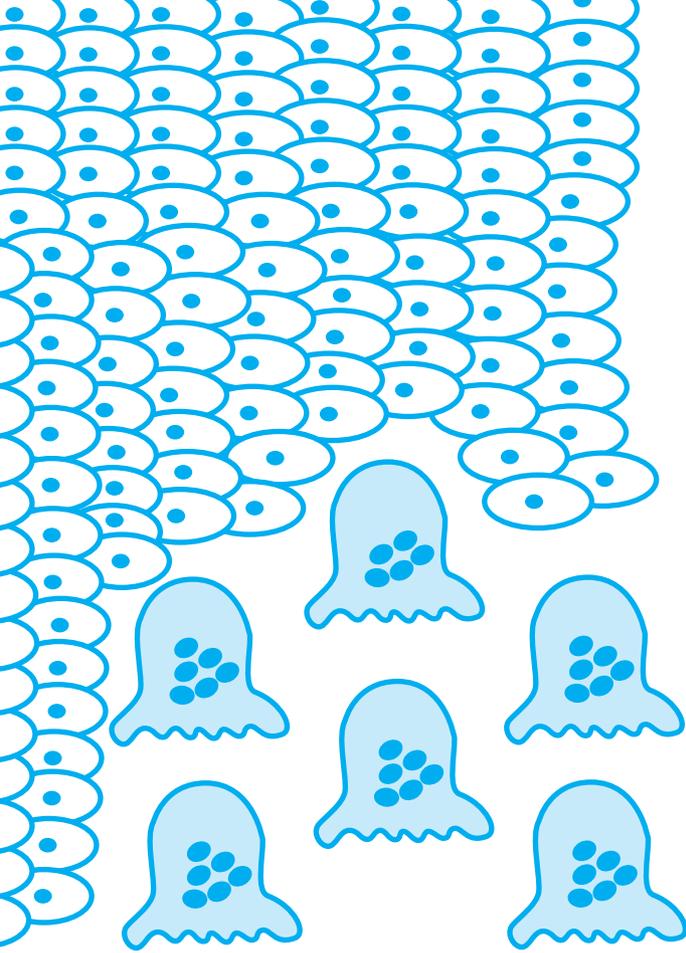# Handbook of Cancer-Related Bone Disease

2nd edition

Handbook of Cancer-Related Bone Disease

2nd edition

Edited by RE Coleman, P-A Abrahamsson and P Hadji

Contents

Contributors

Jean-Jacques Body PhD MD

Professor Jean-Jacques Body received his training at the Université Libre de Bruxelles and at the Mayo Clinic, Rochester, MN, USA. He is an internist, an endocrinologist and a medical oncologist. He is now Head of the Department of Medicine at University Hospital Brugmann, Brussels. He is Professor of Internal Medicine at the Université Libre de Bruxelles.

His particular research interests are tumour bone disease and osteoporosis. He was involved in numerous trials in cancer patients with all the bisphosphonates available in Europe and with denosumab. He has a long standing interest in the biochemical markers of bone turnover in metastatic bone disease and in osteoporosis. More recently, he became interested in risk factors for fractures in postmenopausal women.

Brendan F Boyce MD

Professor Brendan Boyce is currently Director of Anatomic Pathology at University of Rochester Medical Center, Rochester, New York, USA. He is a general diagnostic surgical pathologist, who received his MD in Glasgow in 1972, completing his training at the Royal Infirmary Glasgow and at the University of Lyon, France. An interest in the pathology of metabolic bone disease developed in 1976 when he began to collaborate with Dr Iain Boyle and his group in Glasgow and continued during his fellowship in Lyon in 1977, with Dr Pierre Meunier.

His current research interest is the study of the regulation of the formation, activation and survival of osteoclasts. In recent years, many genes have been identified as regulators of these aspects of osteoclast function, and his research team are presently focussed on the roles of NF-κB and src tyrosine kinase in osteoclasts and the role of NF-κB in the regulation of chondrocyte differentiation. With his colleague, Dr Lianping Xing, along with members of the Center for Musculoskeletal Research in Rochester, they are also studying the roles of these gene products in the increased bone resorption and decreased bone formation that characterize a number of bone diseases, including post-menopausal osteoporosis, inflammatory joint disease, metastatic bone disease and the loosening of joint prostheses.

Øyvind S Bruland PhD MD

Øyvind S Bruland is Professor of Clinical Oncology at University of Oslo, Norway and a senior consultant at the Department of Oncology, The Norwegian Radium Hospital. His clinical experience and research are mainly devoted to primary bone and soft tissue cancers, and skeletal metastases from prostate cancer and breast cancer. In particular, targeted radionuclide therapy, recently based on the natural bone seeker Radium-223, is at centre stage.

Eugene McCloskey MB MRCP MD FRCPI

Eugene McCloskey is Professor of Adult Bone Disease at the University of Sheffield. He has worked in the field of calcium and bone disorders since 1986. Following medical school at Trinity College, Dublin, Ireland, Dr McCloskey initially trained in general medicine and endocrinology, and subsequently in rheumatology before specialising in Metabolic Bone Diseases. He has a long-standing interest in the mechanisms of malignant hypercalcaemia and osteolytic bone disease. This led to several clinical trials of bisphosphonates in multiple myeloma and breast cancer that have established the role of anti-osteoclastic therapy in malignant disease. Within the field of osteoporosis, Dr McCloskey has been principal investigator in a large number of MRC and pharmaceutical funded studies. He is an acknowledged expert in the fields of vertebral fracture definition and epidemiology as well as non-invasive assessments of bone strength and fracture risk. He is on the board of the Bone Research Society and is a member of the IOF Committee of Scientific Advisors.

His current research interests encompass benign and malignant bone disease. Within osteoporosis, interests include the evaluation of techniques used in the diagnosis and management of osteoporosis, fracture risk assessment and the development of the WHO Risk Algorithm (FRAX). In breast cancer and multiple myeloma, research interests have focussed on the development of bisphosphonates as inhibitors of bone complications and metastases.

Michael Gnant PhD MD FACS

Professor Michael Gnant is Professor of Surgery at the Medical University of Vienna, Austria, and is President of

the Austrian Breast and Colorectal Cancer Study Group. His medical career began in 1988 when he graduated in medicine in Vienna. He specialised in surgery (1994) and surgical oncology. In 1997–1998 he worked at the National Cancer Institute, NIH, Bethesda, USA, and in 2004 he became Professor at the Medical University of Vienna.

Professor Gnant's research interests include several fields of surgical oncology, in particular breast and pancreatic cancer, immunotherapy using antibodies, vaccination with dendritic cells, endocrine intervention, dormant tumor cells, and the use of bisphosphonates. He has been the Principal Investigator of more than 20 clinical trials.

Lorenz C Hofbauer MD

Lorenz Hofbauer is Professor of Medicine and Endocrinology at the Technical University of Dresden, Germany. He graduated from the University of Munich in 1994 and in 1995 obtained a MD degree in the thyroid field. He did a post-doctoral fellowship at the Mayo Clinic, Rochester, MN, USA from 1996 to 1999. In 1999, he joined Philipps-University of Marburg, Germany to complete his clinical training in internal medicine, endocrinology, and diabetes. He also led a research group focussing on the RANKL/OPG biology in skeletal, malignant, and vascular diseases. From 2004 to 2007 he was a Heisenberg senior fellow and consultant in Medicine. Since 2007, he heads the Division of Endocrinology, Diabetes, and Bone Diseases at the University Medical Center at the Technical University of Dresden, Germany. He coordinates the bone research program at the Center of Regenerative Therapies Dresden (CRTD) since 2009 and leads the SKELMET consortium, a national network dedicated to exploring the mechanisms of skeletal metastases.

Ingunn Holen BSc MSc PhD

Dr Ingunn Holen obtained a BSc, MSc, and a PhD from the University of Oslo, Norway. She worked at the Cancer Research Centre at the Norwegian Radium Hospital 1989–1995 and since 1995 has worked in various research groups at the University of Sheffield, UK with focus on bone biology and metastatic bone disease. She is currently Reader in Bone Oncology and Head of the Laboratory Research Team in the Academic Unit of Clinical Oncology at the University of Sheffield.

Dr Holen has wide experience in the studies of tumour-induced bone disease, with particular emphasis on therapeutics including bisphosphonates. Her main research interests are the molecular mechanisms involved in tumour cell–bone cell interactions in breast and prostate cancer, and how these can be targeted by combining current therapies. The aim is to establish promising drug combinations in laboratory models of bone metastases in breast and prostate cancer, and to subsequently take these forward to clinical studies.

Peter Hoskin MD FRCP FRCR

Professor Peter Hoskin is Consultant Clinical Oncologist at Mount Vernon Cancer Centre, Northwood UK and Professor of Clinical Oncology at University College London. He trained in clinical oncology at the Royal Marsden Hospital. This included a time as Research Fellow there and at St Bartholomow's Hospital London studying pain control in advanced cancer. He has extensive experience in the management of bone metastases with radiotherapy and is widely involved in research into radiotherapy fractionation, and its use in combination therapy for bone pain. His current research interests include the role of bone markers in predicting response to local radiotherapy and evaluation of radiotherapy against bisphosphonates and in combination with pregabalin for bone pain. He is European Co-Chair of the International Consensus Group on Palliative Radiotherapy responsible for developing guidelines and consensus statements in this area.

Andreas A Kurth

Professor Andreas Kurth is Director of Orthopaedic Surgery at the University Medical Center of the Johannes Gutenberg University Mainz, Germany. Professor Kurth studied Human Medicine and Sports Science at the University of Frankfurt and Zürich. After graduation he trained in Orthopaedics and Trauma surgery at the University Clinic, Frankfurt. He completed his scientific and clinical training at Harvard Medical School, USA. After returning from the USA he specialised in orthopaedics and was made Director of Orthopaedic Oncology at University Clinic in Frankfurt. Over eight years he helped develop the reconstructive orthopaedic oncology services at Frankfurt University Hospital. Professor Kurth joined Johannes Gutenberg University Mainz in 2009 to establish innovative surgical and medical methods on the spinal column and joints, and to conduct further research into the biological basis for the development of medical procedures to reconstruct diseased bone.

Allan Lipton MD

Professor Allan Lipton is a specialist in internal medicine and medical oncology at the MS Hershey Medical

Center of Pennsylvania State University. Professor Lipton received his medical degree from the New York University School of Medicine and completed an internship and residency at Cornell Medical Division, Bellevue Hospital, New York, USA. He completed a fellowship in hematology at Memorial Sloan–Kettering Hospital for Cancer and Allied Diseases and New York Hospital, and a fellowship in medical oncology at Memorial Sloan–Kettering Hospital for Cancer and Allied Diseases. He also completed a Dernham Fellowship of the American Cancer Society at the Salk Institute for Biologic Studies, San Diego, California.

Sebastiano Mercadante MD

Professor Sebastiano Mercadante is Director of Anesthesia & Intensive Care Unit, Pain Relief & Palliative Care Unit, La Maddalena Clinic for Cancer, Palermo, Italy. Awarded an MD in 1979 from University of Palermo, Professor Mercadante specialized in Anesthesiology in 1980 and in the Science of Nutrition in 1984 before becoming Professor of Palliative Medicine at the University of Palermo.

La Maddalena Cancer Center opened in 1999 and the Pain Relief & Palliative Care Unit was soon established. The aim of the Unit is to diminish the physical and psychological distress of patients during the treatment of oncological diseases, as well as during the end stage, when curative approaches are no longer possible. In contrast to many palliative care facilities, the unit has developed a unique acute and aggressive treatment in response to cancer-related symptoms. Research interests include opioid switching, opioid pharmacokinetics, breakthrough pain, bowel obstruction, opioid toxicity and possible alternative therapies.

Tilman D Rachner MD

Tilman Rachner is a clinician scientist at the Division of Endocrinology, Diabetes, and Bone Diseases at the Dresden University Medical Center, Dresden, Germany. He studied Medicine at Philipps-University of Marburg, and the Universities of Zurich and St John's, Newfoundland, Canada before graduating in 2009. In the same year he obtained his MD degree in the field of osteooncology. Since 2010 he has worked as a clinician scientist. His research interests include the mevalonate pathway and wnt signalling as therapeutic approaches to malignant bone disease.

Anke J Roelofs MSc PhD

Dr Anke Roelofs graduated from the University of Groningen in the Netherlands in 2003 with an MSc in Medical Biology. She then moved to the Institute of Musculoskeletal Sciences at the University of Oxford where she obtained a PhD working in the laboratory of Professor Graham Russell investigating the anti-tumour mechanisms of action of bisphosphonates and related compounds.

Since 2005, she has worked with Professor Mike Rogers and colleagues in the Musculoskeletal Research Programme at the University of Aberdeen, where she is currently a Post-doctoral Research Fellow. Until recently, her main research interests were the pharmacology and mechanisms of action of bisphosphonates, as well as the mechanisms of breast cancer metastasis. Since 2011, she is a Research Fellow in the Musculoskeletal Regenerative Medicine group at the University of Aberdeen, focussing on mesenchymal stem cell-based therapy for the treatment of osteoarthritis.

Michael J Rogers BSc (Hons) PhD

Professor Mike Rogers studied Biochemistry in the Department of Molecular Biology & Biotechnology at the University of Sheffield, receiving his doctorate in 1993, before moving to the University of Aberdeen in 1997. In 2003 he was awarded a personal Chair in Musculoskeletal Pharmacology and continued to study the actions of bisphosphonates, the role of the mevalonate pathway in bone metabolism, and signalling pathways involved in regulating osteoclast activity and apoptosis. After leading the Musculoskeletal Programme at Aberdeen for 5 years, Mike moved to the Garvan Institute in Sydney in 2012 as a Senior Principal Research Fellow. His current research now also includes interactions between tumour, bone and immune cells.

G David Roodman PhD MD

Professor David Roodman is the Kenneth Wiseman Professor of Medicine at Indiana University and the director of the Division of Hematology and Oncology at the Indiana University School of Medicine. He is also co-leader of the Hematopoiesis, Hematological Malignancies and Immunology research program at the Simon Cancer Center, Indianapolis, IN, USA. He received an MD from the University of Kentucky College of Medicine in 1973, and a doctorate in biochemistry from the University of Kentucky in 1975. His postdoctoral training included an internship in internal medicine at the University of Kentucky, as well as a residency in medicine and a haematology fellowship at the University of Minnesota.

Professor Roodman's research interests focus on the cellular and molecular events controlling the formation and activity of osteoblasts and osteoclasts in normal

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Professor Oliver Sartor is the Laborde Professor of Cancer Research in the Departments of Medicine and Urology at the Tulane University School of Medicine, New Orleans, LA, USA. Professor Sartor graduated from Tulane University's School of Medicine in 1982 and completed his residency at Tulane in 1986. Professor Sartor was chief of Hematology-Oncology and director of the Stanley S Scott Cancer Center at LSU Medical Center, New Orleans for eight years before taking a post as associate professor in the Lank Center for Genitourinary Oncology at Harvard's Dana-Farber Cancer Institute in Boston, USA. Professor Sartor returned to Tulane in 2008.

Current research interests include clinical trials in advanced prostate cancer with novel agents and novel combinations of agents, including trials with alpharadin a novel bone-seeking isotope. His collaborative projects include novel concepts in germ line assessment of prostate cancer risk and treatment response.

Philip J Saylor MD

Dr Philip J Saylor is an Instructor in Medicine at Harvard Medical School, Boston, MA, USA. He received an MD from the University of Pittsburgh, School of Medicine. He then continued his training with an internal medicine residency at the University of California San Diego and an oncology fellowship at the Dana Farber Cancer Institute and Massachusetts General Hospital Cancer Center, Boston, MA, USA. His clinical appointment is Assistant Physician in the Division of Hematology and Oncology at the Massachusetts General Hospital Cancer Center.

Current research interests are centred on clinical/translational investigation in genitourinary malignancies. His investigative efforts particularly focus on prostate cancer imaging, prostate cancer treatment, and the metabolic consequences of androgen deprivation therapy.

Gemma Shay BSc (Hons) MSc PhD

Dr Gemma Shay graduated from the University of Aberdeen with a BSc in Biochemistry in 2006, and with an MSc in Clinical Biochemistry from the University of Surrey in 2008. She returned to the University of Aberdeen in 2008, where she obtained a PhD in the laboratory of Professor Mike Rogers investigating the anti-tumour mechanisms of action of bisphosphonates. Dr Shay is now a postdoctoral research fellow at the Moffitt Cancer Center, Tampa, FL, USA. Her current research interests focus on understanding the molecular mechanisms that promote the metastasis of cancer to the bone, particularly in prostate cancer.

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Dr Rebecca Silbermann is an Assistant Professor of Medicine at Indiana University School of Medicine, Indianapolis, IN, USA. She received her MD from Brown University, Providence, RI, USA, and completed training with a residency at Strong Memorial Hospital, Rochester, NY, USA, and a hematology/oncology fellowship at the Pittsburgh Cancer Institute, University of Pittsburgh, Pittsburgh, PA, USA.

Current research interests include osteoclast regulation in myeloma bone disease and the role of osteoclasts in angiogenesis in the bone marrow microenvironment.

Matthew R Smith PhD MD

Dr Matthew R Smith is a Professor of Medicine at Harvard Medical School, Boston, MA, USA and the Director of Genitourinary Medical Oncology at Massachusetts General Hospital Cancer Center, Boston. Professor Smith received a PhD from Duke University, Durham, NC, USA in 1991 and an MD from Duke University in 1992. Professor Smith completed his training with a residency at Brigham & Women's Hospital, Boston, a fellowship at the Dana Farber Cancer Institute, Boston, and a postdoctoral fellowship at Massachusetts Institute of Technology, Cambridge, MA, USA.

Preface

The optimal treatment of cancer requires a wide-ranging, multidisciplinary approach to appropriately apply to patient care the quite remarkable progress that has been made across all fields of oncology. This handbook summarises current knowledge of cancer-related bone diseases and describes appropriate management, not only for patients with advanced malignancy affecting the skeleton, but also for those at risk for treatment induced morbidity.

Bone is the most common site for metastasis and is of great clinical relevance in breast, prostate and lung cancers as well as in multiple myeloma. Bone metastasis causes pain, structural damage and adverse effects on quality of life and physical function, as well as consuming a large amount of health care resources. Our understanding of the pathophysiology of metastasis to bone has resulted in the application of bone-targeted treatments to prevent skeletal morbidity and treat complications that may result from both the disease itself as well as those induced by the cancer therapy.

Until recently, the bisphosphonates had been the mainstay of treatment alongside radiotherapy, orthopaedic intervention, appropriate systemic treatments and supportive care including analgesics.

However, through our improved understanding of the biological cross talk between osteoblasts and osteoclasts, targeted therapy with agents such as denosumab have merged and are further improving patient care.

The interactions in the bone microenvironment between stem cells, osteoclasts and osteoblasts, and cancer cells are of fundamental importance to the processes that underpin metastasis. Extensive preclinical investigations, and a widening range of clinical trial results, suggest that treatments able to interrupt these inter-relationships can reduce the risk of metastasis and may offer far more to the patient than just supportive care.

This second edition of this handbook brings together the expertise of the foremost experts in this rapidly developing field and presents a clear summary of clinically relevant information with recommendations for treatment. We hope that the content and format will be of value across the spectrum of clinicians, scientists and health care professionals involved in the management of bone disease in cancer.

Robert Coleman
Per-Anders Abrahamsson
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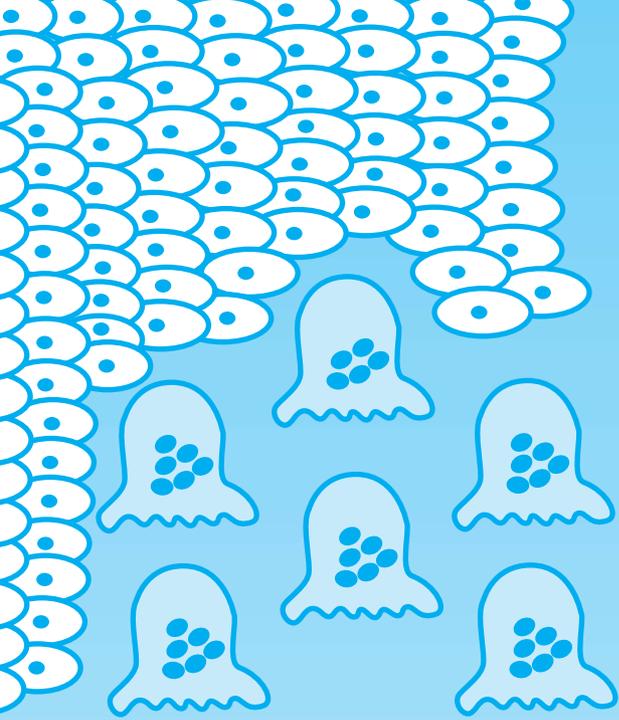
12 Radioisotope treatments for bone metastases

Radioisotope treatments for bone metastases

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◗ Introduction

Bone is the most common site of symptomatic cancer metastasis. Two-thirds of patients with advanced breast cancer and over 90% of patients with advanced prostate cancer have skeletal metastases. Lung, thyroid and renal carcinoma metastasize to bone in approximately 30% to 40% of cases. Multiple myeloma, though not usually thought of as a metastatic disease, involves the skeleton in nearly 100% of cases.

Skeletal metastases may have a devastating impact on a patient's quality of life and can lead to significant debilitation. Pain is the usual dominating symptom. Furthermore, additional clinically serious implications are pathological fracture, nerve entrapment, spinal cord compression, bone marrow insufficiency and hypercalcaemia.[1–4] These are of particular concern to cancer patients with a long expected survival; e.g. those with the diagnosis of skeletal metastases as the first and sole metastatic event.

Patients with skeletal metastases should be treated by a multidisciplinary team. The appropriate combination of analgesic medication, radiotherapy, surgery, chemotherapy, hormone treatment, bisphosphonates or denosumab, and/or a bone-seeking radiopharmaceutical (BSR) is mandatory. Choices depend on the biology of the disease, extent of the skeletal involvement, symptoms, the availability of effective systemic therapies and the life expectancy of the patient. While external beam radiation therapy remains the mainstay of pain palliation of solitary lesions, BSRs have an established role in the therapeutic armamentarium for the treatment of multiple painful osteoblastic lesions and for those patients with pain recurrence at multiple sites after external beam radiotherapy.

◗ Tumour biological aspects

Development of bone metastasis involves a complex pathophysiology between host and tumour cells. Tumour cell migration, adhesion and invasion into the skeleton induce stimulation of osteoclastic and osteoblastic activity – a process mediated by cytokines and tumour-derived factors.[5] Studies performed in the early 1970s clearly demonstrated the importance of stromal factors in prostate epithelial cell growth.[6] These initial findings were expanded both in concept and scope by the observation that cancerous prostate growth was markedly enhanced by the presence of stromal elements from selected sources.[7] Co-inoculation experiments with stroma-derived fibroblasts and human prostate cancer cell lines demonstrated clear synergy of growth,[8] thereby presenting both a heuristic concept and an intellectual framework for subsequent studies both *in vitro* and *in vivo*. These stromal influences are not restricted to growth;

plasticity in epithelial-mesenchymal transitions are subject to microenvironmental influences.[9] Taken together these data support the concept that bone stromal microenvironment alters both cancer cell growth and phenotype. The exquisite tropism of prostate cancer cells to bone[10] and factors secreted by the prostate cancer cells that promote the formation of new bone matrix[11] contributing to the sclerotic phenotype of such metastases,[12] render BSRs an attractive treatment that targets the lethal phenotype of this disease.[13,14]

Therapeutically speaking, targeting stromal elements that promote cancerous growth is a promising alternative to targeting cancer cells from advanced epithelial malignancies given the unstable phenotypes and genotypes typical of these cancer cells.[13,14] Stromal elements are less likely to have genetic heterogeneity and thus a stromal-targeted therapy has the potential to overcome some of the difficulties and mechanisms of resistance associated with more traditional cancer cell directed cytotoxic chemotherapies. The concept of stromal-targeted therapy has rapidly evolved in recent years given the development of anti-angiogenesis inhibitors such as bevacizumab and novel agents such as XL-184.[15] Recognizing that stromal elements other than blood vessels are important in the growth of diverse tumour types helps to provide an intellectual framework for the development of new stromal-targeted therapies.

The propensity of cancer cells to metastasize to bone and the ability of BSRs to target extracellular matrix and affect the microenvironment via alterations in stromal cells such as fibroblasts, osteoblasts, osteoclasts and endothelial cells suggests an alternative and attractive approach to cancer therapeutics. These microenvironmental effects should theoretically be effective despite significant genetic heterogeneity within the actual cancerous cells.[13,14] BSRs provide a multi-targeted approach aimed at both the tumour cell and the tumour microenvironment and have the advantage of being able to target cells, regardless of genotype, within the tumour and the tumour microenvironment. No non-isotopic therapy under development has the opportunity to have such multiplicity of actions, and thus we believe that BSRs have a unique role to play in the development of the next generation of cancer therapies. Recent data with radium-223

demonstrate the ability of this agent to modify the natural history of advanced prostate cancer (see below); a fundamentally important finding that currently changes the way this class of agents should be viewed.

External beam radiotherapy – relevance to BSRs

Skeletal metastases are the single most frequent indication for palliative radiotherapy and external beam irradiation effectively relieves pain from single sites of skeletal metastases.[16–17] Chapter 11 in this book reviews this in detail. Here only aspects of relevance to BSRs will be mentioned.

Metastases to bone are usually multiple and distributed throughout the axial skeleton thus providing a significant limitation to the use of external beam therapy (Figure 12.1). When larger or multiple fields of irradiation are necessary, such as for diffuse metastases in the axial skeleton such as vertebra and pelvis, bone marrow suppression; already often present due to metastatic cell growth within/occupying red bone-marrow, increases substantially.

Radiation doses needed to achieve pain palliation may be different from that resulting in long-term local tumour control. International consensus advocates the standard use of a single fraction (8.0 Gy) in most patients in whom the clinical indication is 'pain relief'.[16–18] Patients not responding or those with new pain arising at a previously irradiated site should be offered retreatment. In contrast, when the aim is 'local tumour control' in patients with solitary bony metastases and long life expectancy or when medullar compression is present, fractionated external beam radiotherapy is advisable (3.0 Gy × 10, or even conventional 2 Gy fractions to higher total doses in selected cases).[18] This seems also to be the case in patients with imminent fractures because re-mineralization is reported to be more favourable after fractionated irradiation.[19]

Experiences from retreatment suggest that effective palliation may be achieved with localized radiation doses as low as single fractions of 4.0 Gy.[20] This might be of relevance to the use of BSRs where dosimetry is complicated and calculations less accurate.
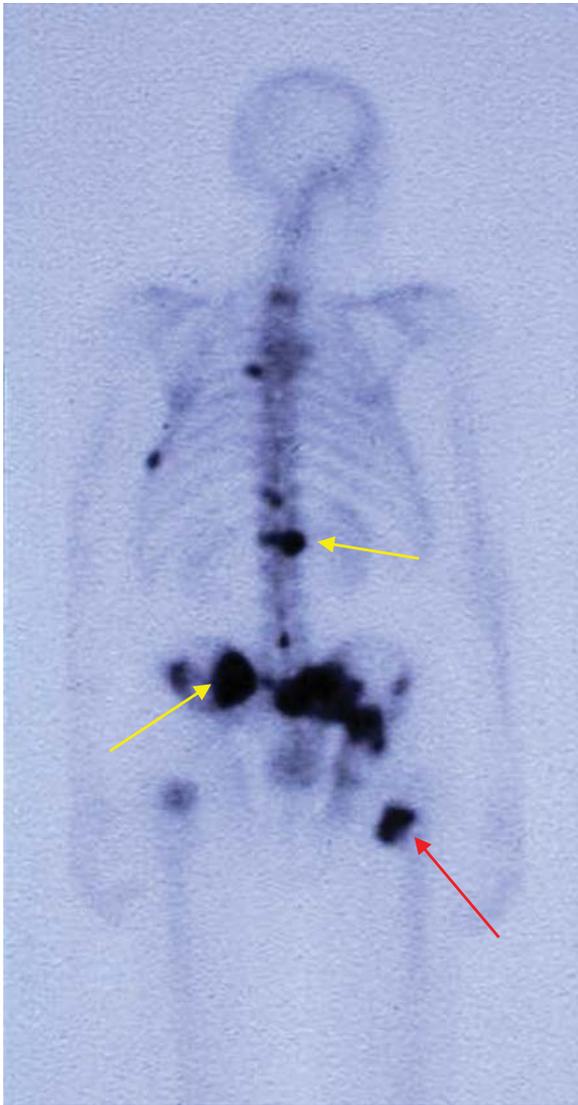
Figure 12.1 *A diagnostic bone scan obtained with ^{99m}Tc-MDP demonstrating high uptake of the radiopharmaceutical in regions of osteoblastic bone metastases. Red arrow denotes a symptomatic lesion subjected to palliative external beam irradiation in this patient with castrate-resistant prostate cancer. Yellow arrows denote two of many asymptomatic lesions that will be targeted by a therapeutic BSR.*

◗ Bone-seeking radiopharmaceuticals

Currently, two principal chemical classes of therapeutic BSRs are regulatory approved – cationic and anionic bone seekers (i.e. calcium analogues and radiolabelled polyphosphonates). In the commercially available formulations, the current radioisotopes are beta-emitters. Strontium-89 dichloride (Metastron, GE Healthcare, Chalfont St. Giles, United Kingdom) is approved in the United States and in most European countries, and more recently, ^{153}Sm-EDTMP (^{153}Sm-lexidronam, Quadramet, Schering AG, Berlin, Germany and EUSA, Oxford, UK) has been approved. In the latter, the beta-emitter samarium-153 is in complex with ethylenediaminetetramethylene phosphonic acid (EDTMP).

While each of these agents is shown to have efficacy in the treatment of painful osseous metastases from prostate cancer, they may also have utility in the treatment of skeletal metastases from breast cancer and perhaps from other cancers as well. As noted above, the BSRs offer an effective alternative to external beam irradiation in patients with multiple skeletal metastases and the histological cancer type and the organ of cancer origin is less important for the BSR as compared to more conventional therapeutic agents.

The target for all the BSRs is calcium-hydroxyapatite. This is particularly abundant[12] in sclerotic metastases from prostate cancer (Figures 12.1 and 12.2) but also present, although more heterogeneously distributed, in mixed sclerotic/osteolytic metastases (e.g. in breast cancer). This is evident from the biodistribution image (Figure 12.1) common to all BSRs – exemplified as 'hot-spots' visualized on a routine diagnostic bone-scan by ^{99m}Tc-MDP; a radiolabelled bis-phosphonate. Following administration, delivery of ionizing radiation to targeted areas of amplified osteoblastic activity occurs, and multiple (symptomatic and asymptomatic) metastases are treated simultaneously (Figure 12.1). The sensitivity to visualize sclerotic metastases is markedly increased when moving from a conventional 2D bone-scan, via a 3D tomographic SPECT to a PET modality by the bone-seeking ^{18}F (Figure 12.3).

BSRs effectively relieve pain, and this has been the basis for regulatory approvals. Their salient characteristics and usefulness in controlling pain from widespread metastatic bone disease have been thoroughly reviewed.[21–26] Important characteristics of the various BSRs are presented in Tables 12.1 and 12.2. In addition to the
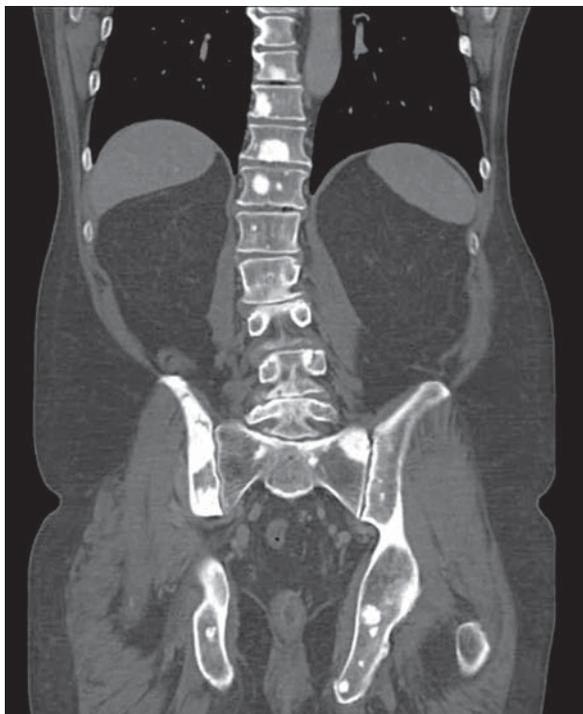
Figure 12.2 *Sclerotic, osteoblastic metastases in the axial skeleton visualized on a CT (3 mm coronal section) scan in a patient with castrate-resistant prostate cancer. Note the calcified phenotype also in the central part of metastases; being larger or smaller lesions.*

commercially available formulations mentioned above, [186 or 188]Re-hydroxyethylene diphosphonate (HEDP) has also been extensively utilized[27–30] and also [117m]Sn-DTPA that emits conversion electrons is associated with effective palliation of pain.[31,32] Clinical development of these agents may resume in the near future. A new generation of BSR that emits alpha-particles and is based on the bone-seeking properties of radium-223 has shown encouraging results in phase II clinical development.[33] Results with phase III data in patients with bone-metastatic castrate-resistant prostate cancer (CRPC) show that this agent can prolong survival[34] These important new data will be discussed in more detail below.

Randomized trials represent the best source of data for assessing clinical responses, especially those trials that assess patient-reported outcomes (PROs) such as pain. As a rule regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) have required randomized placebo controlled assessments for

palliative agents given the high rate of success for placebos in studies evaluating pain as an end-point.

As mentioned above, BSRs are approved for the palliative treatment of advanced bone metastatic cancers but have not gained a wide acceptance in the oncological community. The reasons for this lack of general usage may include both economic and licensing issues. Particularly in the United States, oncologic care is controlled by medical oncologists that are not certified in radiopharmaceutical administration and, hence, may be financially disincentivized to recommend this form of therapy.

Studies with [32]P

Phosphorous-32 is an older radiopharmaceutical that is still available in several countries. [32]P as orthophosphate has been used for over 50 years in the palliative treatment of multiple painful osseous metastases. In fact this agent was the first BSR used in clinical medicine and was used to target bone metastases in patients with breast and prostate cancer in the 1950s.[35–36] [32]P is not FDA approved despite its long record of usage. Main disadvantages of this BSR are dose-limiting myelosuppression[37] and the lack of randomized trials performed with this agent limiting the interpretation of data. However, one more recent trial[38] is covered below in the portion of the chapter covering a comparison of BSR. The clinical use of ^{32}P in pain palliation today is relatively limited in the developed world.

Strontium-89 study review

Strontium-89 is a bone-seeking radionuclide due to its alkaline earth metal characteristics with similarities to calcium. It has a long physical half-life (50.5 days) and acts *in vivo* as a calcium-mimetic in binding to sclerotic bone lesions, Patients may benefit from a single i.v. infusion of 148 MBq (4 mCi) of [89]SrCl$_2$, pain relief may occur within the first weeks and sometimes lasts for several months. Clinical phase II studies with ^{89}Sr have shown effective palliation of pain in some but not all studies in metastatic prostate cancer. Initial reports using non-blinded trial designs suggested palliative responses in up to 75% of the patients, with as many as 25% being able to stop taking analgesics.[39–41] Double-blind studies have compared radioactive

**Table 12.1   Physical properties of selected bone-seeking radiopharmaceuticals**

RADIO PHARMACEUTICAL	HALF-LIFE (DAYS)	PARTICLE	MEAN DECAY ENERGY (MeV)	MAXIMUM SOFT TISSUE RANGE (mm)
^{153}Sm-EDTMP	1.9	Beta minus	0.27	3.4
^{89}SrCl$_2$	50.5	Beta minus	0.58	6.0
^{223}RaCl$_2$	11.4	Alpha	28.2*	<0.1
^{186}Re-HEDP	3.8	Beta minus	0.34	4.4
^{188}Re-HEDP	0.7	Beta minus	0.78	10
^{32}P	14.3	Beta minus	0.70	8.5
^{117m}Sn-DTPA	13.6	Conversion electrons	0.15	<0.3

* Includes daughter radionuclides
Data from Nuclides 2000, Nuclide Explorer, version 1.2, Institute for Transuranium Elements, Karlsruhe, Germany

and stable strontium and confirmed the therapeutic effect of ^{89}Sr.[42] However, effective pain palliation was observed in a considerably lower percentage of patients than that reported in the non-placebo-controlled phase II trials.

The initial randomized studies with ^{89}Sr were small. In the trial reported by Lewington and colleagues[42] assessing metastatic prostate cancer and comparing ^{89}Sr to placebo, only a single time point 5 weeks post-dosing was assessed and only 26 of 32 patients were included in the efficacy analysis. The authors concluded that pain relief occurred with ^{89}Sr and that one third of patients had a complete response. Assessment methods
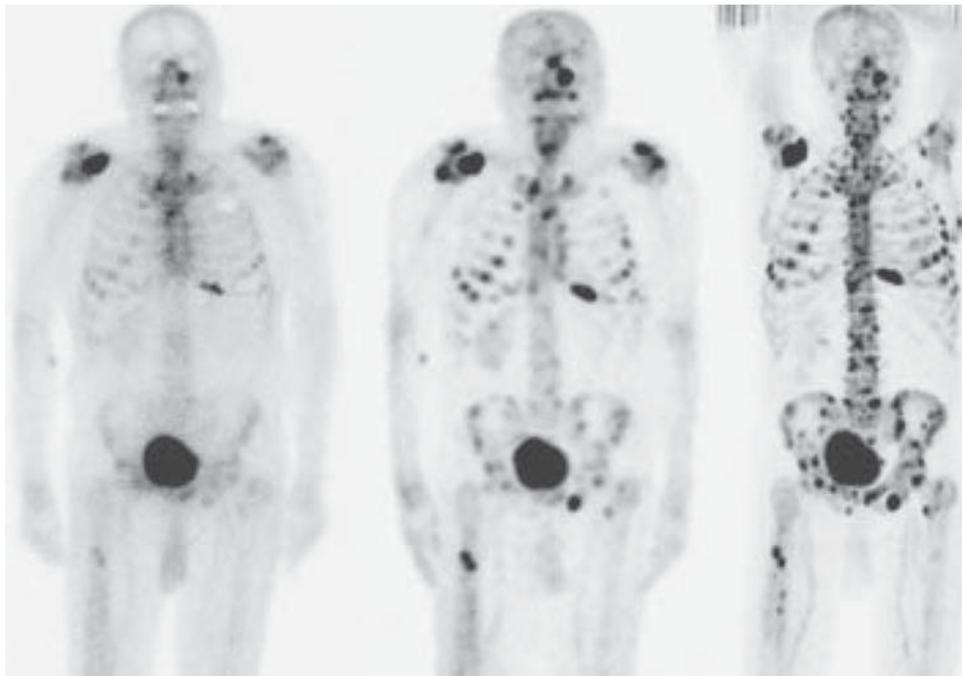
Figure 12.3 *Comparison of conventional planar bone-scan (left), 3D single photon emission tomography (SPECT) (centre) and ^{18}F PET (right) in the same patient with castrate-resistant prostate cancer and disseminated bone involvement.*

Table 12.2 Differing characteristics of alpha and beta particles

CHARACTERISTIC	ALPHA	BETA
Range (μm)	40–90	25–6000
Linear Energy Transfer (LET; keV/μm)	60–230	0.02–0.4
Relative mass	7000	1
DNA hits to kill a cell	1–5	100–1000
Cytotoxic against G_0 cells	Yes	No
Effective against 'radio-resistant' cells?	Yes	No

and analgesic reporting were, however, sparsely described. Duration of pain relief and analgesic consumption changes could not be ascertained from this initial randomized study.

Another small study involving 49 patients with CRPC utilized ^{89}Sr at an intravenous dose of 2 mCi or placebo administered monthly for three doses. This trial noted no pain differences in the treatment groups. However, the BSR group had a longer survival than did the placebo group.[43] No other randomized trial of ^{89}Sr monotherapy has demonstrated prolonged survival; thus these data need to be interpreted with caution.

In the first larger (n = 126) multi-centre placebo controlled study of ^{89}Sr, bone-metastatic CRPC patients requiring external beam radiation for palliation of bone pain were randomized to 10 mCi of ^{89}Sr or placebo immediately after completion of the external beam.[44] The dose utilized in this trial, conducted in multiple Canadian centres and termed the Trans-Canada Study, was higher than in any other of the randomized trials. Pre-defined end-points for this trial included analgesic use, new painful sites of metastatic bone disease, reduction of pain at the sites originally irradiated, and overall survival. No differences were noted in survival or the pain relief at the primary site, however there was a significant improvement in the ^{89}Sr arm for discontinuing analgesics (17% vs 2%) and in new sites of bone pain assessed three months after treatment. A subsequent follow-up prostate-specific antigen (PSA) analysis in this trial was conducted in a subset of 54 patients.[45] This subset analysis indicated that the mean time to PSA progression was relatively prolonged in the ^{89}Sr group; 19 vs 6 weeks with placebo, suggesting the possibility of

a direct anti-tumour effect (at least as assessed by PSA). The beneficial palliative findings in the Trans-Canada study were contradicted by results from a more recent large Norwegian study.[46] However, the discrepancy might reflect the considerable difference in injected dose, as the latter used the standard approved dose of 148 MBq (4 mCi) instead of the 10 mCi dose used in the Trans-Canada study.

In a comprehensive multi-centre study performed in 203 patients by the European Organisation for Research and Treatment of Cancer (EORTC), ^{89}Sr at a dose of 4 mCi was compared to local field radiation therapy for patients with pain and bone-metastatic CRPC.[47] Time to subjective progression was 3 months for each treatment arm and duration of pain response (among patients with a response) was approximately 4.5 months for each treatment. There were no statistically significant differences between the treatment arms for either the time to subjective progression or duration of pain response in responding patients.[47] The survival of ^{89}Sr treated patients was statistically significantly shorter as compared to the patients treated with local field radiotherapy alone (median 7.2 vs 11.0 months). Though no other trial has demonstrated shorter survival for ^{89}Sr treated patients, this relatively large randomized multi-centre trial raises concerns that survival could be compromised by treatment with this particular BSR.

In another large multi-centre prospective randomized trial, Quilty and colleagues[48] evaluated intravenous ^{89}Sr vs external beam radiation in a total of 284 men with advanced bone-metastatic CRPC. Patients were randomized between 5.3 mCi (single dose) and external beam radiation. A variety of well-defined end-points were assessed including pain at an index site, new painful sites, need for additional external beam radiation and overall survival. External beam radiation was administered either focally to the painful areas or as hemi-body radiation. For pain at the index site, each modality was effective in 61–66% of patients and no differences were noted between the various treatments. ^{89}Sr was more effective than the focal external beam in terms of preventing new painful sites and fewer patients in the BSR arm required subsequent external beam therapy. Median survival was only 21 weeks in this trial, indicating the treatment of far advanced patients, but no differences were noted by trial treatment arm.

Toxicity was reported as being minimal in each arm but patient follow-up was limited given the short lifespan of patients enrolled in the trial.

Samarium-153 study review

A BSR with shorter physical half-life, such as ^{153}Sm-EDTMP ($t_{\frac{1}{2}}$ of 1.9 days), may have the potential to facilitate more rapid bone marrow recovery. The first major randomized trial using ^{153}Sm was performed by Resche and colleagues.[49] This was a multi-centre, randomized, dose-controlled study performed in patients with a variety of tumours having painful bone metastases. One hundred and fourteen patients received a single dose of 0.5 mCi/kg (n = 55) or 1.0 mCi/kg (n = 59). Most patients (59%) had prostate cancer and 32% had breast cancer. Efficacy was evaluated by patient reported outcomes using evaluations of pain with visual analogue scale (VAS) score and diaries of opioid analgesic use. VAS scores significantly decreased for the 1.0 mCi/kg group 3 and 4 weeks post-dosing but the lower dose did not induce statistically significant changes. Long-term follow-up revealed a significantly longer survival among breast cancer patients receiving the higher dose compared to those treated with the low dose. However, such difference in survival was not observed for the prostate cancer patients.[49] No other trial of ^{153}Sm-EDTMP has demonstrated a survival advantage thus caution is urged in interpreting data from this small trial.

Serafini et al. conducted the first double-blind, placebo-controlled randomized study in a variety of cancer patients with bone metastases using ^{153}Sm-EDTMP.[50] A total of 118 patients were randomized 1:1:1 to receive single doses of placebo or ^{153}Sm-EDTMP at doses of 0.5 or 1.0 mCi/kg. Most patients had prostate cancer (n = 80) or breast cancer (n = 21). Patients who received the 1.0 mCi/kg dose of active drug exhibited significant improvements (as compared to the placebo group) in both pain scores at each of the first four weeks post-dosing. In contrast, the 0.5 mCi/kg dose demonstrated improvement in pain scores at week 1, but no other week. For patients receiving the 1.0 mCi/kg dose, two-thirds of those responding at week 4 were still responding at week 16.

In a trial targeted only to bone metastatic CRPC patients, Sartor and colleagues performed a multi-centre placebo-controlled study and enrolled 152 patients.[51] Patients were randomized in a 2:1 ratio to ^{153}Sm-EDTMP or placebo and were followed for up to 16 weeks. Pain was measured twice daily by patients using a VAS or a pain descriptor scale. Analgesic scores were also recorded daily. Patients randomized to receive the ^{153}Sm exhibited significant improvements in the VAS pain scores for weeks 2–4 ($P < 0.02$) and in the descriptor pain scores for weeks one through four. Cross-over for non-responding placebo-treated patients at four weeks prevented statistical analysis beyond that time point. Patients treated with ^{153}Sm also had significant decreases in opioid analgesic use during weeks 3 and 4.

▶ Comparison of different BSRs

One trial has compared, in a direct randomized fashion, ^{89}Sr to ^{153}Sm-EDTMP.[52] Baczyk et al. performed this study in a single Polish institution and randomized patients to receive either BSR. The study involved 100 patients, 60% with prostate cancer and the remainder with breast cancer. ^{89}Sr was used at a single dose of 4 mCi and ^{153}Sm at a single dose of 1 mCi/kg. Responses were measured at only one time point, two months after treatment. The authors concluded that 80% of patients responded in both arms. Analgesic use at the 2 month post-dosing time point was reduced by 45% and 55% in the ^{153}Sm and ^{89}Sr arms, respectively. Adverse events were not recorded in the usual fashion but 5 cases of severe pancytopenia were noted; 3 patients treated with ^{89}Sr and 2 patients treated with ^{153}Sm. Timing of the pancytopenia was not commented upon, neither were the kinetics of the response nor toxicity assessed in detail. This small and limited trial suggests that at two months after injection, both of these isotopes are effective in palliation.

A single institution German trial[30] evaluated ^{188}Re-HEDP, ^{186}Re-HEDP, ^{153}Sm-EDTMP and ^{89}Sr effects in 79 bone-metastatic patients (61 with prostate and 18 with breast cancer). The study was not a randomized study but pain scores and analgesic use were determined weekly after each treatment. Thirty-one patients were treated with ^{188}Re-HEDP, 15 patients with ^{186}Re-HEDP, 15 with ^{153}Sm-EDTMP, and 18 patients with ^{89}Sr. No apparent differences between the treatments were

reported in this non-randomized study; approximately 70% of patients receiving each treatment had pain improvements as measured using a VAS.

As noted above, one trial has compared ^{32}P and ^{89}Sr but this trial too also had a number of limitations. This single institution small randomized comparative trial conducted in India yielded similar outcomes.[38] Thirty-one patients with painful metastatic bone disease were treated with oral ^{32}P at 12 mCi or intravenous ^{89}Sr at 4 mCi. Pain score declines of >50% were observed in 14/16 subjects in the ^{32}P arm and in 14/15 subjects in the ^{89}Sr arm. Surprisingly, no toxicity issues were noted after either treatment. This trial emphasizes the potential utility of ^{32}P as a palliative agent and has implications for cost-conscious health systems given the relatively low costs of procuring this radiopharmaceutical in many countries. Countries with limited access to traditional external beam radiotherapy may find BSRs a particularly cost-effective palliative approach for patients with bone-metastatic cancers.

▶ Repeated BSR dosing

Studies with repeated BSR dosing are limited, and [153]Sm-EDTMP and [223]Ra (see below) are the only BSRs to date with significant trials reporting repeated dosing. For [153]Sm, retreatment has primarily been reported in the setting of an initial palliative response followed by symptom recurrence in patients with good bone marrow function. Sartor *et al.* reported on 54 multiple administrations to 18 patients (range 2–11 doses/patient) with prostate (n = 15) and breast (n = 3) cancer.[53] Percentage decreases from baseline in white blood cell (WBC) and platelet (PLT) counts did not increase as a function of increasing number of administrations and there was no significant increase in the percentage of patients with Grade 3 or 4 hematologic toxicities.

▶ Alpha-particle emitting BSR

Radium-223 is a natural bone-seeker that binds to hydroxyapatite as a calcium mimetic. It decays with a physical half-life of 11.4 days by releasing a series of alpha-particles through a series of daughters before reaching a stable isotope of lead.[54] Alpha-emitters are relatively heavy charged particles (helium nuclei with two positive charges) that produce high-linear energy transfer (LET) radiation with a tissue range of <100 micrometres. In contrast, beta-emitting radioisotopes have a relatively low radiobiological effects and a track length in tissues of up to several millimetres (Table 12.1). In comparison with ^{89}Sr and [153]Sm-EDTMP, a bone-seeking alpha-emitter might therefore have a greater anti-tumour effect, by virtue of high LET radiation, but with relative sparing of the bone marrow due to the short track length. This much more energetic and localized radiation is virtually dose-rate independent resulting in potent cell-killing via double-strand break DNA damage (Table 12.2). The induction of predominantly non-reparable double DNA-strand breaks renders an alpha-emitting BSR such as [223]Ra an intriguing alternative to the beta-emitters.[54–56] Such dense irradiation may provide an important advantage in patients with both chemo-naïve and chemoresistant disease as the mechanisms of alpha-particle cytotoxicity are independent of the mechanisms of chemotherapy resistance. In addition, micrometastases with dormant clonogenic tumour cells residing in cell cycle growth phase G0 may be eliminated by alpha-emitters as a consequence of high LET radiation.[54,55]

In its chloride formulation [223]Ra has been studied extensively in pre-clinical models. In mice, the biodistribution of [223]Ra has been shown to correspond to that of ^{89}Sr, with targeting of the bony skeleton, and with retention of its various daughter isotopes within the inorganic bone matrix.[57] Modelling the dose deposition in relation to tumour deposits within the bone marrow suggests a significant reduction in dose to the normal bone marrow with [223]Ra in comparison with [89]Sr.[57] In a rat model of metastatic breast cancer, [223]Ra showed significant anti-tumour effects in the absence of bone marrow toxicity.[58] Animals treated with ≥100 kBq/kg radium-223 had 40% survival beyond the 67-day follow-up period compared to 0% in control animals. Treatment with conventional chemotherapeutics, a beta-emitting BSR or the bis-phosphonate pamidronate gave no survival benefit in this animal model.

Alpha-emitters are more toxic than beta-emitters when comparing effects on single cells. These
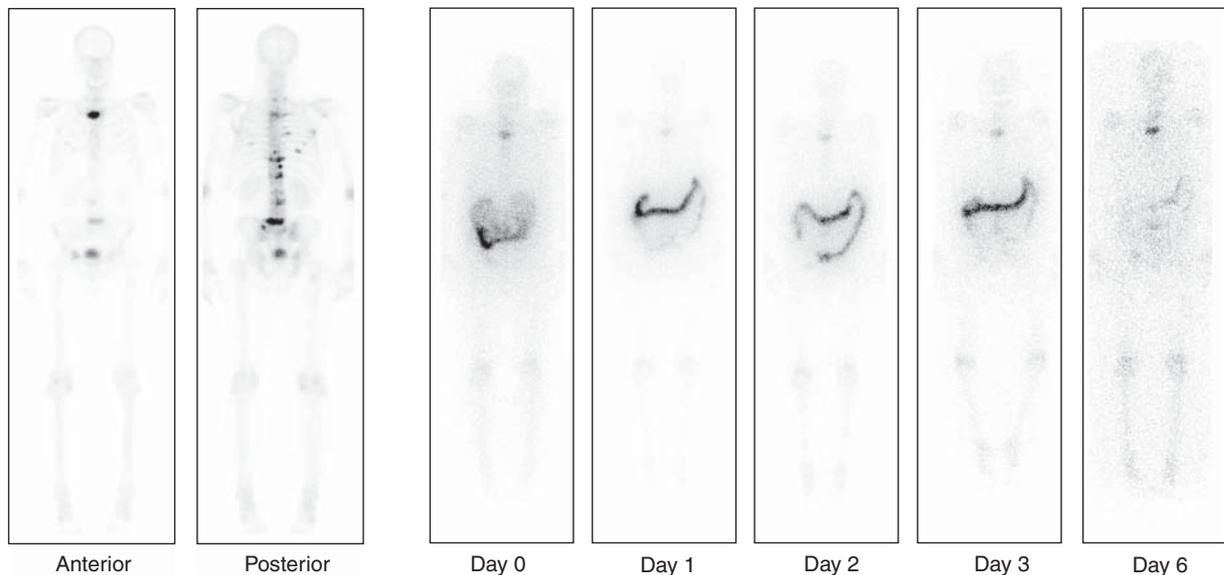
Figure 12.4 *A diagnostic bone scan by Tecnetium-99 m MDP (left) and gamma camera images of radium-223 (right) illustrating corresponding uptake in osteoblastic metastases in a patient with metastatic prostate cancer, and excretion via the intestine. Images courtesy of The Royal Marsden Hospital.*

potentially adverse properties can be compensated for because of the potential for alpha-particles to radiate much smaller volumes of normal cells given their short-track length.[54,55] This feature results in smaller dose delivered to the haematopoetic bone marrow.[57] On the other hand, the spatial distribution of the hydroxyapatite target within an osteoblastic metastasis (Figure 12.2) provides a volume distribution of the radionuclide. This makes it less likely that tumour cells evade the alpha-particles despite the limited track lengths. The promise of targeting tumour stem cells has been much discussed,[14] and the targeted alpha-particle approach might be capable of eliminating the stem cells thought to be at the source of the problem in metastatic solid tumours.

A phase I trial of a single i.v. injection of Alpharadin was performed in 25 patients with metastatic bone disease, comprising 15 patients with CRPC and 10 with metastatic breast cancer.[59] Administered activities up to 250 kBq/kg were well tolerated; with reversible grade 3 leucopenia in 3/25 patients and no grade 2+ thrombocytopenia. Dose-limiting toxicity was not observed at these doses after a single injection. Excretion of [223]Ra is mainly through the intestine (Figure 12.4).

Results from a phase II randomized clinical trial of external beam radiation plus either saline or [223]Ra injections (given 4 times at 4-week intervals) gave promising results on survival.[33] Radium-223 treatment resulted in a statistically significant decrease in both bone-stromal markers such as bone alkaline phosphatase and prostate cancer tumour markers (PSA). A favourable adverse event profile was observed with minimal bone marrow toxicity for patients who received [223]Ra. A significant adjusted overall survival benefit for [223]Ra was observed in this randomized phase II,[33] which in turn led to a large phase III trial known as ALSYMPCA (Alpharadin in the treatment of patients with symptomatic bone metastases in castration-resistant prostate cancer). Eligibility criteria for the ALSYMPCA trial required symptomatic bone-metastatic CRPC with a minimum of two or more bone lesions detected on bone scintigraphy. Patients could have no visceral metastases and no soft-tissue metastases measuring more than 3 cm. Patients were required to have progressed despite prior docetaxel, have not been fit enough to receive docetaxel, have not been willing to receive docetaxel, or have been treated at a site where docetaxel was not available. The treatment arms for the phase III trial (see Clinicaltrials.gov NCT00699751) were straight forward. Patients were randomized 2:1 to best standard of care and 50 kBq/kg intravenous [223]Ra every 4 weeks for six

Table 12.3   **Phase III trials including symptomatic metastatic CRPC patients that report a survival benefit**

REFERENCE	TRIAL DESIGN: EXPERIMENTAL AND CONTROL ARMS	MEDIAN SURVIVAL (MONTHS)	PROLONGATION IN MEDIAN SURVIVAL	HAZARD RATIO (SURVIVAL)
Petrylak et al.[79]	Docetaxel/estramustine vs mitoxantrone/prednisone	17.5 vs 15.6	1.9	0.80
Tannock et al.[80]	Docetaxel/prednisone vs mitoxantrone/prednisone	18.9 vs 16.5	2.4	0.76
De Bono et al.[81]	Cabazitaxel/prednisone vs mitoxantrone/prednisone	15.1 vs 12.7	2.4	0.70
De Bono et al.[82]	Abiraterone/prednisone vs placebo/prednisone	14.8 vs 10.9	3.9	0.65
Parker et al.[34]	Radium-223/best supportive care vs placebo/best supportive care	14.0 vs 11.2	2.8	0.70

cycles, or to placebo plus best standard of care. Best standard of care allowed in the ALSYMPCA trial including various hormonal manipulations and palliative external beam radiation. Chemotherapy, other BSRs and hemi-body radiation were not allowed during the trial treatment period. The trial enrolled 922 patients from 19 countries in Europe, Australia, Canada and the USA.

In the statistical analysis for ALSYMPCA, the primary end-point was overall survival. Patients were stratified for bisphosphonates use (yes or no), prior docetaxel use (yes or no) and for alkaline phosphatase levels (more or less than 220 U/L). The trial was powered for a 90% power with a projected hazard ratio of 0.76 using a two-sided alpha of 0.05. There was one pre-planned interim analysis at 320 events with a pre-specified P value of 0.00306. A total of 640 events were planned for the final analysis. In addition to overall survival, a variety of secondary end-points were pre-specified including time to first skeletal-related event (external beam radiotherapy to bone, spinal cord compression, fracture, or surgery to bone), PSA progression, and time to alkaline phosphatase progression.

At the pre-planned interim analysis, the trial was stopped by the independent data-safety and monitoring committee as a consequence of meeting the pre-defined overall survival end-point with a hazard ratio of 0.699 ($P = 0.0022$). These data are comparable to other therapies in advanced prostate cancer (see Table 12.3). Date from secondary end-points were all in favor of radium-223 and these

results have been presented as a late-breaking abstract at the European Society of Medical Oncology (ESMO) 2011 meeting in Stockholm.[34] The median survival in the placebo group was 11.2 months as compared to the median survival in the radium-223 group of 14.0 months. The lack of toxicity in this large phase III trial was notable. Adverse events were more common in the placebo group. Grade 3 or 4 neutropenia was 2% and grade 3 or 4 thrombocytopenia was 4%. No other grade 3 or 4 toxicity varied by treatment arm, in fact the overall serious adverse event (SAE) rate was lower in the ^{223}Ra group as compared to the placebo group. These data underscore not only the effectiveness of this alpha-particle BSR, but also the safety in large scale clinical trials.

▶ Combination of BSRs and chemotherapy

Several clinical studies to date have reported on the feasibility of combining BSRs and chemo-therapy.[60–65] A renewed interest is seen nowadays,[66] with recent studies employing concomitant use of BSRs and chemotherapy showing that apart from feasible, the combination also seems effective.

Provocative randomized studies with BSRs (^{89}Sr) and chemotherapeutics were reported nearly a decade ago in prostate cancer.[60] The largest

[89]Sr/chemotherapy trial was performed at MD Anderson in bone-metastatic CRPC patients and the randomization was between ^{89}Sr in combination with weekly doxorubicin for 6 doses or doxorubicin alone following an 'induction' chemotherapy.[60] A total of 103 patients received the induction chemotherapy consisting of ketoconazole, adriamycin, vinblastine and estramustine and 72 patients were randomized. Patients that were unable to tolerate the chemotherapy, or those patients who progressed despite the induction were not randomized. In patients randomized to ^{89}Sr, median progression-free survival (13 vs 7 months) and median overall survival (28 vs 19 months) were significantly improved as compared to doxorubicin alone. Follow-up data from larger trials are currently lacking but these results are both substantial and important and need verification in an independent and larger study.

Recent studies have renewed the interest in combining BSRs and chemotherapy. Both of these recent studies used [153]Sm-EDTMP and docetaxel in bone metastatic CRPC patients. Morris et al. used docetaxel at 75 mg/M^2 q 3 weeks (considered as the standard of care for this agent) added a dose escalated [153]Sm-EDTMP in a repetitive fashion.[67] Interestingly full doses (1 mCi/kg) of [153]Sm q 6 weeks could be relatively safely administered in combination with 75 mg/m^2 docetaxel q 3 weeks. Dose-limiting toxicity was thrombocytopenia in this small phase I trial. A small number of deemed 'docetaxel-refractory' patients responded to a combinations of [153]Sm-EDTMP and docetaxel suggesting that the combination of these agents is able to reverse docetaxel resistance. If confirmed, these findings have major significance. Randomized studies are planned using these agents in combination for patients with advanced prostate cancer.

In another recent study reported by Fizazi et al., estramustine/docetaxel q 3 weeks were planned and stable/responding bone metastatic prostate cancer patients after 4 cycles were treated with a single dose of [153]Sm-EDTMP combined with docetaxel doses at 20 mg/m^2 q week × 6 doses.[68] Toxicity was minimal, only two episodes of grade 3 thrombocytopenias were observed after combined therapy. The median overall survival was 29 months, which is beyond that expected for patients with this disease state. Large trials with docetaxel alone suggest median survivals in the range of 19 months. Additional studies will be needed to determine if these results can be replicated but both the Fizazi and Morris studies indicate the promise of a combined modality approach, at least in prostate cancer patients.

Studies with [223]Ra and docetaxel in bone metastatic CRPC are ongoing but have yet to be reported. This combination of agents may be particularly interesting given the relatively low myelosuppression of the alpha-emitter, the effect of [223]Ra in prolonging survival, the possible synergy between these two agents and the ability to deliver repeated doses of [223]Ra with little toxicity.

Combination of BSRs and chemotherapy has also been reported in osteosarcoma with several interesting results. The characteristic feature of osteosarcoma is the formation of osteoid; i.e. primitive bone matrix produced by the malignant cells per se. Following the initial experiences with [153]Sm-EDTMP alone,[69,70] fourteen patients with osteoblastic lesions were treated with a large dose of (30 mCi/kg) [153]Sm-EDTMP and gemcitabine, a known radiosensitizer, administered 1 day after [153]Sm. Patients then received autologous stem cell reinfusion 2 weeks later.[71] Toxicity was restricted to bone marrow suppression which was important to know given that other potential toxicity was considered to be a possibility prior to therapy. At the 6–8-week assessment, there were six partial remissions and two mixed responses but unfortunately these responses were not durable.[71]

Multiple myeloma is not usually viewed as a disease appropriate for BSRs given the presence of lytic bone metastases, but pretreatment with bisphosphonates or bortezomib may change the equilibrium of the lytic/blastic phenotype sufficiently to allow BSR targeting. This concept of therapeutic stromal manipulation may also be of significance in other cancers with lytic bone disease such as breast cancer (Figure 12.5) and lung cancer. Trials in multiple myeloma are limited but data using [153]Sm-EDTMP/ bortezomib combinations have been published with interesting results.[72] Patients were enrolled in six cohorts and given bortezomib on days 1, 4, 8 and 11 and [153]Sm in a dose escalating fashion (0.25, 0.5 or 1.0 mCi/kg) on day 3 of a 56-day cycle. The most common toxicities were neutropenia and thrombocytopenia. Dose-limiting toxicity was reached at 0.5 mCi/kg [153]Sm-EDTMP in combination with
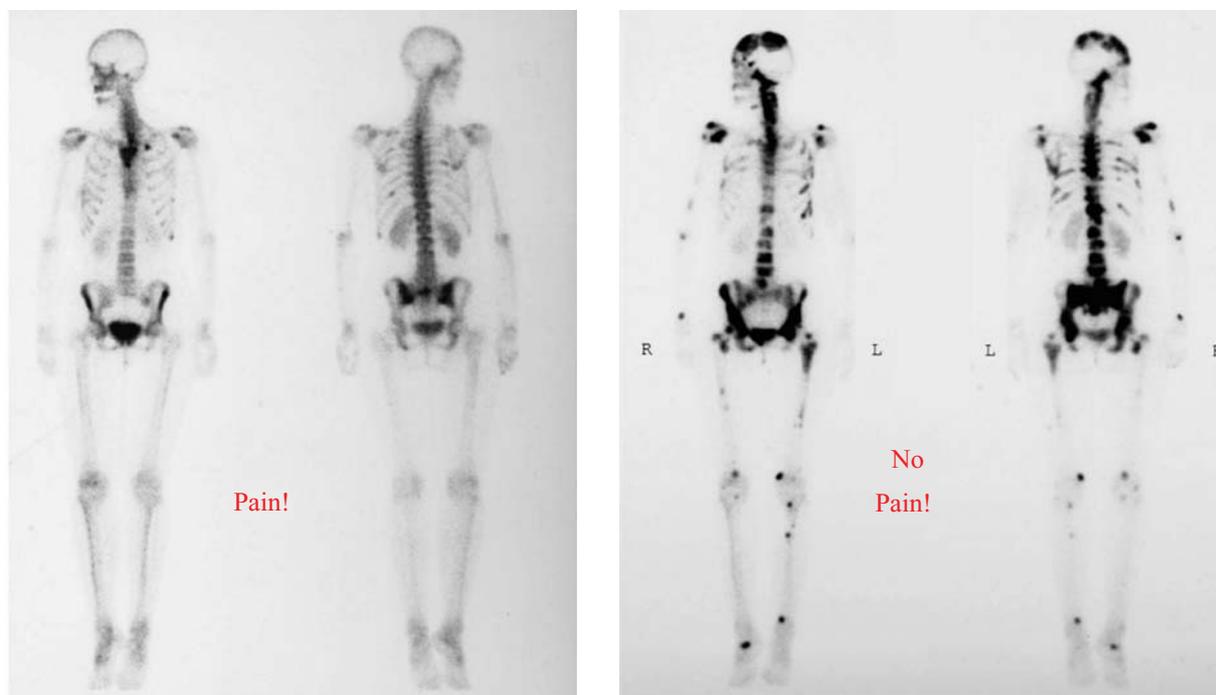
Figure 12.5 *Increased uptake on a diagnostic* ^{99m}*Tc-MDP bone scan in a breast cancer patient before and during bisphosphonate therapy (left panel: at initiation of bisphosphonate therapy having painful skeletal metastases; right panel: after 6 months of therapy – with virtually no pain). Note that the increased bone scan uptake change from mixed lytic/blastic to pronounced sclerotic phenotype induced by bisphosphonate treatment that should correlate with increased targeted uptake by a therapeutic BSR.*

1.3 mg/m² bortezomib, in the schedule noted above. Responses occurred in some patients refractory to bortezomib alone suggesting synergy between the two agents.

Combination of BSRs and bisphosphonates

Several studies have shown that the combination of BSRs and bisphosphonates is feasible and seems effective.[73–76] No study has ever shown that the efficacy or uptake of BSRs is inhibited by bisphosphonate administration. From our perspective we see no reason that these agents cannot be administered in proximity to one another[77]. There is a theoretically beneficial rational for combining BSRs and agents such as bisphosphonates (or denosumab) given the propensity of these bisphosphonates to enhance the blastic/lytic ratios of bone metastatic lesions[77]. More blastic lesions are more likely to have enhanced BSR uptake

compared to more lytic lesions (Figure 12.5). In the ALSYMPCA trial, the stratified analysis of patients treated with both ^{223}Ra and bisphosphonates, had a particular positive result (HR 0.582) which provides credence to the hypothesis that there could be a positive interaction between BSRs and agents which diminish osteolytic activity.[34]

Current clinical indications and future perspectives

BSR therapy today with beta-emitting isotopes is clinically indicated in the context of bone pain attributable to cancerous bone lesions with avid tracer uptake on a diagnostic bone scan. If, as anticipated, ^{223}Ra is approved by regulatory agencies in bone metastatic CRPC, we regard this as a watershed event. This agent is the first BSR to prolong survival in a large phase III trial and the first alpha-pharmaceutical to be applied in large scale trials in human disease.

Imaging studies are necessary given that the presence of an osteoblastic reaction provides the target necessary for selective uptake of all the BSRs (Figure 12.1). Virtually all clinical studies utilized patient populations with osteoblastic lesions, typically those having increased uptake on a ^{99m}Tc-MDP bone scan but we point out that relative to other forms of bone-lesion imaging (such as F18 NaF PET imaging) traditional bone scans vastly under-estimate the extent of bone-metastatic disease (Figure 12.3). This has important therapeutic implications given the currently available BSR data.

Following i.v. administration of a beta-emitting BSR, bone marrow is an innocent bystander and unequivocally the dose-limiting organ. Due to the mm-range of beta-emissions (Table 12.1), the cross-irradiation of the bone marrow represents an ever-present concern. Leucopenia and in particular thrombocytopenia severely limits the clinical use of the FDA approved beta-emitting BSRs, especially when dosages are increased to deliver potential anti-tumour radiation levels and/or repeated treatments are attempted. Furthermore, disease-associated bone marrow suppression, and suppression associated with previous or concomitant chemotherapy, is often already present in these patients.

In slight contrast to the experience from selected patients in published clinical trials, the general clinical experience is that beta-emitting BSRs too often may result in delayed and unpredictable recovery of bone marrow function. Clinical trials were predominantly performed in chemo-naïve patients but in practice, many patients have been pretreated with chemotherapy before the BSR are administered. The other concern is that the use of future chemotherapy will be compromised and some studies addressing the topic may be interpreted in this way.[64] Economic issues regarding chemotherapy and BSR use is also an issue that has influenced usage in the United States.[78] Economic incentives for chemotherapy administration have decreased in recent years, thus perhaps newer BSRs may have more favourable usage patterns in the future as compared to the past. The finding that survival is altered by ^{223}Ra in advanced prostate cancer patients promises to dramatically change the way this BSR is used in the future.

All BSR therapy should be viewed in the context of other therapeutic choices. For patients with extensive soft-tissue and/or visceral disease, bone lesions may represent only a small proportion of the cancer volume and thus use of BSRs may be inappropriate. For patients with diseases known to be highly chemo- or hormonally-responsive, systemic treatment with appropriate non-isotopic agents may be appropriate. For patients with limited symptomatic bone disease, external beam radiation is a leading option. For those patients with risk of pathologic fractures or spinal cord compression, priority must be given to treatment of those

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Box 12.1   Indications and relative contraindications for palliative use of bone-seeking radiopharmaceuticals

- Histologic diagnosis of cancer required
- Increased uptake on a diagnostic radionuclide bone scan mandatory
  - Lack of uptake (such as osteolytic lesions) implies poor BSR targeting
- Bone pain attributable to the cancer, requiring analgesic medications, and correlated with bone scan findings
  - Significant soft-tissue component of the pain make BSR a sub-optimal choice
- Assessment for spinal cord compression, pathologic fracture, or high risk for pathologic fracture
  - These conditions require specialized and non-BSR management strategies
- Ascertainment of past therapeutic interventions and current options
  - Single lesions or regional pain may best be treated with external beam radiation
- Assessment of bone marrow function and reserve by complete blood counts
- Assessment of renal function to assess disposition of the radioisotope
- Careful discussions with patients regarding possibility of pain flare and post-injection monitoring requirements (isotope dependent)

conditions. Careful analysis of these and other factors are required before BSR administration (see Box 12.1).

In addition to indications such as those listed above, contraindications to BSR should also be reviewed prior to administration (Box 12.1). Currently approved BSRs may induce leucopenia and thrombocytopenia thus haematological analysis is required pretreatment. For [153]Sm-EDTMP, clearance is via renal excretion and experience in patients with compromised renal status is quite limited. [89]Sr, too, is partially cleared via the kidneys, thus caution is also advised for those with poor renal function. Interestingly [223]Ra appears to be excreted primarily via the small bowel (Figure 12.4) and this isotope may prove to be safe in those with renal compromise.

Future perspectives in the field of BSRs are bright. [223]Ra prolonging survival in a large phase III trial will invigorate the field. In addition novel studies with [223]Ra are being planned to take advantage of potential synergy between this novel BSR and other therapies including both immune-modulating agents and chemotherapy. Additional studies on these concepts are planned and given the current excitement in the field, we anticipate that much progress will occur over the next several years.

◗ Disclosures

Dr Bruland is a patent holder for radium-223, minority stockholder of Algeta, and scientific advisory board member for Algeta.

Dr Sartor is an Investigator for Algeta and Cytogen, Consultant to Algeta and Bayer.

◗ References

1   British Association of Surgical Oncology 1999 The management of metastatic bone disease in the United Kingdom. *Eur J Surg Oncol* **25** 3–23.

2   Hage WD 2000 Incidence, location, and diagnostic evaluation of metastatic bone disease. *Orthop Clin N Am* **31** 515–528.

3   Nielsen OS, Munro AJ, Tannock IF 1991 Bone metastases: pathophysiology and management policy. *J Clin Oncol* **9** 509–524.

4   Lipton A, Berenson JR, Body JJ, *et al.* 2006 Advances in treating metastatic bone cancer: summary statement for the First Cambridge Conference. *Clin Cancer Res* **12** 6209s–6212s.

5   Guise TA, Mundy GR 1998 Cancer and bone. *Endocr Rev* **19** 18–54.

6   Franks LM, Riddle AW, Carbonell AW, *et al.* 1970 A comparative study of the ultrastructure and lack of growth capacity of adult human prostate epithelium mechanically separated from its stroma. *J Pathol* **100** 113–119.

7   Chung LW, Anderson NG, Neubauer BL, *et al.* 1981 Tissue interactions in prostate development: roles of sex steroids. *Prog Clin Biol Res* **75A** 177–203.

8   Chung LW, Cunha GR 1983 Stromal-epithelial interactions: II. Regulation of prostatic growth by embryonic urogenital sinus mesenchyme. *Prostate* **4** 503–511.

9   Yates C 2011 Prostate tumor cell plasticity: a consequence of the microenvironment. *Adv Exp Med Biol* **720** 81–90.

10   Sikes RA, Nicholson BE, Koeneman KS, *et al.* 2004 Cellular interactions in the tropism of prostate cancer to bone. *Int J Cancer* **110** 497–503.

11   Lin SH, Cheng CJ, Lee YC, *et al.* 2008 A 45-kDa ErbB3 secreted by prostate cancer cells promotes bone formation. *Oncogene* **27** 5195–5203.

12   Roudier MP, Morrissey C, True LD, *et al.* 2008 Histopathological assessment of prostate cancer bone osteoblastic metastases. *J Urol* **180** 1154–1160.

13   Loberg RD, Logothetis CJ, Keller ET, *et al.* 2005 Pathogenesis and treatment of prostate cancer bone metastases: targeting the lethal phenotype. *J Clin Oncol* **23** 8232–8241.

14   Tu SM, Lin SH, Logothetis CJ 2002 Stem-cell origin of metastasis and heterogeneity in solid tumours. *Lancet Oncol* **8** 508–513.

15   Hussain M, Smith MR, Sweeney C, *et al.* 2011 Cabozantinib (XL184) in metastatic castration-resistant prostate cancer (mCRPC): results from a phase II randomized discontinuation trial. *J Clin Oncol* **29** (Suppl) abstract 4516.

16   Sze WM, Shelley M, Held I, *et al.* 2003 Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy – a systemic review of randomized trials. *Clin Oncol* **15** 345–352.

17   Chow E, Harris K, Fan G, *et al.* 2007 Palliative radiotherapy trials for bone metastases: a systemic review. *J Clin Oncol* **25** 1423–1436.

18   Bruland ØS, Hird A, Chow E 2008 Radiotherapy of skeletal metastases. In *Primer on the Metabolic Bone*

Diseases and Disorders of Mineral Metabolism, 7th Edn, pp 404–407. Eds CJ Rosen, JE Compston, J Lian. Washington DC, USA: American Society for Bone and Mineral Research.

19 Koswig S, Budach V 1999 Remineralization and pain relief in bone metastases after different radiotherapy fractions (10 times 3 Gy vs. 1 time 8 Gy). A prospective study. *Strahlenther Onkol* **175** 500–508.

20 Jeremic B, Shibamoto Y, Igrutinovic I 1999 Single 4 Gy re-irradiation for painful bone metastasis following single fraction radiotherapy. *Radiother Oncol* **52** 123–127.

21 Silberstein EB 2000 Systemic radiopharmaceutical therapy of painful osteoblastic metastases. *Semin Radiat Oncol* **10** 240–249.

22 Pandit-Taskar N, Batraki M, Divgi CR 2004 Radiopharmaceutical therapy for palliation of bone pain from osseous metastases. *J Nucl Med* **45** 1358–1365.

23 Lewington VJ 2005 Bone-seeking radionuclides for therapy. *J Nucl Med* **46** 38s–47s.

24 Finlay IG, Mason MD, Shelley M 2005 Radioisotopes for the palliation of metastatic bone cancer: a systematic review. *Lancet Oncol* **6** 392–400.

25 Bauman G, Charette M, Reid R, *et al.* 2005 Radiopharmaceuticals for the palliation of painful bone metastases – a systematic review. *Radiother Oncol* **75** 258.e1–258.e13.

26 Reisfield GM, Silberstein EB, Wilson GR 2005 Radiopharmaceuticals for the palliation of painful bone metastases. *Am J Hosp Palliat Care* **22** 41–46.

27 de Klerk JM, van het Schip AD, Zonnenberg BA, *et al.* 1996 Phase 1 study of rhenium-186-HEDP in patients with bone metastases originating from breast cancer. *J Nucl Med* **37** 244–249.

28 Palmedo H, Guhlke S, Bender H, *et al.* 2000 Dose escalation study with rhenium-188 hydroxyethylidene diphosphonate in prostate cancer patients with osseous metastases. *Eur J Nucl Med* **27** 123–130.

29 Palmedo H, Manka-Waluch A, Albers P, *et al.* 2003 Repeated bone-targeted therapy for hormone-refractory prostate carcinoma: randomized phase II trial with the new, high-energy radiopharmaceutical rhenium-188 hydroxyethylidenediphosphonate. *J Clin Oncol* **21** 2869–2875.

30 Liepe K, Korzerke J 2007 A comparative study of 188Re-HEDP, 186Re-HEDP, 153 Sm-EDTMP and ^{89}Sr in the treatment of painful skeletal metastases. *Nucl Med Commun* **28** 623–630.

31 Krishnamurthy GT, Swailem FM, Srivastava SC, *et al.* 1997 Tin-117 m(4+)DTPA: pharmacokinetics and imaging characteristics in patients with metastatic bone pain. *J Nucl Med* **38** 230–237.

32 Srivastava SC, Atkins HL, Krishnamurthy GT, *et al.* 1998 Treatment of metastatic bone pain with tin-117m stannic diethylenetriaminepentaacetic acid: a phase I/II clinical study. *Clin Cancer Res* **4** 61–68.

33 Nilsson S, Franzén L, Parker C, *et al.* 2007 Bone-targeted radium-223 in symptomatic, hormone refractory prostate cancer: a randomized, placebo-controlled, phase 2 study. *Lancet Oncol* **8** 587–594.

34 Parker C, Heinrich D, O'Sullivan JM, *et al.* 2011 Overall survival benefit of radium-223 chloride (Alpharadin) in the treatment of patients with symptomatic bone metastases in castration-resistant prostate cancer (CRPC): a phase III randomized trial (ALSYMPCA). *Eur J Cancer* **47**(Suppl 2) 3.

35 Friedell HL, Storaasli JP 1950 The use of radioactive phosphorus in the treatment of carcinoma of the breast with widespread metastases to bone. *Am J Roentgenol Radium Ther* **64** 559–575.

36 Kaplan E, Fels IG, Kotlowski BR, *et al.* 1960 Therapy of carcinoma of the prostate metastatic to bone with P32 labeled condensed phosphate. *J Nucl Med* **1** 1–13.

37 Silberstein EB 1993 The treatment of painful osseous metastases with phosphorus-32-labeled phosphates. *Semin Oncol* **20** (Suppl 2) 10–21.

38 Nair N 1999 Relative efficacy of ^{32}P and ^{89}Sr in palliation in skeletal metastases. *J Nucl Med* **40** 256–261.

39 Silberstein EB, Williams C 1985 Strontium-89 therapy for the pain of osseous metastases. *J Nucl Med* **26** 345–348.

40 Blake GM, Zivanovic MA, Blaquiere RM, *et al.* 1988 Strontium-89 therapy: measurement of absorbed dose to skeletal metastases. *J Nucl Med* **29** 549–557.

41 Silberstein EB 1996 Dosage and response in radiopharmaceutical therapy of painful osseous metastases. *J Nucl Med* **37** 249–252.

42 Lewington VJ, McEwan AJ, Ackery DM, *et al.* 1991 A prospective, randomised double-blind crossover study to examine the efficacy of strontium-89 in pain palliation in patients with advanced prostate cancer metastatic to bone. *Eur J Cancer* **27** 954–958.

43 Buchali K, Correns HJ, Schuerer M, *et al.* 1988 Results of a double blind study of 89-strontium therapy of skeletal metastases of prostatic carcinoma. *Eur J Nucl Med* **14** 349–351.

44 Porter AT, McEwan AJB, Powe JE, *et al.* 1993 Results of a randomized phase III trial to evaluate the efficacy of strontium-89 adjuvant to local field external-beam irradiation in the management of endocrine-resistant metastatic prostate cancer. *Int J Radiat Oncol Biol Phys* **25** 805–813.

45 Porter AT, Crispen RG, Sadasiban R, *et al.* 1997 Tumoricidal effect of strontium-89 in prostate cancer

based on PSA and pain delay. Presented at the 1997 ASCO Annual Meeting, abstract 1214.

46   Smeland S, Erikstein B, Aas M, *et al*. 2003 Role of strontium-89 as adjuvant to palliative external beam radiotherapy is questionable: results of a double-blind randomized study. *Int J Radiat Oncol Biol Phys* **56** 1397–1404.

47   Oosterhof GO, Roberts JT, de Reijke TM, *et al*. 2003 Strontium (89) chloride versus palliative local field radiotherapy in patients with hormonal escaped prostate cancer: a phase III study of the European Organisation of Research and Treatment of Cancer, Genitourinary Group. *Eur Urol* **44** 519–526.

48   Quilty PM, Kirk D, Bolger JJ, *et al*. 1994 A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. *Radiother Oncol* **31** 33–40.

49   Resche I, Chatal JF, Pecking A, *et al*. 1997 A dose-controlled study of ^{153}Sm-ethylenediaminetetra-methylenephosphonate (EDTMP) in the treatment of patients with painful bone metastases. *Eur J Cancer* **33** 1583–1591.

50   Serafini AN, Houston SJ, Resche I, *et al*. 1998 Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. *J Clin Oncol* **16** 1574–1581.

51   Sartor O, Reid RH, Hoskin PJ, *et al*. 2004 Samarium-153-lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. *Urology* **63** 940–945.

52   Baczyk M, Czepczyński R, Milecki P, *et al*. 2007 ^{89}Sr versus ^{153}Sm-EDTMP: comparison of treatment efficacy of painful bone metastases in prostate and breast carcinoma. *Nucl Med Commun* **28** 245–250.

53   Sartor O, Reid RH, Bushnell DL, *et al*. 2007 Safety and efficacy of repeat administration of samarium Sm-153 lexidronam to patients with metastatic bone pain. *Cancer* **109** 637–643.

54   Bruland ØS, Jonasdottir TJ, Fisher DR, *et al*. 2008 Radium-223: from radiochemical development to clinical applications in targeted cancer therapy. *Curr Radiopharmaceuticals* **1** 203–208.

55   Bruland ØS, Nilsson S, Fisher DR, *et al*. 2006 High-linear energy transfer irradiation targeted to skeletal metastases by the alpha-emitter 223Ra: adjuvant or alternative to conventional modalities? *Clin Cancer Res* **12** 6250s–6257s.

56   Hall EJ 2000 *Radiology for the Radiologist*, 5th Edn, pp 112–123. Philadelphia, PA, USA: Lippincott Williams & Wilkins.

57   Henriksen G, Fisher DR, Roeske JC, *et al*. 2003 Targeting of osseous sites with alpha emitting 223Ra: comparison with beta emitter ^{89}Sr in mice. *J Nucl Med* **74** 252–259.

58   Henriksen G, Breistøl K, Bruland, ØS *et al*. 2002 Significant antitumor effect from bone-seeking, alpha particle-emitting radium-223 demonstrated in an experimental skeletal metastases model. *Cancer Res* **62** 3120–3125.

59   Nilsson S, Larsen RH, Balteskard L, *et al*. 2005 First clinical experiences with alpha emitter radium-223 in the treatment of skeletal metastases from breast and prostate cancer. *Clin Cancer Res* **11** 4451–4459.

60   Tu SM, Millikan RE, Mengistu B, *et al*. 2001 Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomized phase II trial. *Lancet* **357** 336–341. Erratum *Lancet* **357** 1210.

61   Sciuto R, Festa A, Rea S, *et al*. 2002 Effects of low-dose cisplatin on ^{89}Sr therapy for painful bone metastases from prostate cancer: a randomized clinical trial. *J Nucl Med* **43** 79–86.

62   Akerley W, Butera J, Wehbe T, *et al*. 2002 A multiinstitutional, concurrent chemoradiation trial of strontium-89, estramustine, and vinblastine for hormone refractory prostate carcinoma involving bone. *Cancer* **94** 1654–1660.

63   Pagliaro LC, Delpassand ES, Williams D, *et al*. 2003 A phase I/II study of strontium-89 combined with gemcitabine in the treatment of patients with androgen independent prostate carcinoma and bone metastases. *Cancer* **97** 2988–2994.

64   Tu SM, Kim J, Pagliaro LC, *et al*. 2005 Therapy tolerance in selected patients with androgen-independent prostate cancer following strontium-89 combined with chemotherapy. *J Clin Oncol* **23** 7904–7910.

65   Tu SM, Mathew P, Wong FC, *et al*. 2009 Phase I study of concurrent weekly docetaxel and repeated samarium-153 lexidronam in patients with castration-resistant metastatic prostate cancer. *J Clin Oncol* **27** 3319–3324.

66   Sartor O 2009 Radiopharmaceuticals and chemotherapy combinations in metastatic castrate-resistant prostate cancer: a new beginning. *J Clin Oncol* **27** 2417–2418.

67   Morris MJ, Pandit-Taskar N, Carrasquillo J, *et al*. 2009 Phase I study of samarium-153 lexidronam with docetaxel in castration-resistant metastatic prostate cancer. *J Clin Oncol* **27** 2436–2442.

68   Fizazi K, Beuzeboc P, Lumbroso J, *et al*. 2009 Phase II trial of consolidation docetaxel and samarium-153 in

patients with bone metastases from castration-resistant prostate cancer. *J Clin Oncol* **27** 2429–2435.

69   Bruland ØS, Skretting A, Solheim ØP, *et al.* 1996 Targeted radiotherapy of osteosarcoma using [153]Sm-EDTMP. A new promising approach. *Acta Oncol* **35** 381–384.

70   Anderson PM, Wiseman GA, Dispenzeri A, *et al.* 2002 High dose 153-samarium ethylene diamine tetramethylene phosphonate: low toxicity of skeletal irradiation in patients with osteosarcoma and bone metastases. *J Clin Oncol* **20** 189–196.

71   Anderson PM, Wiseman GA, Erlandson L, *et al.* 2005 Gemcitabine radiosensitization after high-dose samarium for osteoblastic osteosarcoma. *Clin Cancer Res* **11** 6895–6900.

72   Berenson JR, Yellin O, Patel R, *et al.* 2009 A phase I study of samarium lexidronam/bortezomib combination therapy for the treatment of relapsed or refractory multiple myeloma. *Clin Cancer Res* **15** 1069–1075.

73   Hoskin PJ 2003 Bisphosphonates and radiation therapy for palliation of metastatic bone disease. *Cancer Treat Rev* **29** 321–327.

74   Vassiliou V, Bruland ØS, Janjan N, *et al.* 2009 Combining systemic bisphosphonates with palliative external beam radiotherapy or bone-targeted radionuclide therapy: interactions and effectiveness. *Clin Oncol* **21** 665–667.

75   Krempien R, Huber PE, Harms W, *et al.* 2003 Combination of early bisphosphonate administration and irradiation leads to improved remineralization and restoration of osteolytic bone metastases in an animal model. *Cancer* **98** 1318–1324.

76   Arrington SA, Damron TA, Mann KA, *et al.* 2008 Concurrent administration of zoledronic acid and irradiation leads to improved bone density, biomechanical strength, and microarchitecture in a mouse model of tumor induced osteolysis. *J Surg Oncol* **97** 284–290.

77   Sartor O, Hoskin P, Bruland OS 2012 Targeted radio-nuclide therapy of skeletal metastases. *Cancer Treat Rev* [in press].

78   Berenson A 2007 Market forces cited in lymphoma drugs' disuse. In *New York Times* July 14th 2007. Available at www.nytimes.com/2007/07/14/health/14lymphoma.html.

79   Petrylak DP, Tangen CM, Hussain MHA, *et al.* 2004 Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* **351** 1513–1520.

80   Tannock IF, de Wit R, Berry WR, *et al.* 2004 Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* **351** 1502–1512.

81   de Bono JS, Oudard S, Ozguroglu M, *et al.* 2010 Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* **376** 1147–1154.

82   de Bono JS, Logothetis CJ, Molina A, *et al.* 2011 Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* **364** 1995–2005.