Metastatic Bone Disease

An Integrated Approach to Patient Care

R. Lor Randall
Editor

Second Edition

Springer

Metastatic Bone Disease

R. Lor Randall
Editor

Metastatic Bone Disease

An Integrated Approach to Patient Care

Second Edition

Springer

Editor
R. Lor Randall
Department of Orthopedic Surgery
University of California
Sacramento, CA, USA

ISBN 978-3-031-52000-6 ISBN 978-3-031-52001-3 (eBook)
https://doi.org/10.1007/978-3-031-52001-3

© The Editor(s) (if applicable) and The Author(s), under exclusive license to Springer Nature Switzerland AG 2016, 2024
This work is subject to copyright. All rights are solely and exclusively licensed by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed. The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.
The publisher, the authors, and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Paper in this product is recyclable.

Preface/Acknowledgments to the Second Edition

I am grateful to know that the first edition was so well received that Springer asked me to craft a second edition on this immensely important topic. Keeping with the intent of the first edition, we wanted to provide timely and integrated information for a "pandemic" within our cancer patient population. Secondary oncologic involvement of the musculoskeletal system remains a tremendous physical, psychological, and social burden for patients and society. For every dollar spent on oncology care, approximately 20 cents of that goes to managing skeletally related events. It is a primary source of anxiety, pain, and suffering for patients and their families, as they strive to enjoy the precious time on a shortened horizon.

Since the first edition, I have had the privilege of joining the healthcare mission at UC Davis. I am so grateful for my two decades in Utah and miss my colleagues and that community a great deal. Nonetheless, UCDH is a spectacular mission and organization, serving as a destination and safety-net resource for Northern California and beyond. I want to thank our Vice-Chancellor and CEO, David Lubarsky, MD, for his extraordinary vision and commitment to expand the scope of our care to meet the demands of the region. Many thanks also to our Dean, Susan Murin, MD, for her first-rate stewardship of our academic mission and her support of our School of Medicine departments. I am grateful to Primo "Lucky" Lara, MD, for his incredible leadership of our cancer mission. The greater UCDH community and its principled dedication to making the world a better place is second to none, and I am honored to have them all as colleagues. The faculty and trainees in our department and throughout UCDH are of the highest caliber and are passionately dedicated to our mission, in the face of strong socioeconomic headwinds. Particular recognition goes to my orthopedic oncology partner Steven W. Thorpe, MD, who leads our program and is a stalwart champion of our purpose and execution of our mission. Also, many thanks to my Executive Analyst, Debra A. Sample, who was so vital to bringing this second edition to fruition. Of utmost importance, I want to recognize the immense inspiration of our patients who continually face their mortality and make us so proud by their determination and strength. James Oliver Johnson, MD, my former professor at UCSF, a world-class orthopedic oncologist and human being, and my initial inspiration to focus my energies in oncology

passed away this year. I will carry him with me forever. Lastly, to my wife Susannah and my teenagers James and Alexa, everything starts and finishes with you. You are my supreme joy and my source of strength.

Sacramento, CA, USA R. Lor Randall

Preface/Acknowledgments: A Better Place

When I was approached about producing a medical textbook, my initial reaction was, "do we really need another orthopedic textbook (especially in hard-copy)?" Subsequently I reflected on how myopic our field has become. As orthopedic surgeons, our perspective on patient health has become so anatomically and technically focused. I hold the members of my chosen field in the highest regard. Yet, for example, when I talk to an arthroplasty surgeon about arthritis, invariably it is about the latest technologies and techniques and not about the underlying disease processes. For the practicing orthopod, our appreciation of the pathophysiology of the orthopedic disease we treat remains diminished as compared to our fund of knowledge regarding orthopedic tactics. This has always bothered me and is in part why I went into academics and why I gravitated to oncology. Certainly I find the surgeries gratifying but my goal has always been to better understand the pathologic processes of neoplasia, especially in translocation-associated sarcomas. Furthermore, I wanted to build meaningful relationships with my patients. These people, individually and collectively, have been my inspiration, my heroes. It is to them and their families to whom I dedicate this enterprise.

So as I thought about a textbook, I wanted to create something that integrated the biology and the spirit of the people afflicted with a disease that not only threatened their lives but also their quality of life. As I was already working on a sarcoma textbook with colleagues, I turned to the most common condition that I treat: metastatic cancer to bone or metastatic bone disease (MBD).

Thus, for those clinicians who intend to read or reference this book, I hope that you will embrace the integrated approach. The authors are all recognized in their respective fields, many of whom are outside orthopedics. I am eternally grateful to them for committing the time and thought, away from so many other precious and important responsibilities, to contribute their insights and knowledge to the subject. Like our Sarcoma Services in Utah, it is truly a transdisciplinary approach with broad and varied perspectives on issues.

Finally, I would like to recognize the other sources of inspiration, beyond the patients whom I so cherish and value. These individuals instilled in me the desire to make the world a better place by continuing to push the academic agenda. First, my mentors and colleagues. So many wonderful professionals have been a positive influence in my life. I will not list them all here but I am ever grateful to my professors at Brown, Yale, and UCSF. James O. Johnston,

MD, of UCSF fame, is the man who ignited the cancer fire within me. Chappie Conrad and Jim Bruckner, my fellowship mentors at the University of Washington/Fred Hutchinson Cancer Consortium, stoked that fire and I am forever grateful to them as well. I would also like to thank Susie Crabtree, our study coordinator, and Diane Miller, my administrative assistant, for their tireless and fastidious dedication to the mission and professional support. Of course the clinical team for our Sarcoma Services, which manages our MBD patients, is second to none and I want to recognize them as well.

Second, but first in my life, my family. My wife Susannah is the most brilliant, beautiful, funny woman with whom one could be so fortunate to spend one's life. It is her keen intellect and curiosity about life that refuels my fire daily. My kids James and Alexa instill in me the drive to never give up trying to make the world a better place. I love you three beyond words. My mother and father, both of whom left my life prematurely, I am grateful for the gifts that they either directly or indirectly bestowed upon me.

Salt Lake City, UT, USA R. Lor Randall

Contents

Part I

The Problem

1 Bone Metastases: Epidemiology and Societal Effect

Rahul Bhale, Robert U. Ashford, and R. Lor Randall

Introduction

As patients with cancer live longer, the incidence of metastatic bone disease is increasing [1]. According to American Cancer Society Statistics, it is estimated that 1.96 million people will be diagnosed with cancer in 2023 and is expected to continue to increase [2]. Accurate figures are not readily available for how many of these patients will go onto develop bone metastases because data on recurrence is not collected by cancer registries [3]. A recent estimate of prevalence from the MarketScan and Medicare estimated that 280,000 US citizens were living with skeletal metastases [4] although other estimates are nearer 400,000 [5].

Skeletal metastases are the final common pathway of many malignancies and can result in skeletal related events (SREs) such as pathological fracture, spinal cord compression, bone pain, and hypercalcemia [6, 7].

Patients will typically present to the orthopedic surgeon as a pathological fracture or a lytic lesion (impending pathological fracture), and the management can be complex although it is often underestimated. Orthopedic opinions are often sought far too late and earlier referral may offer the opportunity for either less complex surgery or indeed any surgery, such as prophylactic stabilization of impending fractures. Late referral can render reconstruction impossible.

In this introductory chapter, we identify the epidemiology of bone metastases and the effect on patients, their relatives, and society in general.

Epidemiology of Metastatic Bone Disease

Incidence of Bone Metastases

In the USA, nearly 1.96 million people are diagnosed with cancer every year [2]. Of these, half of patients suffer a cancer that frequently metastasizes to bone [8]. In fact, bone is the third most common site of metastatic malignancy after lung and liver. It is estimated that 400,000 Americans go on to develop skeletal metastases each year [5].

Bone metastases can occur in just about any primary malignancy. The most common cancers to metastasize to bone are breast, prostate, thyroid, lung, and kidney [9]. In autopsy studies, the incidence in breast and prostate cancers is as high as 73% [10]. A quarter of patients with skeletally

R. Bhale
Department of Orthopaedic Surgery, University of California, Davis, Sacramento, CA, USA

R. U. Ashford
Leicester Orthopaedics, University Hospitals of Leicester, Leicester, UK

R. L. Randall (✉)
Department of Orthopaedic Surgery, University of California, Sacramento, CA, USA
e-mail: rlrandall@ucdavis.edu

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2024

R. L. Randall (ed.), *Metastatic Bone Disease*, https://doi.org/10.1007/978-3-031-52001-3_1

metastatic renal cell cancer will have proximal femoral metastases [11]. The most common sites of bone metastases are spine, pelvis, femur, and rib, and lytic lesions are more likely to fracture [11, 12]. 20% of patients with bone metastases will have an upper extremity metastasis (in over half of these it is in the humerus) [13].

Certain socioeconomic factors have been shown to render healthcare disparities among patients with metastatic bone disease. Namely, Jawad et al. [14] reported that (1) Non-Hispanic Black patients had higher incidences of bone metastases for prostate and breast primary sites, (2) Non-Hispanic American Indian Alaskan Native patients had higher incidences of bone metastases for cancers originating from renal and colon primary sites, and (3) patients of lower socioeconomic status had higher incidence of bone metastases ($P < 0.05$) [14]. Further, lower socioeconomic status and lack of insurance have been reported to be an independent risk factor for worse disease-specific survival [15].

In a population-based study from Denmark, 35,912 patients were diagnosed with breast cancer in an 8-year period. Of these, 178 (0.5%) had bone metastases at diagnosis, and a further 1272 (3.6%) developed skeletal metastases at a mean of 3.4-year follow-up. Of the patients with or developing skeletal metastases, approximately 45% suffered an SRE [16]. The incidence in SRE was highest in the first year following diagnosis of the metastases. Similar population-based studies have been carried out in Denmark for prostate and lung cancers (Table 1.1).

In lung cancer (most studies being of NSCLC), a review by Kuchuk reports an incidence at diagnosis of skeletal metastases of 20–40% [20]. Bone-only metastases were present in less than 7%. The presence of bone-predominant metastases did not improve survival. However, an SRE was not further detrimental to survival.

Skeletal metastases will typically present to trauma surgeons, orthopedic oncologic surgeons, oncologists, and surgical oncologists—the latter two usually because they are managing the primary tumor. Primary management should incorporate early orthopedic opinion and appropriate surgical and oncologic management. The use of conventional internal fixation may be inappropriate and as such, surgical treatment should be planned and undertaken in daylight hours with experienced anesthetists and in conjunction and following discussions with the managing oncologists. Heroic operations in the face of a short life expectancy are usually unjustified. Similarly, ill-thought-out internal fixation in a patient with a reasonable life expectancy can result in implant failure. Surgery in the absence of radiotherapy may result in disease progression and can result in complex periprosthetic fractures. Revision surgery is always more challenging than primary surgery for both the patient and the surgeon (and often the anesthesiologist).

Many patients with skeletal metastases will have concomitant visceral metastases. This is commonest in lung, renal, and breast cancer. Solitary bone metastases occur most frequently

Table 1.1 Incidence and survival of metastases and SREs in patients with breast, prostate, and lung cancers in Denmark based on population studies

	Prostate	Lung	Breast
Study years	1999–2007	1999–2010	1999–2007
Patients	23,087	29,720	35,912
Mets at diagnosis	569 (3%)	254 (0.9%)	178 (0.5%)
Developed mets	2578 (11.5%)	1692 (5.8%)	1272 (3.6%)
Developed SRE	1329 (5.9%)	905 (3%)	590 (1.6%)
1-year survival			
– No bone mets	87%	37.4%	93.3%
– Bone mets no SRE	47%	12.1%	59%
– Bone mets + SRE	40%	5.1%	40.2%
Reference	Nørgaard et al. [17]	Cetin et al. [18]	Jensen et al. [16] and Yong et al. [19]

in renal cancer. Most patients have multiple skeletal metastases [21] rather than solitary ones.

The incidence of patients with bone metastases having an SRE is high. In a large study of 1819 patients with newly diagnosed skeletal metastases in breast, prostate, or lung cancer, 22% of patients had an SRE concomitant with diagnosis of the metastasis [22]. Of those not presenting with an SRE, 46.8% of lung cancer patients experienced an SRE during follow-up. The figure was 46.4% for prostate cancer and 51.9% for breast cancer [22]. This figure is higher than from other series but suggests that the risk of developing an SRE in any patient with a skeletal metastasis approached 1 in 2. A more recent study conducted by Baek et al. [23] evaluating a cohort of 52,231 patients reported the cumulative SRE incidences to be 47%, 31.4%, and 38% in breast cancer, prostate cancer, and multiple myeloma, respectively.

Site of Bone Metastases

Swanson et al. followed 947 patients with renal cell cancer from first diagnosis. 252 (26.7%) developed skeletal metastases. The most common sites were spine, pelvis, and proximal femur [11]. A similar distribution was seen by Lipton [24] as most common sites of metastasis.

Kakhi et al. utilized isotope bone scanning to review the most common site for bone metastases in prostate, breast, gastrointestinal, and lung cancers. The spine, ribs, and pelvis were the most common sites affected in all of the cancers with the addition of the sternum in breast cancer. The most common appendicular bone was the femur, most commonly the proximal femur [25].

Incidence of Skeletal-Related Complications

Bone metastases are a common cause of morbidity, and skeletal events are common in patients. They are detrimental to quality of life. They result in admission to hospital (Table 1.2), and once the patient has been admitted, the rate of admission increases [26].

Table 1.2 3-year incidence rates of hospital admission due to MBD and admission following a previous SRE in 28,162 patients with breast, prostate, and lung cancer

	3-year incidence rate of admission per 1000 patients	Previously admitted following SRE—rate of admission per 1000 patients
Breast cancer	95	211
Prostate cancer	163	150
Lung cancer	156	260

Data adapted from Pockett et al. [26]

Table 1.3 Incidence of SREs from placebo wing of multicenter trials in advanced malignancy

	Breast	Prostate	NSCLC and other solid tumors	Myeloma
Pathological fracture (%)	52	25	22	37
Radiotherapy (%)	43	33	34	34
Surgery (%)	11	4	5	5
Spinal cord compression (%)	3	8	4	3
Reference	Lipton et al. [27]	Saad et al. [28]	Rosen et al. [29]	Berenson et al. [30]

The placebo wings of multicenter randomized trials give evidence as to the incidence of different types of SREs in patients with skeletal metastases (Table 1.3).

Cancer Survival

Survival varies dependent on primary tumor pathology and visceral tumor load. Longer mean survivals are seen in thyroid (26 months), breast (19 months), and prostate cancer (18 months). Poorer mean survivals are a feature of lung cancer (6 months) and cancer of unknown primary. The presence of visceral metastases results in poorer survival rates [31].

In 1995, Bauer reported that after surgical treatment of skeletal metastases, the 1-year survival was 30% and the 3-year survival was 8% [32]. Pathologic fracture, visceral or brain metastases, and lung cancer were negative prognostic variables for survival, whereas solitary bone metastases, breast and kidney cancer, myeloma, and lymphoma were positive. In 2004, Hansen, on behalf of the Scandinavian Sarcoma Group (SSG), reported 1-year survival of 40% and a 3-year survival of 20% [33]. In 2013, the SSG reported 1195 surgically treated non-spinal metastases. The 1-year survival was 41% and the 5-year survival was 2%. The longest median survival was in myeloma patients (26.3 months), thyroid cancer (22.7 months), breast cancer (12 months), and kidney cancer (10 months). Melanoma had the worst prognosis (2.3 months) [21]. In 2022, Groot et al. [34] reported that the 1-year survival rate was worse for patients who had undergone operative treatment for realized pathological fractures than for impending fractures (46% versus 38%).

Implications of Increasing Survival

Increasing survival of patients with bone metastases has a number of effects for the orthopedic surgeon treating the metastases:

- Tumor that is not adequately treated (en bloc excision or surgery plus radiotherapy) will continue to grow resulting in some cases in extreme bone destruction or stresses being put on implants (Fig. 1.1).
  - Fixation that is reliant on bone healing is likely to fail because of implant failure (Fig. 1.2) leading to more complex and more costly operations, prolonged inpatient stays, and increasing mortality.

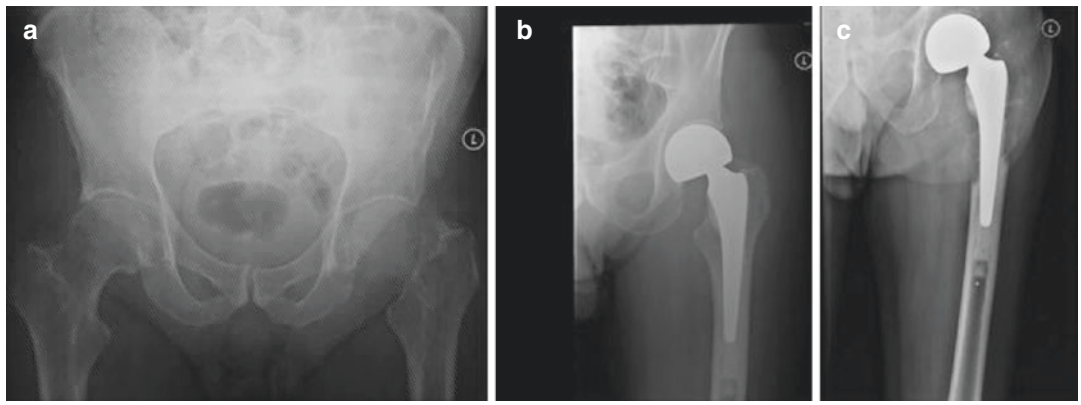

Fig. 1.1 Seventy-six male with known diffuse large B-cell lymphoma sustained a pathological femoral neck fracture (**a**) treated by hemiarthroplasty (**b**). Adjuvant radiotherapy was not given resulting in bone loss around the implant (**c**). The hemiarthroplasty was converted to a proximal femoral replacement

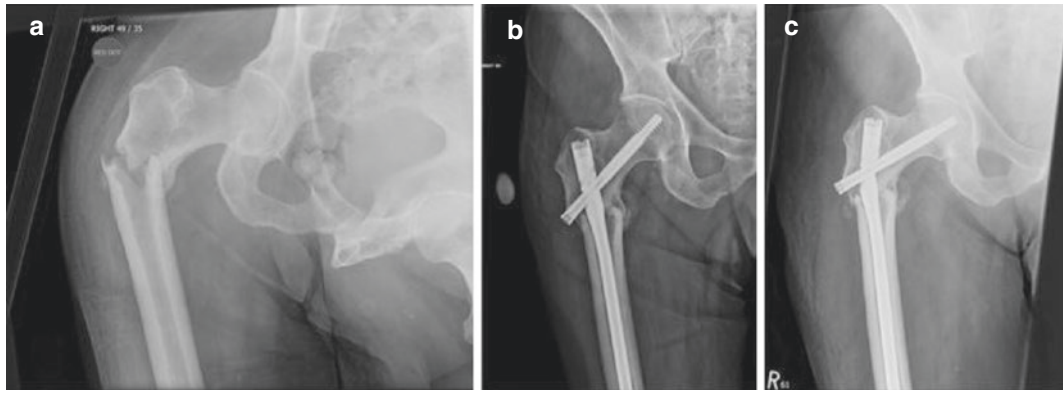

Fig. 1.2 Male with multiple myeloma. Pathological fracture proximal femur (**a**) treated by long Affixus nail (Biomet) (**b**). The nail failed (**c**) and was revised to a proximal femoral replacement

Incidence of Pathological Fractures

The majority of the workload for metastatic bone disease for non-spinal metastases is for pathological fracture. The incidence of pathological fracture varies between different primary tumors. Tumors that tend to produce lytic metastases have a higher fracture rate than those that produce sclerotic metastases. Table 1.4 highlights some of the evidence for pathological fracture rate. The majority of evidence comes from the placebo wing of randomized controlled trials of the efficacy of bisphosphonate therapy.

Table 1.4 Pathological fracture rate based on longitudinal studies and placebo wing of bisphosphonate studies (solid tumor study was of non-breast and prostate metastatic malignancy—tumors included NSCLC (54%), renal (10%), small-cell lung cancer (8%), thyroid (2%), head and neck (2%), cancer of unknown primary (7%), and others (23%))

Tumor type	Reference	Criteria	Pathological fracture rate
Breast cancer	Coleman et al. [35]	Breast cancer with bone metastases	78/498 (16%)
Prostate cancer	Saad et al. [36]	Prostate cancer with bone metastases	46/208 (22.1%)
Lung cancer	Joshi et al. [37]	Lung cancer with bone metastases	21.6%
Renal cancer	Lipton et al. [24] Swanson et al. [11] Forbes et al. [38]	Renal cancer with bone metastases Newly diagnosed renal cell cancer	42% 15% 12%
Other solid tumors (see description)	Rosen et al. [29]	Bone metastases from non-breast/prostate cancers	55/250 (22%)

Predicting Pathological Fracture

While this is covered elsewhere in the text, a pragmatic approach is recommended by the authors. If the patient has functional pain and a large lytic metastasis then prophylactic surgical stabilization should be considered.

Life expectancy is an important consideration in planning any surgical intervention in skeletal metastases. The Scandinavian Sarcoma Group proposed the following scoring system [21] (Table 1.5). A score of 0–1, the majority survive 12 months; a score of 2–3 six months; and a score of 4 is associated with a survival that may not reach 3 months.

In addition to the published literature issues such as patient weight, comorbidities, compliance, ability to bear weight, local and systemic pain, use of pain medication, use of bisphosphonates, concurrent chemotherapy, function both current and previous, specific concurrent bone sites of tumor involvement, overall disease load including non-bone lesions, response of other sites to nonsurgical oncologic treatment, activity level, patient and functional expectations, among others may be important [39].

Table 1.5 SSG life expectancy after bone metastases

Score	0	1
Number of metastases	Single	Multiple
Visceral metastases	None	Yes
Breast/thyroid/renal/myeloma	Yes	Other
Karnofsky score 70	Above (self-care)	Below (needs help)

Data from Ratasvuori [21]

Impact on Survival of Pathological Fractures

A pathological fracture is associated with reduced survival. In a study of 3049 patients with bone metastases, a pathological fracture had up to a 32% increased risk of death compared to the absence of a pathological fracture [40] (Table 1.6). Vertebral fractures have been reported as increasing in mortality ranging from 23 to 90% [41].

Table 1.6 Incidence of pathological fracture and implications on survival: data based on Saad et al. [40]. Hazard ratios are adjusted for previous skeletal related events and ECOG performance status of more than 2

	N	Fracture rate (%)	Hazard ratio of any fracture	Hazard ratio of nonvertebral fracture
Myeloma	513	43	1.26	1.18
Breast cancer	1130	35	1.32	1.24
Prostate cancer	640	19	1.23	1.28
Lung cancer and other solid tumors	766	17	1.06	0.97

Quality of Life and Bone Metastases

It is well documented that SREs have a negative effect on quality of life [42–48], and therefore, the goal of any surgical treatment should be to therefore maintain quality of life. Further goals of palliative surgery are pain relief, lifelong reconstruction, and maintaining function. Surgery should enable immediate weight-bearing as well as return to activity [5]. Bone complications further diminish quality of life by increasing medical costs (discussed further later on in this chapter) [49], having a negative impact on survival [50] and impairing mobility [51]. In a multicenter prospective study, Blank et al. [52] reported trends of improved function and decreased pain, measured by Patient-Reported Outcomes Measurement Information System (PROMIS) scores, seen after operative management of metastatic bone disease.

The Economic and Social Burden of Skeletal Related Events in Metastatic Bone Disease

The NIH estimated the direct medical costs of cancer in 2005 to be $74 billion [3]. Schulman and Kohles estimated that $12.6 billion (17%) of the total direct medical cost of cancer was due to metastatic bone disease [53]. The cost of care directly attributable to skeletal metastases was estimated at $14,580 per patient in 2004 ($18,272 when inflation applied to 2014) [54]. Several studies have looked at the costs to the healthcare environment of skeletal metastases. In Europe, spinal cord compression and bone surgery are the most expensive of the SREs with costs as high as €12,000 for spinal surgery and €9000 for bone surgery [55, 56]. Similar figures were seen in Canada with costs of surgical treatment of skeletal metastases in 1995 as CA $8824 (2014 inflation applied US $10,005). Radiotherapy (single fraction) was €1900 per course [57]. However, earlier work from the USA demonstrated that radiotherapy was more costly [47]. The mean cost incurred by cancer patients in the last 6 months before death is $75,000 largely because of increased inpatient costs [58]. Avoiding inpatient admission and appropriate management of skeletal metastases should reduce this cost.

Table 1.7 Costs associated with metastatic cancers and skeletal related events. Data converted to US dollars at average rate for year of data collection as stated in publication and then adjusted to 2014 (www.usinflationcalculator.com)

	Prostate	Breast, prostate, and myeloma
Radiotherapy	$12,811	
Surgery	$69,619	$36,961
Spinal cord compression	$59,169	$57,859
Reference	Hagiwara et al. [59]	Barlev et al. [60]

Authors have looked at the costs of SREs in individual cancers. From a US insurance database, Lage et al. [47] reported 89% of patients undergoing radiation therapy, 23% a pathological fracture, and 12% undergoing bone surgery with a mean cost of $12,469 per annum [47].

When these figures are updated to 2014 (inflation applied to mean value for year of publication and converted where appropriate to US dollars), it can be seen that costs of SREs are very high (Table 1.7), particularly surgery for skeletal metastases and spinal cord compression. The total direct medical cost of metastatic bone disease that was estimated by Schulman and Kohles would have increased to $15.9 billion [53].

In 2018, Zhong et al. [61] similarly reported the profound impact of skeletal-related events on healthcare costs. Namely, the total 6-month cost of treating patients with SREs was $43,746 compared with $25,956 in the matched control cohort ($P < 0.05$). The total cost per patient over the 12-month period was $22,171 higher among patients with SREs than among patients without SREs ($P < 0.05$) [61].

The costs demonstrated are only the hospital/healthcare costs of treatment. The burden is greater than just healthcare costs. Indirect costs include employment time lost (and indeed loss of employment), and transport to and from hospital appointments or treatments, both for the patient and their relatives/carers. These costs are borne by patients, carers, employers, and society as a

whole. There has been little research published on indirect costs [62].

In terms of employment, one Swedish study found that 18% of patients under 50 and 39% of patients between 50 and 64 retired early due to metastatic breast cancer. The annualized indirect costs of early retirement were $8938 and $18,916, for the two groups, respectively (converted to US$ from Swedish Krona and inflation applied to 2014) [63].

As far as caregivers are concerned, 5% in one Canadian series either gave up their job or declined promotion directly attributable to metastatic cancer. Many caregivers also utilized holiday leave or accumulated time to maintain income [64]. Caregivers have also been shown to have a mean of 2.2 absence days per month [65] and an average of $118 lost income per month (inflation applied). There are also other out-of-pocket expenses. Other expenses will include childcare, domestic help, medical equipment, nutritional supplements, and medical diets [66].

When quality of life in patients with skeletal metastases has been assessed, there has been very little assessment on ability to work. Tharmalingam et al. [67] reviewed 47 studies of quality of life in skeletal metastases and none directly had work as an outcome. It is, therefore, difficult to accurately gauge.

The economic burden of metastatic bone disease is substantial and will continue to increase [68].

Summary

With modern chemotherapy, improved survival in many cancers has resulted in skeletal metastases increasing in number. Pathological fractures are the most significant implication of this for orthopedic surgeons in terms of workload, including impending, primary, and revision fixation. From a patient perspective, there are implications on quality of life as well as finances and employment. From a societal point of view, there are huge financial implications and significant healthcare disparities that must be addressed. All of these need to be considered when managing the orthopedic patient with skeletal metastases.

References

1. Weber KL, Randall RL, Grossman S, Parvizi J. Management of lower-extremity bone metastasis. J Bone Joint Surg Am. 2006;88(Suppl 4):11–9. https://doi.org/10.2106/JBJS.F.00635.
2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73(1):17–48. https://doi.org/10.3322/caac.21763.
3. Cancer.Net. Oncologist-approved cancer information from the American Society of Clinical Oncology. https://www.cancer.net/. Accessed 29 January 2023.
4. Estimated number of prevalent cases of metastatic bone disease in the US adult population - PubMed. https://pubmed.ncbi.nlm.nih.gov/22570568/. Accessed 1 June 2023.
5. Yu HHM, Tsai YY, Hoffe SE. Overview of diagnosis and management of metastatic disease to bone. Cancer Control J Moffitt Cancer Cent. 2012;19(2):84–91. https://doi.org/10.1177/107327481201900202.
6. So A, Chin J, Fleshner N, Saad F. Management of skeletal-related events in patients with advanced prostate cancer and bone metastases: incorporating new agents into clinical practice. Can Urol Assoc J. 2012;6(6):465–70. https://doi.org/10.5489/cuaj.12149.
7. Hong S, Youk T, Lee SJ, Kim KM, Vajdic CM. Bone metastasis and skeletal-related events in patients with solid cancer: a Korean nationwide health insurance database study. PLoS One. 2020;15(7):e0234927. https://doi.org/10.1371/journal.pone.0234927.
8. Jacofsky DJ, Haidukewych GJ. Management of pathologic fractures of the proximal femur: state of the art. J Orthop Trauma. 2004;18(7):459–69. https://doi.org/10.1097/00005131-200408000-00013.
9. Macedo F, Ladeira K, Pinho F, et al. Bone metastases: an overview. Oncol Rev. 2017;11(1):321. https://doi.org/10.4081/oncol.2017.321.
10. Galasko C. The anatomy and pathways of skeletal metastases. Boston: G. K. Hall; 1981.
11. Swanson DA, Orovan WL, Johnson DE, Giacco G. Osseous metastases secondary to renal cell carcinoma. Urology. 1981;18(6):556–61. https://doi.org/10.1016/0090-4295(81)90455-6.
12. Heymann D. Bone cancer: progression and therapeutic approaches. 1st ed. Amsterdam: Elsevier; 2010.
13. Look Hong NJ, Hornicek FJ, Raskin KA, et al. Prognostic factors and outcomes of patients with myxofibrosarcoma. Ann Surg Oncol. 2013;20(1):80–6. https://doi.org/10.1245/s10434-012-2572-3.
14. Jawad MU, Pollock BH, Wise BL, et al. Sex, racial/ethnic and socioeconomic disparities in patients with metastatic bone disease. J Surg Oncol. 2022;125(4):766–74. https://doi.org/10.1002/jso.26765.
15. Jawad MU, Pollock BH, Wise BL, et al. Socioeconomic and insurance-related disparities in disease-specific survival among patients with metastatic bone disease. J Surg Oncol. 2023;127(1):159–73. https://doi.org/10.1002/jso.27097.

16. Jensen AØ, Jacobsen JB, Nørgaard M, Yong M, Fryzek JP, Sørensen HT. Incidence of bone metastases and skeletal-related events in breast cancer patients: a population-based cohort study in Denmark. BMC Cancer. 2011;11:29. https://doi.org/10.1186/1471-2407-11-29.
17. Nørgaard M, Jensen AØ, Jacobsen JB, Cetin K, Fryzek JP, Sørensen HT. Skeletal related events, bone metastasis and survival of prostate cancer: a population based cohort study in Denmark (1999 to 2007). J Urol. 2010;184(1):162–7. https://doi.org/10.1016/j.juro.2010.03.034.
18. Cetin K, Christiansen CF, Jacobsen JB, Nørgaard M, Sørensen HT. Bone metastasis, skeletal-related events, and mortality in lung cancer patients: a Danish population-based cohort study. Lung Cancer. 2014;86(2):247–54. https://doi.org/10.1016/j.lungcan.2014.08.022.
19. Yong M, Jensen AÖ, Jacobsen JB, Nørgaard M, Fryzek JP, Sørensen HT. Survival in breast cancer patients with bone metastases and skeletal-related events: a population-based cohort study in Denmark (1999-2007). Breast Cancer Res Treat. 2011;129(2):495–503. https://doi.org/10.1007/s10549-011-1475-5.
20. Kuchuk M, Addison CL, Clemons M, Kuchuk I, Wheatley-Price P. Incidence and consequences of bone metastases in lung cancer patients. J Bone Oncol. 2013;2(1):22–9. https://doi.org/10.1016/j.jbo.2012.12.004.
21. Ratasvuori M, Wedin R, Keller J, et al. Insight opinion to surgically treated metastatic bone disease: Scandinavian Sarcoma Group Skeletal Metastasis Registry report of 1195 operated skeletal metastasis. Surg Oncol. 2013;22(2):132–8. https://doi.org/10.1016/j.suronc.2013.02.008.
22. Oster G, Lamerato L, Glass AG, et al. Natural history of skeletal-related events in patients with breast, lung, or prostate cancer and metastases to bone: a 15-year study in two large US health systems. Support Care Cancer. 2013;21(12):3279–86. https://doi.org/10.1007/s00520-013-1887-3.
23. Baek YH, Jeon HL, Oh IS, Yang H, Park J, Shin JY. Incidence of skeletal-related events in patients with breast or prostate cancer-induced bone metastasis or multiple myeloma: a 12-year longitudinal nationwide healthcare database study. Cancer Epidemiol. 2019;61:104–10. https://doi.org/10.1016/j.canep.2019.05.013.
24. Lipton A, Colombo-Berra A, Bukowski RM, Rosen L, Zheng M, Urbanowitz G. Skeletal complications in patients with bone metastases from renal cell carcinoma and therapeutic benefits of zoledronic acid. Clin Cancer Res. 2004;10(18 Pt 2):6397S–403S. https://doi.org/10.1158/1078-0432.CCR-040030.
25. Kakhki VRD, Anvari K, Sadeghi R, Mahmoudian AS, Torabian-Kakhki M. Pattern and distribution of bone metastases in common malignant tumors. Nucl Med Rev Cent East Eur. 2013;16(2):66–9. https://doi.org/10.5603/NMR.2013.0037.
26. Pockett RD, Castellano D, McEwan P, Oglesby A, Barber BL, Chung K. The hospital burden of disease associated with bone metastases and skeletal-related events in patients with breast cancer, lung cancer, or prostate cancer in Spain. Eur J Cancer Care. 2010;19(6):755–60. https://doi.org/10.1111/j.1365-2354.2009.01135.x.
27. Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. Cancer. 2000;88(5):1082–90. https://doi.org/10.1002/(sici)1097-0142(20000301)88:5<1082::aid-cncr20>3.0.co;2-z.
28. Saad F, Gleason DM, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst. 2004;96(11):879–82. https://doi.org/10.1093/jnci/djh141.
29. Rosen LS, Gordon D, Tchekmedyian NS, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, phase III, double-blind, placebo-controlled trial. Cancer. 2004;100(12):2613–21. https://doi.org/10.1002/cncr.20308.
30. Berenson JR, Lichtenstein A, Porter L, et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. J Clin Oncol. 1998;16(2):593–602. https://doi.org/10.1200/JCO.1998.16.2.593.
31. Rose PS, Buchowski JM. Metastatic disease in the thoracic and lumbar spine: evaluation and management. J Am Acad Orthop Surg. 2011;19(1):37–48. https://doi.org/10.5435/00124635-201101000-00005.
32. Bauer HC, Wedin R. Survival after surgery for spinal and extremity metastases. Prognostication in 241 patients. Acta Orthop Scand. 1995;66(2):143–6. https://doi.org/10.3109/17453679508995508.
33. Hansen BH, Keller J, Laitinen M, et al. Survival after surgery for bone metastases in the pelvis and extremities. Acta Orthop Scand Suppl. 2004;75(311):11–5. https://doi.org/10.1080/00016470410001708270.
34. Groot OQ, Lans A, Twining PK, et al. Clinical outcome differences in the treatment of impending versus completed pathological long-bone fractures. J Bone Joint Surg Am. 2022;104(4):307–15. https://doi.org/10.2106/JBJS.21.00711.
35. Coleman RE, Rubens RD. The clinical course of bone metastases from breast cancer. Br J Cancer. 1987;55(1):61–6. https://doi.org/10.1038/bjc.1987.13.
36. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2002;94(19):1458–68. https://doi.org/10.1093/jnci/94.19.1458.

37. Joshi AD, Carter JA, Botteman MF, Kaura S. Cost-effectiveness of zoledronic acid in the management of skeletal metastases in patients with lung cancer in France, Germany, Portugal, the Netherlands, and the United Kingdom. Clin Ther. 2011;33(3):291–304.e8. https://doi.org/10.1016/j.clinthera.2011.04.002.
38. Forbes GS, McLeod RA, Hattery RR. Radiographic manifestations of bone metastases from renal carcinoma. AJR Am J Roentgenol. 1977;129(1):61–6. https://doi.org/10.2214/ajr.129.1.61.
39. Damron TA, Ward WG. Risk of pathologic fracture: assessment. Clin Orthop. 2003;415(Suppl):208–11. https://doi.org/10.1097/01.blo.0000093851.72468.1d.
40. Saad F, Lipton A, Cook R, Chen YM, Smith M, Coleman R. Pathologic fractures correlate with reduced survival in patients with malignant bone disease. Cancer. 2007;110(8):1860–7. https://doi.org/10.1002/cncr.22991.
41. Association between vertebral fracture and increased mortality in osteoporotic patients - PubMed. https://pubmed.ncbi.nlm.nih.gov/12854835/. Accessed 1 June 2023.
42. Weinfurt KP, Li Y, Castel LD, et al. The significance of skeletal-related events for the health-related quality of life of patients with metastatic prostate cancer. Ann Oncol. 2005;16(4):579–84. https://doi.org/10.1093/annonc/mdi122.
43. Weinfurt KP, Castel LD, Li Y, Timbie JW, Glendenning GA, Schulman KA. Health-related quality of life among patients with breast cancer receiving zoledronic acid or pamidronate disodium for metastatic bone lesions. Med Care. 2004;42(2):164–75. https://doi.org/10.1097/01.mlr.0000108746.69256.45.
44. Saad F, Olsson C, Schulman CC. Skeletal morbidity in men with prostate cancer: quality-of-life considerations throughout the continuum of care. Eur Urol. 2004;46(6):731–9; discussion 739-740. https://doi.org/10.1016/j.eururo.2004.08.016.
45. Lipton A. Management of bone metastases in breast cancer. Curr Treat Options in Oncol. 2005;6(2):161–71. https://doi.org/10.1007/s11864-005-0023-0.
46. Wardley A, Davidson N, Barrett-Lee P, et al. Zoledronic acid significantly improves pain scores and quality of life in breast cancer patients with bone metastases: a randomised, crossover study of community vs hospital bisphosphonate administration. Br J Cancer. 2005;92(10):1869–76. https://doi.org/10.1038/sj.bjc.6602551.
47. Lage MJ, Barber BL, Harrison DJ, Jun S. The cost of treating skeletal-related events in patients with prostate cancer. Am J Manag Care. 2008;14(5):317–22.
48. Clemons MJ, Dranitsaris G, Ooi WS, et al. Phase II trial evaluating the palliative benefit of second-line zoledronic acid in breast cancer patients with either a skeletal-related event or progressive bone metastases despite first-line bisphosphonate therapy. J Clin Oncol. 2006;24(30):4895–900. https://doi.org/10.1200/JCO.2006.05.9212.
49. Groot MT, Boeken Kruger CGG, Pelger RCM, Uyl-de Groot CA. Costs of prostate cancer, metastatic to the bone, in the Netherlands. Eur Urol. 2003;43(3):226–32. https://doi.org/10.1016/s0302-2838(03)00007-1.
50. Oefelein MG, Ricchiuti V, Conrad W, Resnick MI. Skeletal fractures negatively correlate with overall survival in men with prostate cancer. J Urol. 2002;168(3):1005–7. https://doi.org/10.1016/S0022-5347(05)64561-2.
51. Riggs BL, Melton LJ. The worldwide problem of osteoporosis: insights afforded by epidemiology. Bone. 1995;17(5 Suppl):505S–11S. https://doi.org/10.1016/8756-3282(95)00258-4.
52. Blank AT, Lerman DM, Shaw S, et al. PROMIS® scores in operative metastatic bone disease patients: a multicenter, prospective study. J Surg Oncol. 2018;118(3):532–5. https://doi.org/10.1002/jso.25159.
53. Schulman KL, Kohles J. Economic burden of metastatic bone disease in the US. Cancer. 2007;109(11):2334–42. https://doi.org/10.1002/cncr.22678.
54. Cameron D. Patient management issues in metastatic bone disease. Semin Oncol. 2004;31(5 Suppl 10):79–82. https://doi.org/10.1053/j.seminoncol.2004.07.027.
55. Hechmati G, Cure S, Gouépo A, et al. Cost of skeletal-related events in European patients with solid tumours and bone metastases: data from a prospective multinational observational study. J Med Econ. 2013;16(5):691–700. https://doi.org/10.3111/13696998.2013.779921.
56. Dahlberg L, Lundkvist J, Lindman H. Health care costs for treatment of disseminated breast cancer. Eur J Cancer. 2009;45(11):1987–91. https://doi.org/10.1016/j.ejca.2009.03.023.
57. Will BP, Berthelot JM, Le Petit C, Tomiak EM, Verma S, Evans WK. Estimates of the lifetime costs of breast cancer treatment in Canada. Eur J Cancer. 2000;36(6):724–35. https://doi.org/10.1016/s0959-8049(99)00340-8.
58. Chastek B, Harley C, Kallich J, Newcomer L, Paoli CJ, Teitelbaum AH. Health care costs for patients with cancer at the end of life. J Oncol Pract. 2012;8(6):75s–80s. https://doi.org/10.1200/JOP.2011.000469.
59. Hagiwara M, Delea TE, Saville MW, Chung K. Healthcare utilization and costs associated with skeletal-related events in prostate cancer patients with bone metastases. Prostate Cancer Prostatic Dis. 2013;16(1):23–7. https://doi.org/10.1038/pcan.2012.42.
60. Barlev A, Song X, Ivanov B, Setty V, Chung K. Payer costs for inpatient treatment of pathologic fracture, surgery to bone, and spinal cord compression among patients with multiple myeloma or bone metastasis secondary to prostate or breast cancer. J Manag Care Pharm. 2010;16(9):693–702. https://doi.org/10.18553/jmcp.2010.16.9.693.
61. Zhong Y, Valderrama A, Yao J, Donga P, Bilir P, Neumann PJ. Economic evaluation of treating skeletal-related events among prostate cancer

patients. Value Health. 2018;21(3):304–9. https://doi.org/10.1016/j.jval.2017.02.008.
62. Foster TS, Miller JD, Boye ME, Blieden MB, Gidwani R, Russell MW. The economic burden of metastatic breast cancer: a systematic review of literature from developed countries. Cancer Treat Rev. 2011;37(6):405–15. https://doi.org/10.1016/j.ctrv.2010.12.008.
63. Lidgren M, Wilking N, Jönsson B, Rehnberg C. Resource use and costs associated with different states of breast cancer. Int J Technol Assess Health Care. 2007;23(2):223–31. https://doi.org/10.1017/S0266462307070328.
64. Grunfeld E, Coyle D, Whelan T, et al. Family caregiver burden: results of a longitudinal study of breast cancer patients and their principal caregivers. CMAJ. 2004;170(12):1795–801. https://doi.org/10.1503/cmaj.1031205.
65. Chang S, Long SR, Kutikova L, et al. Estimating the cost of cancer: results on the basis of claims data analyses for cancer patients diagnosed with seven types of cancer during 1999 to 2000. J Clin Oncol. 2004;22(17):3524–30. https://doi.org/10.1200/JCO.2004.10.170.
66. Impact of financial burden of cancer on survivors' quality of life - PubMed. https://pubmed.ncbi.nlm.nih.gov/24865220/. Accessed 1 June 2023.
67. Tharmalingam S, Chow E, Harris K, Hird A, Sinclair E. Quality of life measurement in bone metastases: a literature review. J Pain Res. 2008;1:49–58. https://doi.org/10.2147/jpr.s4572.
68. Yabroff KR, Lund J, Kepka D, Mariotto A. Economic burden of cancer in the United States: estimates, projections, and future research. Am Soc Prev Oncol. 2011;20(10):2006–14. https://doi.org/10.1158/1055-9965.EPI-11-0650.

Part II

Biology of Metastases and Tissue of Origin Considerations

2 Mechanisms Underlying Osteolytic and Osteoblastic Bone Metastases

Gabriela G. Loots and Theresa A. Guise

Abbreviations

$1,25\text{-}(OH)_2D_3$	1,25-Dihydroxyvitamin D3
BMP	Bone morphogenetic protein
cAMP	Cyclic adenosine monophosphate
CaSR	Extracellular calcium-sensing receptors
CBFA1	Core-binding factor A1
CCL2	Chemokine (C-C motif) ligand 2
CHO	Chinese hamster ovary
CTGF	Connective tissue growth factor
CXCL12	Chemokine (C-X-C motif) ligand 12
CXCR4	Chemokine (C-X-C motif) receptor 4
DKK1	Dickkopfs 1
ET-1	Endothelin 1
ETAR	Endothelin A receptor
FGF	Fibroblast growth factor
HPC	Hematopoietic progenitor cell
HSC	Hematopoietic stem cell
IFNγ	Interferon γ
IGF	Insulin-like growth factor
IL	Interleukin
JNK	Jun N-terminal kinase
LRP	Lipoprotein receptor-related protein
MAPK	Mitogen-activated protein kinase
M-CSF	Macrophage colony-stimulating factor
MDSC	Myeloid-derived suppressor cell
MMP	Matrix metalloproteinase
NFk-B	Nuclear factor kappa B
OPG	Osteoprotegerin
OPN	Osteopontin
PDGF	Platelet-derived growth factor
PGE2	Prostaglandin G2
PGF	Placental growth factor
PKA	Protein kinase A
PKC	Protein kinase C
PLC	Phospholipase C
PPARγ	Peroxisome proliferator-activated receptor γ
PSA	Prostate-specific antigen
PTH	Parathyroid hormone
PTHrP	Parathyroid hormone-related protein
RANK	Receptor activator of nuclear factor kappa B
RANKL	Receptor activator of nuclear factor kappa B ligand
RUNX-2	Runt-related transcription factor 2

G. G. Loots
Department of Orthopaedic Surgery, University of California, Davis, Sacramento, CA, USA

T. A. Guise (✉)
Department of Endocrine Neoplasia and Hormonal Disorders, MD Anderson Cancer Center, Houston, TX, USA
e-mail: taguise@mdanderson.org

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2024

R. L. Randall (ed.), *Metastatic Bone Disease*, https://doi.org/10.1007/978-3-031-52001-3_2

SDF-1	Stromal cell-derived factor 1
sFRP	Secreted frizzled-related protein
SMAD	Mothers against decapentaplegic homolog
TGFβ	Transforming growth factor β
VCAM1	Vascular cellular adhesion molecule 1
VEGFA	Vascular endothelial growth factor A
VEGFR1	Vascular endothelial growth factor receptor 1
WIF-1	Wnt inhibitory factor 1

Some of the most common cancer types have a propensity to metastasize to bone. When cancer metastasizes to bone, it disrupts normal bone remodeling causing abnormal bone resorption (osteolysis) and bone formation. Bone metastases are classified as osteolytic or osteoblastic based on the radiographic appearance. These phenotypes are two extremes of the spectrum as most solid tumor bone metastases are usually heterogeneous and, in most cases, patients will present with evidence of both osteolytic and osteoblastic lesions at the histologic examination [1].

The three most common human neoplasms, breast, prostate, and lung, are also the top three cancers to metastasize to bone tissues and are strongly associated with skeletal morbidity of pain, fracture, hypercalcemia, and nerve compression syndromes. The American Cancer Society estimates that in 2023, there will be 297,790 new cases of invasive breast cancer in the US alone. This number is 30% higher than the number that was estimated in 2014. The number of new prostate cancer diagnoses this year is estimated at 288,300; however, since 2014, the incidence rate for this cancer has increased by 3% per year overall and by ~5% per year for advanced-stage disease. For lung cancer, the numbers have been generally declining, with an estimated number of new cases of 238,340 for 2023; this has been primarily due to smoking cessation in the general population; however, the numbers of deaths due to lung cancer have continued to remain high. The numbers of estimated deaths in 2023 are 43,700 from breast cancer, 34,700 from prostate cancer, and 127,070 from lung cancer (American Cancer Society, Inc., www.cancer.org), where both breast and prostate are seeing a 10% increase from the 2014 reported numbers. Most of patients succumbing to the disease will have bone metastases, prioritizing cancer-associated bone metastasis as the top cause of morbidity in these patients. To improve therapy and prevention, it is imperative we develop a detailed understand of the pathophysiology of the cancer and its crosstalk with bone cells in the bone microenvironment.

The molecular basis of this preferential growth of cancer cells in the bone microenvironment continues to be an area of active investigation. Although the precise mechanism underlying this process is far from being elucidated, it is now recognized that the unique characteristics of the bone niche provide homing signals to cancer cells and create a microenvironment conducive for the cancer cells to colonize and proliferate. Concomitantly, cancer cells release several regulatory factors that result in abnormal bone destruction and/or formation. This complex bidirectional interplay between tumour cells and bone microenvironment establishes a feed-forward “vicious cycle” that leads to a selective growth advantage for the cancer cells [2] (Fig. 2.1). The molecular insights gained on the underpinnings of bone metastasis in recent years have also provided us with paths to design innovative approaches for therapeutic intervention as outlined below.

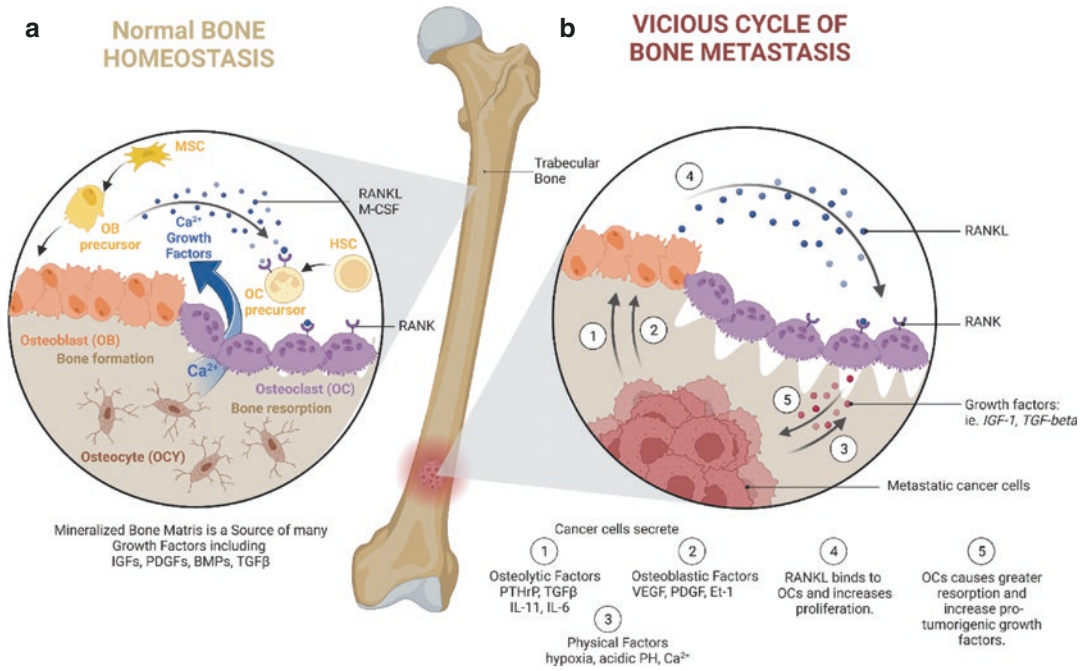

Fig. 2.1 Normal bone remodeling (**a**) and the vicious cycle (**b**) of bone metastasis. Created with BioRender.com

The Bone as a Favorable Premetastatic Niche for Cancer

In order to appreciate how the bone environment provides favorable conditions for the metastatic colonization of primary tumor cells, we need to describe the mineral and cellular components of the bone and the factors they normally produce towards normal bone physiology that offer inducive conditions for primary tumor cells to home, survive, colonize, and grow. Pre-metastatic niches (PMN) have been identified and described for lung and liver tissues [3] but less so for bone tissues. However, the components of PMN in lung and liver are more readily available or accessible in the bone. Here, we will describe the pre-metastatic bone niche and highlight why the bone provides a more favourable environment for cancer homing than other distant sites. Both lung and liver PMNs share several characteristics: (1) recruitment of bone marrow-derived cells (BMDC) or hematopoietic stem and progenitor cells (HSPC) from the bone marrow [4]; (2) synthesis of extracellular matrix proteins (collagens, proteoglycans, laminins, fibronectin, matricellular-associated proteins) [4]; (3) secreted CXCL12 by stromal cells, fibroblasts, and epithelial cells [4]; that promote homing of cancer cells. Below, we will highlight how these properties are inherent to the bone environment, and that cells in bones secrete additional factors that have been shown to promote invasive properties of cancer cells (Table 2.1).

Bone Remodeling

While most tissues in the body have the ability to self-renew, the bone is unique in that it has the ability to remove, remake, and reorganize its existing calcified matrix in a process termed remodeling that occurs in addition to replacing ~10% of its cells per year [5]. Bone remodeling results from the coupled and sequential actions of

Table 2.1 Sources and function of components present in different premetastatic niches

Component	Premetastic niche (lung/liver)	Premetastatic niche (bone)
BMDC/ HSPC	Migrate from bone marrow	Inherent to bone marrow in bones
ECM	Collagens, proteoglycans, laminins, fibronectin, matricellular-associated proteins	Collagens, proteoglycans, laminins, fibronectin, matricellular-associated proteins, osteopontin
CXCL12	Secreted by stromal cells, fibroblasts, epithelial cells	Secreted by stromal cells, fibroblasts, epithelial cells, osteoblast, osteoclast
PTH	None	Induces integrin expression
TGF-β/ IGFs	None	Secreted by bone cells
BMPs	none	Secreted by bone cells; promotes invasion

osteoblasts depositing new bone and osteoclasts resorbing existing bone (Fig. 2.1). This remodeling is highly influenced by many factors including circulating systemic hormones, local bone-derived growth factors, and mechanophysical stresses applied to the skeleton. This process is tightly regulated under normal conditions to functions to preserve the balance between bone destruction and new bone formation. Most other organs in the body also conduct remodeling, but it is mostly triggered by pathological conditions aimed at repairing diseased or damaged tissue; bone is unique in that remodeling is a normal physiological process.

Bone is composed of two biologically and physically different structures: the cortical bone, with its hard and mineralized matrix, and the cancellous or trabecular bone, where most of the bone metabolism takes place. Cortical bone is found prevalently in the long bones of the appendicular skeleton and constitutes 85% of the total bone mass. Trabecular bone represents the remaining 15% of the total bone mass and is predominant in vertebral bodies and the pelvis. The cavities created by the trabecular bone are home for bone marrow, where stromal and hematopoietic stem cells are stored as well as many immune cells at different stages of differentiation [6]. Osteoblast and osteoclasts are derived from different stem cell pools, where osteoblasts are mesenchymal and osteoclasts are hematopoietic in origin (Fig. 2.1). Both osteoblasts and osteoclasts, however, secrete cytokines and growth factors that will directly act on surrounding cells or be included and become part of the mineralized bone matrix [7]. In fact, the mineralized bone matrix is a rich source of many important growth factors, such as insulin-like growth factors (IGF) I and II, platelet-derived growth factors (PDGFs), transforming growth factor β (TGFβ), and bone morphogenetic proteins (BMPs) [8, 9]. These growth factors will be trapped and unable to signal by binding their respective receptors until released from the mineralized bone matrix following osteoclastic bone resorption during bone remodeling [10]. To maintain skeletal homeostasis, osteoblasts, osteoclasts, and hematopoietic cells interact systemically using hormones and locally *via* bone-derived growth factors, such as parathyroid hormone (PTH), 1,25-dihydroxyvitamin D3 (1,25-$(OH)_2D_3$), receptor activator of nuclear factor kappa B (RANK) ligand (RANKL), thyroxine, prostaglandins, BMPs, TGFβ, IGF, and interleukin (IL) 1 and 6, in response to hormonal changes and mechanical stress [11–13]. This complex balance between bone formation and bone resorption is profoundly compromised under pathologic conditions, including rheumatoid arthritis, osteoporosis, and bone metastases (Fig. 2.1a).

Osteoblasts

Osteoblasts differentiate from mesenchymal stem cells located in the bone marrow stroma. They regulate bone mineralization and synthesize the dense cross-linked collagen that will form the bone matrix. Essential for osteoblast differentiation is the transcription factor RUNX2, or core binding factor A1 (CBFA1). Mice lacking Runx2 show arrest in osteoblast maturation and,

therefore, do not develop bone [14, 15]. Several systemic and local factors produced by osteoblasts play an important role in bone metabolism. Some of these factors are prostaglandins, receptors for PTH, estrogen, vitamin D3, and several cytokines, such as TGFβ, PDGF, and fibroblast growth factor (FGF) [16, 17]. Osteoblasts hold a very important function in regulating osteoclast formation and differentiation, stimulating it through the expression on their cell surface of the receptor activator of nuclear factor kappa B (RANK) ligand (RANKL), which interacts with its cognate receptor RANK, expressed in the osteoclast precursor membrane. Osteoblasts can also inhibit osteoclast differentiation by the secretion of osteoprotegerin (OPG), a soluble RANK receptor, which functions as RANKL antagonist.

A major regulator of osteoblast differentiation and function is the Wnt signaling pathway [13]. The activation of Wnt/β-catenin signaling results in increased bone mass, and overexpression of Wnt10 in animal models also leads to increased bone mass. In osteoblastic precursor cells, overexpression of Wnt7B and β-catenin induces differentiation of these cells into mature osteoblasts [18, 19]. Evidence indicates that both canonical and noncanonical Wnt signaling pathways are implicated in mediating these effects. Osteoblasts express several Wnt proteins, which stimulate osteoblastogenesis via a number of different mechanisms, such as attenuating adipocyte differentiation induced by the peroxisome proliferator-activated receptor γ (PPARγ) [20]. Canonical Wnt signaling is transduced through frizzled receptors and low-density lipoprotein receptor-related proteins (LRPs) 5 and 6, which function as co-receptors. Therefore, dysregulation of these receptors is implicated in skeletal diseases. For example, mutations in LRP5 and LRP6 genes conferring gain or loss of function, respectively, lead to high bone mass or osteoporosis [21]. Other regulators of Wnt signaling pathway in bones are antagonist proteins of the Wnt/frizzled receptors and Wnt/LRP complexes, including secreted frizzled-related proteins (sFRPs), Wnt inhibitory factor 1 (WIF-1), sclerostin, and Dickkopfs 1 (DKK1). In particular, DKK1 inhibits the canonical Wnt signaling by binding to LRP5/6, causing the internalization and degradation of the two co-receptors [22]. In animal models, overexpression of DKK1 caused significant osteopenia, while lack of DKK1 resulted in increased bone formation. Moreover, DKK1 is capable of altering the ratio RANKL/OPG, and therefore regulating the RANK/RANKL/OPG axis. In addition to the mechanisms above mentioned, Wnt signaling pathway also participates in bone metabolism regulation by interacting with bone-derived local factors and systemic hormones, such as PTH and BMPs.

Osteoclasts

Osteoclasts are polarized, multinucleated cells that derive from precursor cells of the monocyte/macrophage lineage, which differentiate into osteoclasts. The bone microenvironment plays an important role in osteoclastogenesis and osteoclast activity, regulating these processes via locally produced cytokines and systemic hormones. RANKL is a potent inducer and a key effector in osteoclastogenesis. It is commonly expressed on the cell surface in osteoblasts and stromal cells, but it is also secreted in a soluble form by activated T cells. Osteotropic factors, such as PTH, 1,25-dihydroxyvitamin D3, and prostaglandins, regulate RANKL production. The interaction of RANKL with its cognate receptor RANK on osteoclasts precursors stimulates osteoclast differentiation by downstream activation of the nuclear factor kappa B (NFk-B) and Jun N-terminal kinase (JNK) signaling pathways. The relevance of the interaction of RANK/RANKL in osteoclastogenesis has been proved also in animal models. Transgenic mice lacking RANK or RANKL were unable to produce osteoclasts and presented with a severe osteopetrotic phenotype [23]. An important protein in balancing RANKL function is its decoy receptor OPG, normally expressed in the bone marrow [13, 24]. Overexpression of OPG leads to severe osteopetrosis in mice, while mice that lack OPG show osteopenia [24]. The ratio RANKL/OPG, therefore, rules osteoclastogenesis.

Osteoclast formation is stimulated by IL-1, IL-6, IL-34, prostaglandins, and macrophage colony-stimulating factor (M-CSF) primarily produced by osteoblasts [25]. Some immune cells, such as T-cells, instead, negatively influence osteoclastogenesis by producing IL-4, IL-8, and interferon γ (IFNγ). Furthermore, active osteoclasts secrete proteases that cause degradation of the mineralized bone matrix leading to release of acids and minerals into the extracellular space. Osteoclasts adhere to the bone surface via αvβ3 integrin, forming an actin ring and secreting acid, collagenases, and proteases that demineralize the bone matrix and degrade matricellular proteins, including type I collagen. It is critical that the osteoclasts adhere to the bone matrix during bone resorption, as the use of inhibitors of osteoclast attachment causes disruption of the bone resorption process [26].

Calcium Homeostasis

Calcium is the primary inorganic component of the mineralized bone matrix. Serum calcium concentration is highly regulated by a complex system of calcitropic hormones, which act at the levels of bone, kidney, and gut. PTH and vitamin D in its biologically active form (calcitriol or 1,25-$(OH)_2D_3$) act on these organs and maintain the levels of ionized calcium stable in blood. Serum calcium concentration is maintained within a very narrow range by the interaction of these two calcitropic hormones with their target tissues in bone, kidney, and gut. Under normal conditions, the net calcium exchange from extracellular fluid to these organs is zero [27]. Physiologically, PTH and vitamin D are the most important calcitropic hormones in humans. Calcitonin plays instead a less relevant role. In the bone microenvironment, calcium levels are maintained within a narrow physiologic range (~1.1–1.3 mmol/L) [28]. Active osteoclastic bone resorption causes extracellular calcium (Ca^{2+}) levels to rise up to 8–40 mmol/L [29].

Calcium effects are mediated through the extracellular calcium-sensing receptor (CaSR). CaSR is a G-protein-coupled receptor which responds to high concentration of Ca^{2+} inhibiting cyclic AMP (cAMP) and activating phospholipase C (PLC) [30]. CaSR is expressed in normal tissues and regulates the secretion of parathyroid hormone-related protein (PTHrP). In the presence of low concentration of Ca^{2+}, CaSR increases PTHrP secretion, which activates bone resorption and causes release of calcium from the bone matrix. High Ca^{2+} levels or CaSR agonists reduce PTHrP secretion [31, 32].

Tumor Contribution to Pre-metastatic Niche in Bone

A first concept, proposed by Batson in 1940, hypothesized that the vertebral system of veins acts like a conduit for cancer cell dissemination to the skeletal system [33]. However, this hypothesis does not explain the preferential homing of cancer cells to the bone or other sites of metastases. The exact mechanism that drives certain cancer cells to the bone is still unclear, but there is increasing evidence that the bone microenvironment and the factor present in normal bone and bone matrix, as described above, play a major role in the crosstalk between primary tumors and the bone, to prime the pre-metastatic niche. In 1989, Paget proposed the "seed and soil" hypothesis to explain the tropism of tumor cells for specific organs to form metastases. "When a plant goes to seed, its seeds are carried in all directions, but they can only grow if they fall on congenial soil" [34]. In this metaphor, the tumor cells are the seeds that will grow and form metastases only in the microenvironment of the organ that provides a fertile nourishing soil. This concept remains a basic principle of the understanding of tumor metastasis and is a basic underpinning of research in the field today [35]. Moreover, in the case of the bone tissue, destruction of the mineralized matrix is necessary in order for the tumor cells to invade the bone. This bone resorption is mediated by osteoclasts activated by the cross talk between the tumor cells and the bone microenvironment [2].

More recently, the model of the pre-metastatic niche (PMN) has been formulated (Fig. 2.2a).