825 AUS$	2,846 AUS$	1,021 AUS$

(Reproduced from Ref. [20], with permission)

the cost effectiveness plan for both single fraction and multiple fraction radiotherapy with a 95 % confidence ellipse comparing both treatments with analgesics alone. Unlike the multiple fraction regimen, most data points are below the willingness to pay line in quadrants I and IV for the single fraction regimen, making the single fraction regimen the best cost effective treatment.

In 2005, Pollicino et al. published the results of an economic analysis on patients included in the TROG 96.05 trial [20]. This trial showed no significant benefit of multiple fraction radiotherapy over single fraction radiotherapy for neuropathic pain in 272 patients [21]. Pollicino et al. performed a cost minimization analysis of both radiotherapy regimens. They looked at direct costs of treatment, i.e. including any retreatments during follow-up, analgesics, co-analgesics, and hospital admissions. Costs for radiotherapy were calculated using methodology from a previous study [22]. Use of medication was recorded prospectively during the trial. Data on hospital admission related to the treatment or because of pain were retrospectively obtained from the medical records. Table 25.3 shows the results of this calculation: the single fraction treatment was AUS$ 1,021 cheaper than the multiple fraction regimen, mostly due to difference in costs for the initial treatment, and costs incurred for hospital admissions. Next, a sensitivity analysis was performed, varying assumptions relating to individual cost components showing the incremental cost ranging from AUS$ 745 to AUS$ 1,468.

The most complete study comes from the Dutch Bone Metastasis Study Group (DBMS), a large prospective trial on 1,157 patients that showed the equal effectiveness of a single fraction of 8 Gy compared to 24 Gy in 6 fractions [23, 24]. Van den Hout et al. performed a prospective full societal cost utility analysis on the DBMS database [3]. For utility, survival on 1,157 patients was registered by the data managers. For quality of life, the EuroQol utility [25] was registered in 13 weekly and 23 monthly patient based questionnaires. Of all 1,157 patients, response to the questionnaires was 74 %. Patients who received the single fraction regimen turned out to have an additional QALE of 1.7 week when compared to the multiple fraction patients (Table 25.4).

For the calculation of the costs, full societal costs were gathered for the first 3 months. Costs of radiotherapy consisted of direct medical costs (randomized schedule, retreatment), and non-medical costs (travel, time, out-of-pocket). For the treatment, in three radiotherapy centers a cost analysis was performed. Costs were

Table 25.4 Quality adjusted life expectancy (average in weeks, with standard deviations)

	8 Gy×1 (n=579)		4 Gy×6 (n=578)		p-value[a]
Life expectancy	43.0	(35.2)	40.4	(34.4)	0.20
QALE ≤12 weeks	4.0	(3.9)	3.9	(3.9)	0.47
QALE	17.7	(24.0)	16.0	(23.8)	0.21

(Reproduced from Ref. [3], with permission)
[a]Standard two-sided unequal-variances t-tests

Table 25.5 Medical costs of a typical radiotherapy department

	Total costs (in k$)		Allocation base		
			Treatments	Fractions	Gray
Personnel	1,977	→[a]	63 %	34 %	3 %
Equipment	1,217	→	34 %	35 %	31 %
Material	157	→	50 %	41 %	9 %
Housing	1,489	→	31 %	68 %	1 %
Overhead	551	→	61 %	35 %	4 %
Annual costs (in k$)	5,391		2,522	2,379	490
Annual number			1,503	24,640	61,600
Unit costs (in $)[b]			1,678	96.55	7.95
Costs per 8 Gy×1 schedule	$ 1,838	←[c]	1×	1×	8×
Costs per 4 Gy×6 schedule	$ 2,448	←	1×	6×	24×

(Reproduced from Ref. [3], with permission)
[a]Separate cost items are allocated to the allocation base(s) that they are proportional to
[b]Obtained by dividing the annual costs by the annual number, for each allocation base
[c]Obtained by multiplying the unit costs with the number of units of the schedule

allocated to three bases: treatments, fractions and Gray (Table 25.5). Total costs of radiotherapy amounted to US$ 1,838 for a SF and US$ 2,448 for the multiple fraction regimen.

A total of 166 patients filled out 6 bi-weekly questionnaires on other societal costs (medical: hospitalization, consultations, medication, nursing, and non-medical: time, travel, out-of-pocket, domestic help, labour). Full societal costs are shown in Table 25.6. The overall difference in the costs to society (radiotherapy and other costs, both medical and non-medical) was estimated at $ 1,753 per patient in favour of the single fraction schedule. The overall difference in medical costs (excluding the non-medical costs of radiotherapy and other non-medical costs) was estimated at $ 1,344. Both differences were marginally significant ($p=0.06$ and $p=0.09$ respectively).

Next, van den Hout et al. tested the cost-effectiveness by comparing the net benefit, that is by testing whether the difference in costs was equal to the willingness-to-pay for the difference in QALYs. The acceptability curve (Fig. 25.5) shows the p-value of this hypothesis for different values of the willingness-to-pay. From a societal perspective, the superior cost-effectiveness of the single fraction was shown at 5 %

Table 25.6 Costs per patient during the first 12 weeks (volumes, average costs in $, and standard deviations)

	8 Gy × 1			4 Gy × 6			
	(n = 80)			(n = 86)			p-value[a]
Costs of radiotherapy		2,438	(1,019)		3,311	(1,682)	<0.001
Initial treatment		1,838	(–)		2,448	(–)	–
Retreatments ≤12 weeks	18 %	466	(900)	5 %	159	(539)	0.01
Time, travel, out-of-pocket	10 h	134	(213)	25 h	704	(1,439	<0.001
Other medical costs		2,072	(3,778)		3,114	(6,039)	0.18
Hospitalization	28 %	914	(3,091)	41 %	2,160	(5,821)	0.08
Systemic therapy	61 %	373	(718)	59 %	247	(475)	0.19
Consultations	6.3	302	(554)	6.4	248	(234)	0.42
Pain medication		79	(114)		56	(113)	0.19
Other medication		322	(857)		247	(530)	0.51
Home nursing care	5 h	81	(251)	9 h	156	(501)	0.22
Other non-medical costs		190	(1,230)		28	(1,479)	0.44
Time, travel	8 h	94	(237)		130	(259)	0.35
Out-of pocket		127	(383)		64	(198)	0.19
Domestic help	42 h	438	(609)	43 h	482	(668)	0.65
(Un)paid labor	56 h	–468	(847)	77 h	–647	(1,192)	0.26
Medical costs		**4,376**	(3,834)		**5,720**	(6,144)	0.09
Societal costs		**4,700**	(4,402)		**6,453**	(7,389)	0.06

(Reproduced from Ref. [3], with permission)
[a]Standard two-sided unequal-variances t-tests

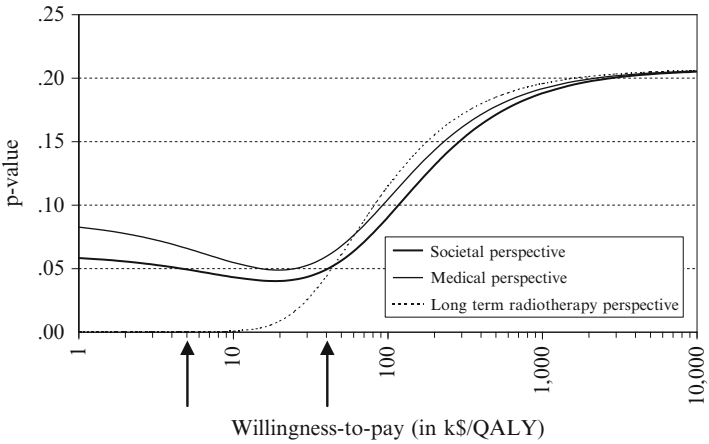


Fig. 25.5 Acceptability curves: p-value of the difference in net benefit WTP × QALYs – Costs, tested using standard two-sided unequal-variances t-tests (Reproduced from Ref. [3], with permission)

significance level if one values a QALY between $ 5,000 and $ 40,000. If one values a QALY at less than $ 5,000 or more than $ 40,000, then superior cost-effectiveness of the single fraction schedule was still likely but not longer shown at the usual 5 % significance level. For example, at $ 50,000 and $ 100,000 per QALY, the statistical significance was p = 0.06 and p = 0.09 respectively.

In 2005, the results from the RTOG 9,714 trial were published, showing no difference in response between 8 Gy single fraction or 30 Gy in 10 fractions in a total of 898 patients with painful bone metastases [26]. The overall response rate was 66 %. Complete and partial response rates were 15 % and 50 %, respectively, in the 8-Gy arm compared with 18 % and 48 % in the 30-Gy arm (P = 0.6). A statistically significant higher retreatment rate, however, was noted in patients undergoing a single fraction treatment. In 2009, Konski et al. published a cost effectiveness analysis of RTOG 9,714 data, again using a Markov model [27]. In this model, the transition probabilities, cost, and utilities were obtained from both the RTOG trial and from the Dutch trial. The expected mean cost and quality-adjusted survival in months for patients receiving 8 Gy in 1 fraction and 30 Gy in 10 fractions was 998 US dollars and 7.26 months and 2,316 US dollars and 9.53 months, respectively. The incremental cost-effectiveness ratio was 6,973 US dollars/quality-adjusted life year. The results were sensitive to the utility of the post treatment state for both single and multiple fraction treatments. The authors concluded that the single fraction treatment was the less expensive treatment.

25.2.1 Costs of High Dose Stereotactic Hypofracionated Radiotherapy and Surgical Interventions for Spinal Metastases

In stereotactic radiotherapy, a single or fractionated high dose can be delivered to the region of interest without giving substantial doses to surrounding tissues. In this way, retreatment to e.g. painful vertebra of the spinal column is possible without compromising the spinal cord. However, these techniques are both time consuming and require a high level of technical development.

Sahgal et al. published an overview summing up the current status of stereotactic body radiotherapy (SBRT) for spinal metastases with respect to its apparatus, clinical indications, outcomes and techniques, and spinal cord tolerance [28]. They also added data on costs of conventional and stereotactic techniques, with conventional techniques adding up to a total of 4,132 USD per treatment, to 11,644 for a single dose stereotactic radiosurgery treatment to 17,065 USD for 3 fractions of stereotactic body radiotherapy.

Haley et al. compared the palliative efficacy and cost effectiveness of external beam radiation therapy (EBRT) to SBRT as primary treatment for bone metastatic disease of the spinal column, using a matched pair analysis in 44 patients [29].

They concluded that external beam radiation therapy was efficacious and cost-effective, as total costs ranged from 29 % to 71 % from total costs for SBRT. However, after EBRT more acute toxicities were seen and patients were more likely to require additional interventions at the treated sites. Stereotactic body radiation therapy showed promise as an emerging modality for selected patients with spine metastases.

Furlan et al. conducted a cost-utility analysis to compare surgery (S) plus radiotherapy (RT) compared to radiotherapy alone based on the landmark randomized clinical trial by Patchell et al. [30, 31]. It was performed from the perspective of the Ontario Ministry of Health and Long-Term Care. Ontario-based costs were adjusted to 2010 US dollars. S + RT was more costly but also more effective than corticosteroids and RT alone, with an incremental cost-effectiveness ratio of US$250.307 per quality-adjusted life year (QALY) gained. First order probabilistic sensitivity analysis revealed that the probability of S + RT being cost-effective was 18.11 %. The cost-effectiveness acceptability curve showed that there was a 91.11 % probability of S + RT being cost-effective over RT alone at a willingness-to-pay of US$1.683.000 per QALY. The results of the study indicate that, by adopting the S + RT strategy, there would still be a chance of 18.11 % of not paying extra at a willingness-to-pay of US$50,000 per QALY. Those results were sensitive to the costs of hospice palliative care, and suggest that adopting a standard S + RT approach for patients with metastatic spinal cord compressions is likely to increase health care costs but would also result in improved outcomes.

25.2.2 Costs of Radiotherapy: Using Modern Equipment in Developing Countries? Linear Accelerator Versus Cobalt

Van der Giessen et al. showed in a study that was carried out radiotherapy institutions in Europe, Africa, Latin America and Asia that a treatment fraction on a modern linear accelerator with functionality comparable to cobalt, costs roughly 50 % more than cobalt therapy [32]. These variations depend more on differences in machine usage and costs of equipment than on national economic status.

25.3 International Variations in the Actual Use of Radiotherapy Treatment Schedules

Since the vast majority of studies that were published up to 2005 show that single fraction palliative radiotherapy is the most effective treatment for patients with pain due to bone metastases in terms of both patient outcome and economic outcome, one would assume that single fraction radiotherapy has by now become the golden standard and most used treatment schedule. However, this seems not the case.

Table 25.7 Pros and cons of single dose radiotherapy in patients with painful bone metastases from the perspective of the patient, doctor, department and society

Perspective	Pros	Cons	Comments
Patient	Convenience One stop treatment Less time in hospital or department Less side effects	Higher percentage of retreatment; 7–25 %	Retreatment percentages are most probably biased by disbelief of single treatment effectiveness and/or reluctance to retreat with higher initial dose
Doctor	Convenience	Reimbursement Lower revenues	In some countries, costing is based upon number of fractions applied
Department	Lower costs Less use of available equipment Ease of scheduling among other therapies	Reimbursement Lower revenues	In some countries, costing is based upon number of fractions applied
Society	Lower costs Less use of available equipment		

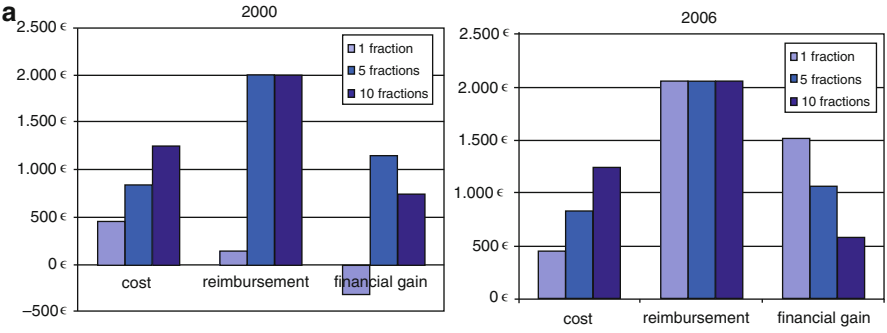
(Reproduced from Ref. [48], with permission)

A large number of national and international surveys have been conducted during the past two decades which enable monitoring of the adoption of the SF schedule [33–44]. In Europe, Northern America, Australia/New Zealand, and Asia, radiation oncologists were asked to give their opinion on hypothetical case scenarios. Also, in a few studies, patient preferences were sought [45–47].

Table 25.7 lists the potential benefits and drawbacks of SF schedules mentioned in the literature from the perspective of patients and physicians, taking into account both departmental and societal considerations [48]. Overall, there seem to be abundant reasons to choose SF as the standard. In contrast to this expectation however, the percentages of SF use reported by radiation oncologists in the surveys has been consistently low. For a variety of case scenarios in the surveys published between 1989 and 2004, the use of SF ranged from 0 % to 42 % of respondents, with the commonest regimen consistently 20 Gy in 5 or 30 Gy in 10 fractions.

In the most recent international survey 2–67 % of respondents recommended SF [39]. A single 8 Gy is now the most common choice in Europe and UK, 20 Gy in 5 fractions in Canada and Australia/NZ, but 30 Gy in 10 fractions is still preferred by the majority in the USA and Asia. Of note, 101 different schedules were recommended, ranging from a single 3 to 60 Gy in 20 fractions! Contrary to literature evidence, case scenario was an independent predictor of choice of SF, in which patient condition, site of the metastasis, and expected outcome in the near future influence preference for larger total doses. The other independent factors in this survey were country of training, location and type of practice, and professional membership affiliation [39]. For patients, sustained pain relief and minimizing the

a



b

	1998	2004
8Gy single fraction	0%	25%
20Gy/4Gy	14%	22%
30Gy/3Gy	82%	47%
other	4%	6%

Fig. 25.6 Reimbursement systems in Belgium (**a**): Cost, reimbursement and profit of three radiotherapy schedules under the fee-for-service (Year 2000) and case payment (Year 2006). (**b**): Use of radiotherapy schedules reported by Belgian Radiation Oncologists (Permission obtained from Prof. Lievens, through personal communication)

risk of future complications were the most important factors when deciding on number of fractions. Practical aspects of treatment (travelling distance, remaining at home and brevity of treatment) were of least importance [45–47].

The researchers behind these surveys did not ask their respondents for the influence of payment system. A realistic but undesirable and foul incentive is the way the different types of reimbursement in a particular country guide clinicians and hospital management to choose their treatments. In some countries, money is being made by applying fractionated regimens. In 2000, Lievens et al. suggested that indeed type of reimbursement in a country might significantly influence choice of fractionation [49]. In a recent survey of 23 of the 25 Belgian radiotherapy centers after changes in the Belgian reimbursement system in 2001 from fee-for-service to case payment, Lievens et al. showed an increase in the use of SF (Fig. 25.6, personal communication with author). Although changes were most evident in university-based and larger hospitals, 86 % of the centers reported a shift towards shorter and more hypofractionated regimens.

Another possible reason that doctors and patients are reluctant to embrace the single dose regimen is the higher retreatment rates that were reported in the literature after the single schedule when compared to multiple schedules [50]. Percentages ranged from 0 % to 24 % retreatment after initial multiple fractions to as much as 11–29 % after single fraction. However, reirradiation in these trials to the previously radiated sites was at the discretion of the treating radiation oncologists who were not blinded to the initial treatment, and there were no guidelines explaining when,

why and what dose of reirradiation should be given. Many patients with relapsed pain or poor response to initial radiation may be lost to follow-up or may not be referred back to the radiation oncologist for consideration of re-irradiation. The response to re-irradiation in the published reports is variable, and no consistent policy for dose fractionation is followed or recommended. Van der Linden et al. studied the additive effect of retreatment in the Dutch study on the response percentages and showed that patients in the single fraction randomization group were retreated earlier and with a lower pain score than patients who received multiple fractions as their initial treatment [24]. They concluded that it was mostly the doctors and patients disbelief in the lower total dose and the possibility of treating further after an initial lower dose that caused this difference. Even so, a 25 % retreatment percentage still means that up to 75 % of patients benefit from a single fraction. The same group also published subgroup analyses of 320 patients with an observed survival of more than 1 year, showing again no differences in response between single and multiple fractions (87 % vs 85 %, resp. $p=0.54$) [51].

The available data clearly demonstrate the continuing influence of geographic, departmental and financial factors on use of SF. Although there is some evidence of a shift towards SF in recent years, particularly in Europe and UK, there remains a striking global resistance to embrace the evidence. Kachnic et al. wrote in their excellent editorial after the publication of the RTOG 9,714 that it remained to be seen if single fraction would become the standard of care in the USA based on practice evidence-based or remuneration-based medicine [52]. The recent ASTRO guideline on palliative radiotherapy, published in 2011, recommends the use of the single fraction regimen [53]

25.4 Conclusions

In summary, all above mentioned studies are very heterogeneous in their design, comparing different outcomes and different time frames, making profound comparison of costs and utility outcome impossible. However, most studies indicate that palliative radiotherapy for bone metastases provides good value for money when compared to other palliative treatment modalities. Therefore, from a societal perspective, when radiotherapy units are available, single fraction or short term radiotherapy should always be considered first to treat pain arising from bone metastases. The beneficial outcome of palliative radiotherapy for bone metastases needs to be repeated continuously to health care professionals, not only to radiation oncologist, but to everyone involved in caring for cancer patients with painful bone metastases. Therefore, continuous medical education to increase awareness on this specific topic is essential.

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Bone Metastases

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The second edition of this book serves both as an introductory and reference book focusing on the field of metastatic bone disease. Featuring contributions from experts in the field, this volume describes the molecular and cellular mechanisms involved in the formation of bone metastases, presents the newer advances made in the understanding of the clinical picture and symptoms of patients, analyses the role of bone markers in research and clinical practice and deals with all aspects of imaging modalities applied for the detection and evaluation of bone metastases.

Moreover, the use of all available treatment methods, such as radiotherapy, surgery and systemic treatments for the management of patients with metastatic bone disease is discussed in detail.

Overall this volume presents a thorough overview of all aspects of skeletal metastases and provides a comprehensive and concise information resource for researchers, oncologists, orthopaedic surgeons and clinicians dealing with patients with metastatic bone disease.

V. Vassiliou, E. Chow, D. Kardamakis (Eds.)

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Index

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